

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204630Orig1s000

OTHER ACTION LETTERS



NDA 204630

COMPLETE RESPONSE

Provepharm SAS
Attention: Clara Li
VP Regulatory and Strategic Development
Clinipace Worldwide RSD
4840 Pearl East Circle, Suite 201E
Boulder, CO 80301

Dear Ms. Li:

Please refer to your New Drug Application (NDA) dated September 13, 2013, received September 13, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (methylene blue) Injection, 0.5%.

We acknowledge receipt of your amendments dated October 27 and 31, November 5, 6, 11, 13, 19, and 25, December 11 and 19, 2013, January 7, February 17, March 4 and 13, April 4, 17, 25, and 30, May 5, 7, 16, 20, 23 and 30 (2), June 2, 13, 16, 18, 20, 23, and 27, July 9, 18, and 30, and August 29, 2014.

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.

CLINICAL

1. The NDA does not contain substantial evidence of effectiveness of (b) (4) for the treatment of acquired methemoglobinemia. Substantial evidence of effectiveness requires data showing that the benefits of a product outweigh its risks. Your data to support efficacy came from Protocol PVP-2013001, a retrospective chart review of patients with acquired methemoglobinemia treated with (b) (4). The primary endpoint of the protocol was the proportion of patients with at least 50% reduction in methemoglobin at one hour after the first dose of (b) (4). Only three patients had a repeat methemoglobin measured within the required timeframe. Although the response rate was high (100%), the 95% confidence interval (CI) was wide (44-100%) due to the small sample size, so the point estimate was not considered credible. No data on the effects of treatment with (b) (4) on heart rate, respiratory rate or mental status at one hour were submitted, so a clinical benefit could not be established. Further, data files for adverse events, vital signs and laboratory testing were not adequate to develop a safety profile.

You also submitted a review of multiple published reports of treatment of acquired methemoglobinemia with methylene blue formulations that were not your product, but you did not provide scientific justification for the applicability of those reports to support the effectiveness of (b) (4)

To address the deficiency, you must submit either the results of a prospective trial of (b) (4) for treatment of acquired methemoglobinemia, or data, such as from a BA/BE trial in humans to assess the relative bioequivalence of methylene blue and Azure B concentrations following intravenous administration of (b) (4) Injection 0.5% or methylene blue injection USP 1%, to establish that reliance on published outcomes with methylene blue USP 1% is scientifically valid.

CLINICAL PHARMACOLOGY

2. Conduct a relative BA/BE trial in humans to assess the relative bioequivalence of methylene blue and Azure B concentrations following intravenous administration of (b) (4) Injection 0.5% (5 mg/mL) solution or methylene blue injection USP 1% (10 mg/mL) solution. Samples should be analyzed using a validated method (refer to the Guidance for Industry titled [Bioanalytical Method Validation](#)) and full PK profiling from both methylene blue formulations should be reported for methylene blue and Azure B.
3. Identify the pathways by which (b) (4) (and its metabolites) are eliminated and excreted in humans.
4. (b) (4)
(b) (4)
5. Conduct a clinical trial in humans to determine the potential of (b) (4) to prolong the QT/QTc interval according to the principles of [ICH E14](#).
6. Evaluate the in vitro partitioning of (b) (4) and its metabolite Azure B into human red blood cells.
7. Evaluate the in vitro ability of (b) (4) (and its metabolites) to act as substrates of cytochrome P450 enzymes, as well as substrates or inhibitors of conjugating enzymes and transporters. For an updated list of potential metabolic pathways and transporters identified by the Agency please refer to the newly released draft guidance titled [Drug Interaction Studies](#).

PRODUCT QUALITY

8. (b) (4)

LABELING

9. 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>.

Please refer to our correspondence dated May 28, 2014, which addresses the proposed proprietary name, [REDACTED]^{(b) (4)}. 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.

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 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>.

If you have any questions, call Kim J. Robertson, Regulatory Health Project Manager, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
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
10/10/2014