CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208232Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208232

COMPLETE RESPONSE

Camargo Pharmaceutical Services
Authorized Agent for Chiasma, Inc.
Attention: Ruth E. Stevens, Ph.D., MBA
Executive Vice President and Chief Scientific Officer
9825 Kenwood Road, Suite 203
Cincinnati, OH 45242

Dear Dr. Stevens:

Please refer to your New Drug Application (NDA) dated June 12, 2015, received June 15, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Mycapssa (octreotide) capsules, 20 mg.

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 two reasons for this action below and, where possible, our recommendations to address these issues.

1. During a recent inspection of (b) (4) located at (b) (4) our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application can be approved.

2. The data in the application do not provide substantial evidence that Mycapssa is effective as the effect captured in study CH-ACM-01 cannot be purported to represent the effect of Mycapssa. Satisfactory resolution of this deficiency is required before this application can be approved.

The following paragraphs provide a summary of our rationale for the deficiency described in item number 2.

The data in the application demonstrate that Mycapssa and Sandostatin IR (listed drug) are not bioequivalent. Specifically, the relative systemic exposure, based on the least squares means for AUC0-t, of octreotide from the single-dose 20 mg fasted dose of Mycapssa relative to the 0.1 mg s.c. dose of octreotide was 0.97 with very wide confidence intervals of 73% – 128% for AUC0-t. Similarly, the C_{max} with a point estimate of 0.64 and 90% confidence intervals of 45.29% - 89.78% failed to meet the bioequivalence criteria. A comparative pharmacokinetic (PK) study evaluating the proposed twice daily (BID) dosing regimen of Mycapssa compared to the three times daily (TID) dosing of Sandostatin was not conducted. Finally, you did not characterize the Mycapssa dose-response relationship or the pharmacodynamic (PD) comparability (growth hormone and IGF-1) between Mycapssa and Sandostatin injection in your application.

Although meeting strict criteria for bioequivalence is not required for products reviewed under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, absence of bioequivalence between Mycapssa and the listed drug necessitated that you demonstrate the safety and effectiveness of Mycapssa with data generated in study CH-ACM-01.

Study CH-ACM-01 was a single-arm, open-labeled, cohort study with a planned primary efficacy endpoint assessment that was to take place 7 months after a baseline assessment. There were no formal inferences pre-specified and the study was to be purely descriptive in nature. Patients enrolled in the study were eligible if they had a past history of acromegaly and were controlled on and tolerated somatostatin analog therapies at the time of study screening. The intervention consisted of switching pre-trial therapies to Mycapssa and observing the biochemical response to the switch. The majority of patients enrolled had received surgery alone or surgery with a combination of radiotherapy as the initial treatment for acromegaly. The majority of patients had been treated for years with long-acting somatostatin analogs with or without pegvisomant and/or bromocriptine prior to the baseline assessment. Your study did not require confirmation of disease activity prior to the baseline assessment to account for the cumulative effects of past therapies on disease activity (e.g., pituitary surgery, drug therapy, radiation or a combination of the above). Drugs (long-acting somatostatin analogs) known to be effective at suppressing growth hormone (GH) and insulin-like growth factor-1 (IGF-1) were withdrawn close to the baseline assessment and had a lingering pharmacodynamic effect during a large portion of the efficacy phase of your study.

After reviewing the data from study CH-ACM-01, we conclude that the estimate of efficacy derived from study CH-ACM-01 does not distinguish the effect of Mycapssa from other effects such as inactive disease at the endpoint visit due to the cumulative effect of past therapies (e.g., pituitary surgery, drugs, radiation or a combination of these) or due to differences in the biological effect of individual tumors or due to confounding from the residual effects of pre-trial therapy (ies) used to control disease activity. At least some responders in your trial could have been responders simply on the basis that they did not have active disease at last assessment or because of the carryover effects of prior treatments on disease activity. Due to important biases in the estimate of efficacy derived from study CH-ACM-01, we cannot determine whether Mycapssa had a clinically important effect on disease control or the magnitude of the Mycapssa-attributable effect on the efficacy estimate in this study.

In our review of the data from study CH-ACM-01 we noted an overall worsening of control in the majority of patients, as evidenced by rising IGF-1 levels between baseline and last on-treatment assessment. For patients with active disease these finding would not be consistent with "maintenance of response" or "maintenance of control". It did not appear that the rate of rise in IGF-1 had stabilized by the final biochemical assessment used to represent Month 7. This is concerning because a subject classified as a responder and whose IGF-1 trajectory is on a rising trend may reveal himself to be a treatment failure at a later assessment time point.

We noted in our review of the application that you had not pre-specified or selected which responder criterion you would use to define response for the purpose of presenting the primary efficacy results in the protocol submitted to the Agency at the End-of Phase-2 (EOP2) meeting.

We disagree with the response criterion that you ultimately selected for the primary efficacy analysis because your criterion is insensitive to detecting small but clinically meaningful changes in disease control. A full responder at baseline who goes from an IGF-1 level of 0.8-fold the upper limit of normal for age to 1.2-fold fold the upper limit of normal for age within a 7 month time frame would be considered a "responder" with your criterion. However, this same patient, with the same IGF-1 trajectory, would be considered a "non-responder" with the criterion used by current professional society guidelines to define disease control [i.e., a criterion that uses an age normalized IGF-1 level (i.e., less than or equal to 1-fold the upper limit of normal for age)]. From a clinical standpoint, it is likely that a sustained 50% increase in IGF-1 levels in 7 months in the example patient described would represent a clinically meaningful change in disease activity. Furthermore, in a study designed to evaluate "loss of control" choice and use of a more conservative failure criterion to estimate drug effect is more likely to represent substantial evidence.

We also noted in our review that the endpoint criterion selected for the primary efficacy analysis of Mycapssa was selected near the time of study completion ((b) (6); Statistical Analysis Plan) close to the date of the last patient last visit (b) (6) We further noted that content of Chiasma power point presentations used to support the open session discussions with the Data Monitoring Committee (DMC) for the May 13, 2013, (75% subject accrual meeting) and August 22, 2013, (100% subject accrual meeting) meetings contain slides showing individual level patient data and aggregate data at a time when the study was ongoing (i.e., prior to study database lock, prior to specifying the primary endpoint for efficacy analysis and prior the finalizing the analysis plan). Finally, we also noted that the DMC was getting routine aggregate efficacy updates with each DMC meeting reports (i.e., not for cause and not for the purpose of determining futility per the charter). Although we recognize the trial was open label, we find this level of access to accruing data during the conduct of a study to be problematic as it may have affected the study findings in ways that cannot be assessed for retrospectively.

To address the deficiency listed in item number 2, you will need to provide substantial evidence that Mycapssa will have the effect it purports to have under the conditions of use recommended in labeling for patients with acromegaly in a new clinical trial. The study design, conduct of the study and primary analysis should minimize biases to the extent possible to ensure the effect size captured is attributable to Mycapssa and not to a confounder. We strongly recommend that your study be randomized, double-blind and controlled. The trial should enroll patients from the United States and be of sufficiently long duration to ensure that control of disease activity is stable at the time point selected for the primary efficacy assessment.

We encourage you to request an End of Review meeting to discuss the path forward for this application.

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* and *Pregnancy and Lactation Labeling Final Rule* 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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

Please submit draft carton and container labeling revised as follows: Add "delayed-release" to the product name on all carton and container labels.

PROPRIETARY NAME

Please refer to correspondence dated July 30, 2015, which addresses the proposed proprietary name, Mycapssa. 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:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA 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 NDA 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. 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 FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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, please call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
04/15/2016