CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209510Orig1s000

OTHER ACTION LETTER(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209510

COMPLETE RESPONSE

Acacia Pharma Ltd
C/O Acacia Pharma, Inc.
Attention: Paul A. Orth, Pharm.D.
U.S. Agent, Global Head of Regulatory Affairs
8440 Allison Pointe Blvd., Suite 100
Indianapolis, IN 46250

Dear Dr. Orth:

Please refer to your New Drug Application (NDA) dated October 5, 2017, received October 5, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Barhemsys (amisulpride) injection, for intravenous use.

We acknowledge receipt of your amendment dated November 5, 2018, which constituted a complete response to our October 5, 2018 action letter.

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 INSPECTIONS

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

PRESCRIBING INFORMATION

1. 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

PROPRIETARY NAME

2. Please refer to correspondence dated January 30, 2019, which addresses the proposed proprietary name, Barhemsys. 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 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. 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

We have the following additional comment/recommendation that is not an approvability issue but should be addressed in the Complete Response action:

The effects of severe renal impairment on amisulpride pharmacokinetics has not been adequately characterized and amisulpride was studied only in a limited number of patients with severe renal impairment in the clinical trials. Because of this limited information, the dosing for patients with severe renal impairment cannot be supported by available data. To inform dosing for patients with severe renal impairment and end-stage renal disease, we recommend that you conduct a pharmacokinetic study following a single dose of amisulpride in patients with severe renal impairment and end-stage renal disease (i.e., eGFR < 30 mL/min/1.73 m^2), and healthy subjects as a control group.

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 FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," December 2017 at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.

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 Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Victor Crentsil, M.D., M.H.S.
Acting Deputy Director
Office of Drug Evaluation III
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/

VICTOR CRENTSIL
05/02/2019 11:25:52 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 209510

COMPLETE RESPONSE

Acacia Pharma Ltd
C/o Acacia Pharma Inc.
Attention: Paul A. Orth, Pharm.D.
Global Head Regulatory Affairs
450 E. 96th St Ste 500
Indianapolis, IN 46240

Dear Dr. Orth:

Please refer to your New Drug Application (NDA) dated October 5, 2017, received October 5, 2017 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Barhemsys (amisulpride) injection, 5 mg/2 mL.

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 INSPECTION DEFICIENCIES

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

PRESCRIBING INFORMATION

1. Submit a revised PI, based on the version appended to this letter.

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents

- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

CARTON AND CONTAINER LABELING

2. Submit draft carton and container labeling based on the version appended to this letter.

PROPRIETARY NAME

3. Please refer to correspondence dated, May 24, 2018, which addresses the proposed proprietary name, Barhemsys. 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.

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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 CAPT Mimi Phan, Regulatory Project Manager, at (301) 796-5408.

Sincerely,

{See appended electronic signature page}

Victor Crentsil, M.D., M.H.S.
Acting Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Prescribing Information Labeling
Container and Carton Labeling

16 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

VICTOR CRENTSIL
10/05/2018