



NDA 204630

ACCELERATED APPROVAL

Provepharm SAS
c/o Clinipace Worldwide RSD
Attention: Clara Li
VP, Regulatory and Strategic Development, U.S. Agent
4840 Pearl East Circle, Suite 201E
Boulder, CO 80301

Dear Ms. Li:

Please refer to your New Drug Application (NDA) dated October 9, 2015, received October 9, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ProveyBlue (methylene blue) injection, 50 mg/10 mL (5 mg/mL).

We acknowledge receipt of your amendment dated October 9, 2015, which constituted a complete response to our October 10, 2014, action letter.

This new drug application provides for the use of ProveyBlue (methylene blue) injection for the treatment of pediatric and adult patients with acquired methemoglobinemia.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 204630.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for ProvayBlue (methylene blue) was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. You are required to conduct such studies with due diligence. If postmarketing studies fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated April 7, 2016. This requirement, along with required completion dates, is listed below.

PMR-3065-1	Design and conduct a study and provide the full final report and data sets to evaluate the safety and efficacy of ProvayBlue (methylene blue) for the treatment of methemoglobinemia. The minimal efficacy endpoints should include achieving a 50% reduction in methemoglobin within one hour of the first dose of ProvayBlue (methylene blue) in addition to normalization of the respiratory rate, heart rate and blood pressure within two hours of the first dose of ProvayBlue (methylene blue).
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The timetable you submitted on April 7, 2016, states that you will conduct this study according to the following schedule:

Date Potential Investigators Identified:	07/2016
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Final Protocol Submission:	12/2016
Study Completion:	03/2020
Final Report Submission:	09/2020

Submit clinical protocols to your IND 118156 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “**Subpart H Postmarketing Requirement(s).**”

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of serious risks from increased exposure of concomitantly administered drugs that are metabolized by CYP450 enzymes including 1A2, 2B6, 2C8, 2C19, 3A4 and 2D6, or from increased exposure of ProVayBlue (methylene blue) due to hepatic or renal impairment.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 3065-2 Conduct a clinical trial (or trials) to determine the extent of *in vivo* drug-drug interaction of ProvayBlue (methylene blue) as a modulator of CYP450 enzyme activity using CYP450 enzyme substrates.

The timetable you submitted on April 7, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 12/2016
Trial Completion: 06/2018
Final Report Submission: 12/2018

PMR 3065-3 Conduct a clinical trial to determine the effect of hepatic impairment on the pharmacokinetics and safety of ProvayBlue (methylene blue).

The timetable you submitted on April 7, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 12/2016
Trial Completion: 12/2018
Final Report Submission: 06/2019

PMR 3065-4 Conduct a clinical trial to evaluate the effect of varying degrees of renal impairment on the pharmacokinetics and safety of ProvayBlue (methylene blue) in subjects with renal impairment.

The timetable you submitted on April 7, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 12/2016
Trial Completion: 12/2018
Final Report Submission: 06/2019

Submit the protocols to your IND 118156 with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Laura Wall, Regulatory Project Manager, at (301) 796-2237.

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

Enclosures:

Content of Labeling
Carton and Container Labeling

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
04/08/2016