



NDA 204630/S-011

**SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING
REQUIREMENTS**

Provepharm SAS
c/o Clinipace Worldwide RSD
Attention: Clara Li
Vice President, Regulatory and Strategic Development
1434 Spruce Street, Suite 100
Boulder, CO 80302

Dear Dr. Li:

Please refer to your supplemental new drug application (sNDA) dated and received April 23, 2020, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ProvayBlue (methylene blue), injection.

This Prior Approval supplemental new drug application provides for changes to the Recommended Dosage for Renal Impairment (2.2), Drug Interactions (7), Renal Impairment (8.6), and Clinical Pharmacology (12) sections of the United States Prescribing Information (USPI).

APPROVAL & LABELING

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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*.²

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have received your submissions dated December 21, 2018 (PMR 3065-2) and October 24, 2019 (PMR 3065-4), and April 23, 2020, containing the final reports for and reporting on the following postmarketing requirements listed in the April 8, 2016 approval letter.

- 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.
- 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.

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

We have reviewed your submissions and conclude that the above requirements were fulfilled.

We remind you that there are postmarketing requirements listed in the April 8, 2016 approval letter that still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.³

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵

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, contact Courtney Hamilton, Regulatory Project Manager at 301-796-6849 or at Courtney.Hamilton@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Nonmalignant Hematology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling

³ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

- Prescribing Information

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/

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