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RESEARCH**

APPLICATION NUMBER:
202317Orig1s000

OTHER ACTION LETTERS



NDA 202317

COMPLETE RESPONSE

Ceptaris Therapeutics, Inc.
Attention: Lisa Wittmer, M.S., Ph.D.
Vice President, Regulatory Affairs
101 Lindenwood Drive, Suite 400
Malvern, PA 19355

Dear Dr. Wittmer:

Please refer to your New Drug Application (NDA) dated July 27, 2011, received July 27, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Mechlorethamine Hydrochloride Gel 0.02%.

We acknowledge receipt of your amendments dated September 2, 6, 7, 16, 2011, October 3, 13, 14, 21, 2011, November 18, 2011, December 2, 5, 7, 23, 2011, January 5, 11, 17, 20, 23, 2012, February 17, 2012, March 6, 2012 and April 20, 2012.

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.

CHEMISTRY, MANUFACTURING AND CONTROL

1. Due to insufficient characterization, comparability between the clinical trial and commercial products has not been demonstrated. Sufficiently characterize clinical trial and commercial products to demonstrate comparability.
2. At time of release, the proposed commercial drug product lots (UIP lots 094I1209B, 013I0210B and 017I0210B) were not sufficiently characterized. Sufficiently characterize the commercial product on release and stability.
3. Impurity levels in the commercial product cannot be qualified by clinical experience as proposed due to insufficient characterization of clinical trial and commercial lots on release and stability. Consequently, the proposed acceptance criteria for impurities in the proposed drug product specifications are not acceptable based on submitted justification. Revise the proposed acceptance criteria for drug product impurities (See also # 14).
4. A product expiry cannot be established due to insufficient release data for the commercial lots of drug product and the lack of established acceptance criteria for the stability

specifications. Provide sufficient data on commercial lots to support a commercially viable product expiry.

5. Specify the supplier(s) of the starting material (b) (4) in section S.2.3.
6. Correct the discrepancy in Table (3.2.S.4) 2 of page 7, section 3.2.S.4 (b) (4)
7. Validation of the analytical method for assay/impurities submitted was for Method (b) (4), which is not the method identified in the drug product specifications. Provide validation for the assay/impurities method (b) (4) identified as the NDA method in the drug product specifications.
8. The validation report submitted for the analytical method for BHT (b) (4) indicates that a placebo formulation (lot 04201009 trial 1) was used in place of product. Identify the test sample used in the submitted validation report. Provide validation of the method with product or demonstrate that the submitted validation conducted with placebo provides comparable results as product.
9. Batch Analysis: Revise Table (3.2.P.5.4)2 titled “Batch Analyses of Drug Product – NDA Stability Lots – Manufactured at UIP; (b) (4) Batch Size; 60g Tubes” to report only data collected at release (b) (4) and by the proposed specification methods submitted in Table 3 “Drug Product Specification – Release”.

Alternately, revise the table to include in the body of the table, for each data point:

- date the test was conducted
- age of lot at test date, measured from date of lot manufacture
- storage conditions of the lot from manufacture to test date
- analysis method used, including method identification to correlate to submitted NDA methods listed in the specifications

Provide analytical procedures for analytical methods not already submitted and discuss correlation of results to those obtained by the NDA method. Explain the suitability of any data collected beyond release and using non-NDA methods for establishing the quality of the commercial product.

10. Specifications: Impurity levels in the commercial product cannot be evaluated for qualification because a maximum daily dose has not been established. Establish a maximum daily dose.
11. Specifications: (b) (4) acceptance criteria in the commercial product cannot be evaluated for release specification due to the absence of clinical trial and commercial lot

release data. Further, the proposed level [REDACTED] (b) (4) in the stability specification is not supported by commercial lot manufacturing experience. Revise the proposed acceptance criteria [REDACTED] (b) (4) in the drug product to reflect lot history.

12. Stability specifications: The proposed specifications submitted for stability of the drug product do not include the test method. Revise the specifications to include attribute, method and acceptance criteria.
13. Expiry: [REDACTED] (b) (4) establish an in-use expiry period, based on study results, to begin at first dispense.

NON-CLINICAL

14. [REDACTED] (b) (4)

A justification based on clinical studies submitted with this application is not acceptable as you did not prospectively collect data; a post-hoc analysis of the impurities is not acceptable for this product [REDACTED] (b) (4)

CLINICAL

15. Due to the lack of comparability between the clinical trial and commercial products, the efficacy and safety results of Study-201 cannot be used as the basis of approval for Valchlor. You will need to conduct one or more clinical trials to demonstrate substantial evidence of efficacy and safety for the proposed commercial drug product.
16. Study-201 lacked adequate duration of follow-up for safety events post-treatment. The median duration of documented post-treatment follow-up for detection of secondary cutaneous malignancies (i.e., non-melanoma cutaneous skin cancer) was one day post-treatment cessation in both treatment arms. A longer duration of follow-up for safety events post-treatment is necessary.

OTHER DEFICIENCIES

17. Under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or statement with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on for approval of the

application were conducted, or that claim a use for the listed or other drug. Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness for NDA 6-695 for Mustargen (mechlorethamine hydrochloride) injection, 10 mg/vial, but does not contain a patent certification or statement worded in accordance with 21 CFR 314.50(i). You must submit an appropriate patent certification or statement with respect to reliance on Mustargen.

CHEMISTRY, MANUFACTURING AND CONTROL COMMENTS

The following are for consideration in advance of a subsequent Module 3 submission:

1. Provide a USAN name for the drug substance in section S.1.1.
2. Provide a CAS number for the starting material (b) (4) in section S.2.3.
3. In section 3.2.S.4, the proposed acceptance criterion for the individual related substances of drug substance specification is above the ICH qualification threshold. Tighten this acceptance criterion according to the ICH Q3A guidelines.
4. In section 3.2.S.4, the proposed acceptance criterion for the total related substances of the drug substance specification appears to be too wide based on your submitted batch history. Tighten this acceptance criterion to more accurately reflect your drug substance manufacturing capability.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, 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>.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We note that your July 27, 2011, submission included a proposed REMS. This portion of your submission was not reviewed for this action. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

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.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference 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's "Guidance for Industry - Formal Meetings Between the 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, call Tyree Newman, Regulatory Project Manager, at (301) 796-3907.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Director (Acting)
Division of Hematology Products
Office of Hematology and Oncology Products
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/

ANN T FARRELL
05/04/2012