

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204630Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 204630

SUPPL # N/A

HFD # 161

Trade Name ProvayBlue

Generic Name methylene blue

Applicant Name Provepharm SAS

Approval Date, If Known April 8, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity? The applicant requested 7 years of exclusivity in their September 13, 2013 submission (their initial submission after their application received a Refuse to File on October 11, 2012).

YES NO

If the answer to (c) is "yes," how many years of exclusivity did the applicant request?
7 years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 1795 B&R #328 Tab

NDA# 001049 Rinatin Tab

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

PVP-2014002 - QT study in healthy volunteers

PVP-2013001 - Collection Of Retrospective Clinical Data (although a retrospective study, it was essential to approval)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

PVP-2014002 – QT study in healthy volunteers

PVP-2013001 - Collection Of Retrospective Clinical Data (although a retrospective study, it was essential to approval)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 118156 YES ! NO
! Explain:

Investigation #2
YES ! NO
! Explain: **The retrospective analysis was not conducted under IND.**

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES ! NO
Explain: ! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain: The retrospective analysis was not conducted under IND.

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Laura Wall, MS

Title: Regulatory Project Manager

Date: April 8, 2016, revised 1/13/17

Name of Office/Division Director signing form: Ann T. Farrell, MD

Title: Director/Division of Hematology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAURA C WALL
01/19/2017

ANN T FARRELL
01/19/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204630 BLA #	NDA Supplement # N/A BLA Supplement #	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: ProvayBlue Established/Proper Name: methylene blue Dosage Form: injection		Applicant: Provepharm SAS Agent for Applicant (if applicable): N/A
RPM: Laura Wall		Division: Division of Hematology Products
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>April 9, 2016</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		Complete response 10/10/14
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 7
 (confirm chemical classification at time of approval)

☐ Fast Track	☐ Rx-to-OTC full switch
☐ Rolling Review	☐ Rx-to-OTC partial switch
☒ Orphan drug designation	☐ Direct-to-OTC
☐ Breakthrough Therapy designation	

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments: Resubmission Class 2

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 4/8/16; 10/10/14
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☐ Included
Original applicant-proposed labeling	☒ Included 10/9/15; 9/13/13
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☐ Included
Original applicant-proposed labeling	☐ Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
Most-recent draft labeling	☒ Included 3/15/16; 9/13/13
❖ Proprietary Name	2/22/16; 12/22/15; 5/28/14; 12/6/13
- Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) - Review(s) (<i>indicate date(s)</i>)	2/22/16; 12/22/15
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: ☒ 3/9/16 DMEPA: ☒ 3/16/16; 6/18/14; 1/28/14 DMPP/PLT (DRISK): None OPDP: ☒ 3/30/16; 8/28/14 SEALD: None CSS: None Product Quality: None Other: None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	11/27/13
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	3/29/16
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included 4/8/16
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>Orphan Designation Status</u>	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	Cycle 2: 4/6/16; 4/5/16; 4/4/16 (2); 3/30/16; 3/25/16; 3/17/16 (4); 3/16/16; 3/10/16 (2); 3/9/16; 3/8/16 (2); 3/4/16; 3/2/16; 2/25/16; 2/24/16; 2/22/16; 2/5/16; 1/29/16; 1/8/16; 12/22/15; 12/3/15; 11/17/15; 11/3/15; 10/30/15; 10/29/15; 10/23/15 Cycle 1: 9/24/14; 9/22/14 (2); 8/25/14 (2); 8/22/14 (2); 7/17/14; 7/9/14; 7/1/14; 6/12/14; 6/2/14; 5/28/14; 5/27/14; 5/21/14 (2); 5/19/14; 5/9/14; 5/8/14; 5/6/14; 5/4/14; 5/1/14; 4/23/14 (2); 4/15/14; 4/14/14; 4/10/14 (3); 4/3/14; 3/19/14; 2/18/14; 2/5/14; 2/4/14; 12/20/13(2); 12/6/13; 11/27/13; 11/18/13; 11/8/13; 11/5/13; 10/15/13; 10/10/13; 10/4/13; 9/27/13
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Internal telecon memorandums 3/17/16; 9/24/14
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☒ No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
• Mid-cycle Communication (<i>indicate date of mtg</i>)	☒ N/A
• Late-cycle Meeting (<i>indicate date of mtg</i>)	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	5/24/13; 12/18/12; 1/30/12

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	☒ No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	4/8/16; 10/3/14
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	3/25/16; 9/10/14
PMR/PMC Development Templates (<i>indicate total number</i>)	4
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	3/25/16; 8/19/14 (cosigned primary)
• Clinical review(s) (<i>indicate date for each review</i>)	3/28/16; 8/19/14
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 17 in the clinical review; Page 12 clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ 6/8/14
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☒ 4/25/14
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☒ 6/17/14; 10/3/13
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review 3/18/16
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review 3/18/16
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	3/18/16; 2/10/16 (QT-IRT); 9/5/14 (Biopharm); 9/4/14; 8/15/14; 7/14/14; 6/30/14 (QT-IRT); 5/29/14; 12/30/13
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	Cancellation of Biopharm inspection request 4/6/16; 9/26/14
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☐ No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	☒ No separate review 3/2/16; 5/28/14
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	3/2/16; 5/28/14; 3/25/14; 11/12/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ See dates for statistical reviews and ECAC/CAC meeting minutes information
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☒ 5/6/14
❖ ECAC/CAC report/memo of meeting	☒ 3/20/14
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	☐ None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	☒ 8/18/14; 11/13/13
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	☒ 4/7/16; 1/25/16 (micro); 9/22/14; 9/11/14; 6/17/14 (micro); 6/2/14; ONDQA Biopharm 9/5/14; 10/3/13 (micro)
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Pg. 55 4/7/16 review; pgs. 44-45 9/22/14 review
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Facilities Review/Inspection	
☐ Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAURA C WALL
04/11/2016

From: [Farrell Ann T](#)
To: [Habtemariam Bahru](#); [Nkah Shila](#); [Rahman Nam Atiqur](#); [Wall Laura](#)
Cc: [Bonapace Charles](#); [Chennamaneni Srinivas Rao](#); [Turner-Rinehardt Sharon](#)
Subject: RE: Biopharmaceutical Inspections Request Consult_NDA-204630
Date: Tuesday, April 05, 2016 4:11:50 PM

agree

From: Habtemariam, Bahru
Sent: Tuesday, April 05, 2016 4:11 PM
To: Nkah, Shila; Farrell, Ann T; Rahman, Nam Atiqur; Wall, Laura
Cc: Bonapace, Charles; Chennamaneni, Srinivas Rao; Turner-Rinehardt, Sharon
Subject: RE: Biopharmaceutical Inspections Request Consult_NDA-204630

Hi Shila,

The initial consult was a routine consult with a flag for dosing discrepancy. The issue with the dosing discrepancy has been resolved.

Also, per our phone conversation earlier today, the site was deemed acceptable based on initial assessment and your SOP would allow cancelation of inspections for sites that are deemed acceptable based on initial assessment. Since we have not outstanding issue that would require inspection, cancelation of the planned inspection is acceptable.

Thanks,
Bahru

From: Nkah, Shila
Sent: Tuesday, April 05, 2016 3:56 PM
To: Farrell, Ann T; Habtemariam, Bahru; Rahman, Nam Atiqur; Wall, Laura
Cc: Bonapace, Charles; Chennamaneni, Srinivas Rao; Turner-Rinehardt, Sharon
Subject: Biopharmaceutical Inspections Request Consult_NDA-204630

Good Afternoon Ann,

Based on information from the assigned ORA investigator, they are unable to conduct the inspection and submit the review by Friday April 8.

The Clinical Pharmacology reviewer (Bahru) informed us that the issues for which the inspection request was submitted appear to have been resolved. Thus, we are considering cancelling the inspection.

Please let us know whether the inspection is still needed. Your input/feedback will be appreciated.

Thanks,

Shila Nkah, M.S.

Project Manager
Office of Study Integrity & Surveillance
Office of Translational Sciences
Center for Drug Evaluation and Research
Food & Drug Administration
White oak Bldg. 51, Rm. 5318
Phone: (301)-796-8347
Email: shila.nkah@fda.hhs.gov
Please consider the environment before printing this e-mail.

From: Habtemariam, Bahru
Sent: Tuesday, April 05, 2016 1:49 PM
To: Nkah, Shila
Cc: Wall, Laura; Hamed, Salaheldin; Chennamaneni, Srinivas Rao; Rogers, Tracey; Rahman, Nam Atiqur
Subject: FW: Acknowledgment of Biopharmaceutical Inspections Request Consult_NDA-204630
Importance: High

Hi Shila,

What is the status of inspection for this NDA? During your last communication, you had indicated you would proceed with the inspections.

Per the e-mail below, the inspection report should be complete by noon Friday.

Bahru

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHILA S NKAH
04/06/2016

From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](#)
Subject: NDA 204630 - FDA Information Request - Please respond by COB April 6, 2016
Date: Wednesday, April 06, 2016 3:43:00 PM

Dear Clara,

Minor changes were made to the descriptions of the four PMRs with regards to NDA 204630 methylene blue. The team requests that you respond to the following Information Request:

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).

2: Conduct a clinical trial to determine the effect of hepatic impairment on the pharmacokinetics and safety of ProvayBlue (methylene blue).

3: 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.

4: 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.

To expedite the review, please send me your response via e-mail and officially to your application by **COB April 6, 2016**.

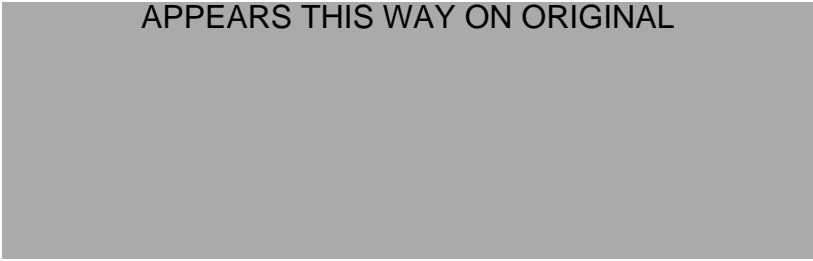
Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL



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/s/

LAURA C WALL
04/06/2016

From: [Wall, Laura](#)
To: [Clara Li \(CLi@clinipace.com\)](mailto:CLi@clinipace.com)
Cc: [Wall, Laura](#)
Subject: NDA 204630 methylene blue - FDA PI revisions to Provepharm SAS.doc
Date: Tuesday, April 05, 2016 12:26:16 PM
Attachments: [NDA 204630 methylene blue PI revisions 4-4-16 to Provepharm SAS PVP.doc](#)

Dear Clara,

Please note the FDA's formatting issues and comments in the attached PI. Please fix these issues as soon as possible, **by early this afternoon**, and send the PI to me via e-mail and officially to your application as the final-agreed upon label.

Kindly confirm receipt.

Thank you,

Laura

4

10 Pages of Draft Labeling have been
Withheld in Full as b4 (CCI/TS)
immediately following this page

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/s/

LAURA C WALL
04/05/2016

From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](#)
Subject: NDA 204630 - FDA Label Revisions - Please respond by 11 a.m. (EST) Tuesday, April 5, 2016
Date: Monday, April 04, 2016 3:40:00 PM
Attachments: [NDA 204630 methylene blue PI revisions 4-4-16 to Provepharm SAS.doc](#)

Dear Clara,

Please refer to the attached labeling revisions to the prescribing information (PI) for NDA 204630 methylene blue. Please also add the month to the revised dates.

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, please send me the revised tracked change labeling via e-mail before you make your official submission electronically. If you agree to all of the FDA's changes, this label can constitute the final-agreed upon label.

Please send me your response **by 11 a.m. (EST) Tuesday, April 5, 2016.**

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

10 Pages of Draft Labeling have been
Withheld in Full as b4 (CCI/TS)
immediately following this page

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/s/

LAURA C WALL
04/04/2016

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 204630 Supplement Number: N/A NDA Supplement Type (e.g. SE5): N/A

Division Name: Hematology PDUFA Goal Date: 04/09/16 Stamp Date: 10/09/2015

Products

Proprietary Name: ProvayBlue

Established/Generic Name: methylene blue

Dosage Form: injection

Applicant/Sponsor: Provepharm SAS

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____
-

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: For the treatment of pediatric and adult patients with acquired methemoglobinemia

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
☐ Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 Disease/condition does not exist in children
 Too few children with disease/condition to study
 Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmps@fda.hhs.gov) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
☐ Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	
☐ All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
☐ Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐ All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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/s/

LAURA C WALL
04/07/2016

From: [Wall, Laura](#)
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](#)
Subject: NDA 204630 - FDA Revisions to methylene blue PI - Please respond by by COB Friday, April 1, 2016
Date: Wednesday, March 30, 2016 5:23:07 PM
Attachments: [NDA 204630 methylene blue PI revisions 3-30-16 to Provepharm.doc](#)

Dear Clara,

Please refer to the attached labeling revisions to the prescribing information (PI) for NDA 204630 methylene blue.

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, please send me the revised tracked change labeling via e-mail before you make your official submission electronically. If you agree to all of the FDA's changes, this label can constitute the final-agreed upon label.

Please send me your response **by COB (EST) Friday, April 1, 2016.**

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

10 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LAURA C WALL
03/30/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: March 17, 2016

Application Number: NDA 204630

Product Name: methylene blue

Sponsor/Applicant Name: Provepharm SAS

Subject: Discuss 4 New PMRs and revisions to the USPI and carton/container labeling

FDA Participants

Division of Hematology Products (DHP)

Albert Deisseroth, MD, PhD, Medical Officer, Clinical Team Leader

Donna Przepiorcka, MD, PhD, Medical Officer, Clinical Team Leader

Barry W. Miller, MS, CRNP, Deputy Director Safety

Qin Ryan, MD, PhD, Medical Officer

Diane Leaman, BS, Safety Regulatory Project Manager

Laura Wall, MS, APHN, Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology V

Bahru Habtemariam, PharmD, Clinical Pharmacology Team Leader

Salaheldin Hamed, PhD, Clinical Pharmacology Reviewer

Product Quality - ONDQA

Anamitro Banerjee, PhD, CMC ONDQA Reviewer

Division of Hematology Oncology Toxicology (DHOT)

Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist

Brenda Gehrke, PhD, Pharmacologist

Office of Surveillance and Epidemiology (OSE)

Carolyn McCloskey, MD, OSE Reviewer

Sarah Harris, PharmD, OSE Senior Regulatory Project Manager

Sponsor/Applicant Participants

(b) (4), Independent pharmacology consultant

(b) (4), Clinical pharmacology consultant, (b) (4)

Michel Feraud, PhD, CEO, Provepharm

(b) (4), Regulatory Counsel, (b) (4)

Clara Li, MS, US Agent and Regulatory Consultant, VP Regulatory & Strategic Consulting, Clinipace Inc.

1.0 BACKGROUND: NDA 204630 methylene blue injection is a 505(b)(2) application that was initially submitted August 13, 2012, and received a Refused to File on October 11, 2012. On September 13, 2013, the NDA was resubmitted and it received a Complete Response on October 10, 2014. Therefore, the current submission received on October 9, 2015, was submitted in response to the Complete Response. The proposed indication for this application is

methylene blue indicated for the treatment of acquired methemoglobinemia in pediatric patients and adults. The PDUFA date for NDA 204630 is April 9, 2016

2.0 DISCUSSION: The FDA informed the Applicant of the four PMRs that are being generated for this application. Provepharm SAS inquired about a general description of what PMRs entail. The FDA explained the PMR process and that we would provide the Applicant with descriptions of each PMR and milestone dates associated with each PMR. In addition, the FDA discussed some of the revisions to the USPI and carton/container labeling and that additional Information Requests would be forthcoming with regards to the label. The Applicant had no questions about the labeling at the present time.

3.0 ACTION ITEMS: The PMR and labeling Information Requests were sent to the Applicant. The Applicant acknowledged receipt of the Information Requests. Further label and PMR negotiations will be forthcoming.

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/s/

LAURA C WALL
03/25/2016

From: [Wall, Laura](#)
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](#)
Subject: NDA 204630 - FDA Information Request - PMR revision - Please respond by COB Monday, March 28, 2016
Date: Friday, March 25, 2016 12:47:23 PM

Dear Clara,

The clinical team requests that you respond to the following PMR comment:

In order to increase the potential for success of this study, we strongly suggest that you include at least some potential investigators in the protocol development process. We also expect a Subpart H requirement to be completed in a timely fashion. To these ends, we recommend the revised milestone dates below for PMR #1:

PMR Schedule Milestones:

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

To expedite the review, please send me your response via e-mail and officially to your application **by COB Monday, March 28, 2016**.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

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/s/

LAURA C WALL
03/25/2016

From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](#)
Subject: NDA 204630 - FDA Revisions to methylene blue PI - Please respond as soon as possible
Date: Thursday, March 17, 2016 10:06:00 AM
Attachments: [ATTACH_1.xpt](#)
[Attach_2.pdf](#)
[NDA 204630 methylene blue PI revisions to App 3-17-16.doc](#)

Dear Clara,

Please refer to the attached labeling revisions to the prescribing information (PI) for NDA 204630 methylene blue. In addition, please refer to the two PDF attachments (these two PDF attachments are referred to in the comments on the label).

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, please send me the revised tracked change labeling via e-mail before you make your official submission electronically.

Please send me your response **by as soon as possible**.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
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PHOENIX AZ 852
16 NOV 2015 PM 4 L



Donna Przepiorka, M.D., Ph.D.
US Food and Drug Administration
CDER/OHOP/DHP
WO 22 RM 2116
10903 New Hampshire Ave.
Silver Spring, MD 20993

20993000299



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

October 26, 2015

Director of Hospital Pharmacy
Banner - University Medical Center
1501 N Campbell Ave.
Tucson, AZ 85724

Regarding the publication: Severe methemoglobinemia detected by pulse oximetry. Annabi EH, et al. Anesth Analg. 2009;108(3):898-9.

We are interested in obtaining more information about methylene blue products used for treatment of methemoglobinemia. Could you possibly let us know whether Methylene Blue USP 1% (any brand) was in use at the hospital at the time of treatment of the patient (estimated to be 2004-2009) in the case report cited above?

You can provide your response below and return this page in the self-addressed envelope enclosed.

Please note, this is not a request for information about the patient in the publication.

Feel free to contact me if you have any questions. Thank you very much for your assistance.

Donna Przepiorka, M.D., Ph.D.
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave., WO22
Silver Spring, MD 20993
Phone 301 796 5358
Fax 301 796 9845
donna.przepiorka@fda.hhs.gov

Mark one with an "X":

Yes, I can confirm that a form of Methylene Blue USP 1% was in use 2004-2009

No, I cannot confirm that Methylene Blue USP 1% was in use 2004-2009

Signature (b) (6) Print Name (b) (6)

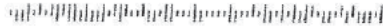
Please return your reply in the self-addressed envelope enclosed by December 1, 2015.

WATERLOO IA 507
02 DEC 2015 PM 1 T



Donna Przepiorka, M.D., Ph.D.
US Food and Drug Administration
CDER/OHOP/DHP
WO 22 RM 2116
10903 New Hampshire Ave.
Silver Spring, MD 20993

20993+0002



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

October 26, 2015

Director of Pharmacy
Mercy Medical Center - North Iowa
1000 4th St SW,
Mason City, IA 50401

Regarding the publication: Benzocaine-induced methemoglobinemia during transesophageal echocardiography. Birchem SK. J Am Osteopath Assoc. 2005; 105(8):381-4.

We are interested in obtaining more information about methylene blue products used for treatment of methemoglobinemia. Could you possibly let us know whether Methylene Blue USP 1% (any brand) was in use at the hospital at the time of treatment of the patient (estimated to be 2000-2005) in the case report cited above?

You can provide your response below and return this page in the self-addressed envelope enclosed.

Please note, this is not a request for information about the patient in the publication.

Feel free to contact me if you have any questions. Thank you very much for your assistance.

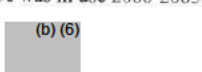
Donna Przepiorka, M.D., Ph.D.
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave., WO22
Silver Spring, MD 20993
Phone 301 796 5358
Fax 301 796 9845
donna.przepiorka@fda.hhs.gov

Mark one with an "X":

Yes, I can confirm that a form of Methylene Blue USP 1% was in use 2000-2005

No, I cannot confirm that Methylene Blue USP 1% was in use 2000-2005

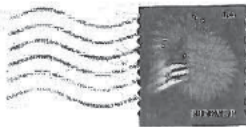
Signature 

Print Name 

Please return your reply in the self-addressed envelope enclosed by December 1, 2015.

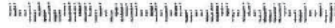
PORTLAND OR 970

NOV 2015 PM 3L



Donna Przepiorka, M.D., Ph.D.
US Food and Drug Administration
CDER/OHOP/DHP
WO 22 RM 2116
10903 New Hampshire Ave.
Silver Spring, MD 20993

20993000299



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

October 26, 2015

Director of Pharmacy
VA Portland Health Care System
3710 SW US Veterans Hospital Rd,
Portland, OR 97239

Regarding the publication: Toxic methemoglobinemia after topical anesthesia for
transesophageal echocardiography. Grauer SE, Giraud GD. J Am Soc Echocardiogr.
1996;9(6):874-6

We are interested in obtaining more information about methylene blue products used for
treatment of methemoglobinemia. Could you possibly let us know whether Methylene Blue USP
1% (any brand) was in use at the hospital at the time of treatment of the patient (estimated to be
1992-1996) in the case report cited above?

You can provide your response below and return this page in the self-addressed envelope
enclosed.

Please note, this is not a request for information about the patient in the publication.

Feel free to contact me if you have any questions. Thank you very much for your assistance.

Donna Przepiorka, M.D., Ph.D.
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave., WO22
Silver Spring, MD 20993
Phone 301 796 5358
Fax 301 796 9845
donna.przepiorka@fda.hhs.gov

Mark one with an "X":

Yes, I can confirm that a form of Methylene Blue USP 1% was in use 1992-1996

No, I cannot confirm that Methylene Blue USP 1% was in use 1992-1996

Signature (b) (6)

Print Name (b) (6)

Please return your reply in the self-addressed envelope enclosed by December 1, 2015.

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/s/

LAURA C WALL
03/17/2016

From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](#)
Subject: NDA 204630 - FDA New PMRs - Please respond by COB (EST) Monday, March 21, 2016
Date: Thursday, March 17, 2016 1:38:00 PM

Dear Clara,

Please refer to methylene blue, NDA 204630 submitted on October 9, 2015. Please find the below new PMRs for NDA 204630. Please provide an email response **by COB (EST) Monday, March 21, 2016**. You will also submit officially when there is final agreement on the PMRs, including the dates.

As we continue our review of your Application, our normal policy is to consider post-marketing studies and labeling at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. We may have additional PMRs/PMCs later. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. It is also necessary for you to provide schedule milestone dates as indicated. Most Milestones only require the applicant to provide the month and year for completion of each category. (However, PREA Milestones require month, day, and year.) For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

PMR Description: Design and conduct a study and provide the full final report and data sets to evaluate the safety and efficacy of ProvayBlue for treatment of methemoglobinemia. The minimal efficacy endpoints should include achieving a 50% reduction in methemoglobin within 1 hour of the first dose of ProvayBlue in addition to normalization of the respiratory rate, heart rate and blood pressure within 2 hours of the first dose of ProvayBlue.

PMR Schedule Milestones:

Date Potential Investigators Identified:	MM/YYYY
Final Protocol Submission:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission:	MM/YYYY
Other:	MM/YYYY

PMR Description: Conduct a clinical trial to determine the effect of hepatic impairment on the PK and safety of methylene blue.

PMR Schedule Milestones:

Final Protocol Submission:	MM/YYYY
Trial Completion:	MM/YYYY
Final Report Submission:	MM/YYYY
Other:	MM/YYYY

PMR Description: Conduct a clinical trial to determine the extent of in vivo drug-drug interaction of methylene blue as a modulator of CYP450 enzyme activity using a cocktail of CYP450 enzyme substrates.

-

PMR Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Trial Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY
	Other:	MM/YYYY

-

PMR Description: Conduct a clinical trial in to evaluate the effect of varying degrees of renal impairment on the pharmacokinetics and safety of methylene blue in subjects with renal impairment.

PMR Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Trial Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY
	Other:	MM/YYYY

-

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Final PMR designation numbers will be assigned later.

Some things you can do to expedite this process:

1. For labeling and PMR/PMCs, reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email. Reply with your edits in a WORD document that you submit by email as well as to the document room. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs agreed upon. We ask the following:

a. For any new studies, it is necessary to submit the protocol for DHP review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.

b. Send the RPM an email courtesy copy of the draft versions, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.

c. It is critical that you advise, prominently, both with the email and cover letter to the EDR that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR NUMBER). This helps the document room and us code the submission properly. All

protocol submissions are made to the IND.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

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/s/

LAURA C WALL
03/17/2016

From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](#)
Subject: NDA 204630 methylene blue Excel file attached
Date: Thursday, March 17, 2016 1:40:00 PM
Attachments: [ATTACH_1.xlsx](#)

Dear Clara,

The excel spreadsheet version of Attachment 1 is attached.

Kindly confirm receipt.

Thank you,

Laura

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

LAURA C WALL
03/17/2016

From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](mailto:Wall.Laura)
Subject: NDA 204630 - FDA Information Request - Revisions to PI - Please respond by Noon (EST) Tuesday, March 22, 2016
Date: Thursday, March 17, 2016 2:00:00 PM

Dear Clara,

The team requests that you respond to the following Information Request:

- 1) Remove the (b) (4) from the non-proprietary name (methylene blue) throughout the PI and from the revised carton and container labels.
- 2) Please update the table of contents, including changing the number and heading for the 8.2 Lactation section.
- 3) For section 8.2, in the first sentence of the risk summary, change (b) (4) to the non-proprietary name “methylene blue”.
- 4) Also in section 8.2, please change (b) (4) to “genotoxicity”.

To expedite the review, please send me your edits to the PI and c/c labeling via e-mail and officially to your application by **Noon (EST) Tuesday, March 22, 2016**. In addition, please send me all of your edits to the label (e-mail sent earlier with the word document of your PI) by **Noon (EST) Tuesday, March 22, 2016**.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

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/s/

LAURA C WALL
03/17/2016

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Wednesday, March 16, 2016 11:44 AM
To: 'Clara Li'
Subject: FDA Information Request NDA 204630- Please Respond by March 25, 2016 or earlier
Importance: High

Hello Clara,

Please see the below CMC Information Requests for NDA 204630.

We refer to your Class 2 resubmission from October 9, 2015 for NDA204630 (eCTD sequence number) and have the following comment

- For the analysis of [REDACTED] (b) (4) as the assay test. Your acceptance criterion of [REDACTED] (b) (4) % for assay is acceptable.

Please provide your response by March 25th, 2016 or earlier

Kindly confirm receipt of this email.

Rabiya

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov



From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](#)
Subject: NDA 204630 - FDA Information Request - Please respond by COB 3/14/16
Date: Thursday, March 10, 2016 10:29:00 AM

Dear Clara,

The team requests that you respond to the following Information Request with regards to NDA 204630:

Please provide revised mock-ups of the carton label and container labeling as seen below:

Provayblue
(methylene Blue) Injection, 0.5%
50 mg/10 ml (5 mg/mL)

To expedite the review, please send me your response via e-mail and officially to your application by **COB 3/14/16**.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

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/s/

LAURA C WALL
03/10/2016

From: Wall, Laura
To: ["Clara Li"](#)
Subject: RE Clarification: NDA 204630 - FDA Information Request - Please respond by COB 3/14/16
Date: Thursday, March 10, 2016 11:00:00 AM

Dear Clara,

For clarification purposes, yes, the conditionally acceptable name is ProvayBlue. Therefore, the mock-up should read:

ProvayBlue
(methylene blue) Injection, 0.5%
50 mg/10 ml (5 mg/mL)

Thank you,

Laura

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Thursday, March 10, 2016 10:35 AM
To: Wall, Laura
Subject: RE: NDA 204630 - FDA Information Request - Please respond by COB 3/14/16

Dear Laura,

I just re-read the email and have some questions. The conditionally acceptable name is ProvayBlue, the generic name is methylene blue. Will you please confirm the capitalization of "B"?

Best regards,
Clara

From: Wall, Laura [<mailto:Laura.Wall@fda.hhs.gov>]
Sent: Thursday, March 10, 2016 8:29 AM
To: Clara Li
Cc: Wall, Laura
Subject: NDA 204630 - FDA Information Request - Please respond by COB 3/14/16

Dear Clara,

The team requests that you respond to the following Information Request with regards to NDA 204630:

Please provide revised mock-ups of the carton label and container labeling as seen below:

Provayblue
(methylene Blue) Injection, 0.5%
50 mg/10 ml (5 mg/mL)

To expedite the review, please send me your response via e-mail and officially to your

application by **COB 3/14/16**.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

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/s/

LAURA C WALL
03/10/2016

From: Wall, Laura
To: ["Clara Li"](#)
Cc: [Wall, Laura](#)
Subject: Clarification - NDA 204630 - FDA Information Request - Please respond by COB March 10, 2016
Date: Wednesday, March 09, 2016 11:06:00 AM

Dear Clara,

For clarification purposes, the team requested the following:

No more than one paragraph per study. The outline should address the primary objective, primary and key secondary endpoints, eligible population (description rather than a list of criteria), proposed dose(s) and schedule of study drug(s), and proposed sample size (just the total number and **number per cohort** – not all the statistical considerations). You may also include a sentence about any special considerations regarding the study conduct (e.g., randomized design, sequential cohorts, etc.), if any.

Kindly confirm receipt.

Thank you,

Laura

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Tuesday, March 08, 2016 10:55 PM
To: Wall, Laura
Subject: RE: NDA 204630 - FDA Information Request - Please respond by COB March 10, 2016

Dear Laura,

I acknowledge receipt of this IR and the due date.

[REDACTED] (b) (4)
[REDACTED]. In light of the due date for this response, can you provide any advice regarding how much information will be adequate in the "general outline"?

Best regards,
Clara

From: Wall, Laura [<mailto:Laura.Wall@fda.hhs.gov>]
Sent: Tuesday, March 08, 2016 8:11 PM
To: Clara Li
Cc: Wall, Laura
Subject: NDA 204630 - FDA Information Request - Please respond by COB March 10, 2016

Dear Clara,

The team requests that you respond to the following Information Request for NDA 204630:

In order to further optimize the dose of methylene blue in children, in the presence of concomitant drug administration, or with organ impairment, further studies will be needed in a post marketing setting. Please provide general outline how you intend to conduct the following studies:

1. [REDACTED] (b) (4)
2. [REDACTED] (b) (4)
A clinical trial evaluating the effect of hepatic impairment on the PK of methylene [REDACTED] (b) (4)
3. [REDACTED] (b) (4)
A clinical trial evaluating the effect of renal impairment on the PK of methylene [REDACTED] (b) (4)
4. [REDACTED] (b) (4) Design and conduct a prospective trial and provide the full final report and data sets to evaluate the safety and efficacy of ProvayBlue for treatment of methemoglobinemia [REDACTED] (b) (4). The minimal efficacy endpoints should include achieving a 50% reduction in methemoglobin within 1 hour of the first dose of ProvayBlue and normalization of the respiratory rate, heart rate and blood pressure within 2 hours of the first dose of ProvayBlue.

To expedite the review, please send me your response via e-mail and officially to your application by **COB March 10, 2016**.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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/s/

LAURA C WALL
03/09/2016

From: [Wall, Laura](#)
To: [Clara Li \(CLi@clinipace.com\)](mailto:CLi@clinipace.com)
Cc: [Wall, Laura](#)
Subject: NDA 204630 - FDA Information Request - Please respond by Noon, March 9, 2016
Date: Tuesday, March 08, 2016 10:29:44 AM

Dear Clara,

The clinical team requests that you respond to the following Information Request:

1. We have reviewed the PSUR dated 14-Jul-2015, and we have the following request: Please submit copies of safety reports GB-PROVEPHARM-000051 and GB-PROVEPHARM-000010, including the initial reports and all follow-up information.

To expedite the review, please send me your response via e-mail and officially to NDA 204630 by Noon (EST), Wednesday, March 9, 2016.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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/s/

LAURA C WALL
03/08/2016

From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:CLi@clinipace.com)
Cc: [Wall, Laura](#)
Subject: NDA 204630 - FDA Information Request - Please respond by COB March 10, 2016
Date: Tuesday, March 08, 2016 10:11:00 PM

Dear Clara,

The team requests that you respond to the following Information Request for NDA 204630:

(b) (4)
Please provide general outline how you intend to conduct the

following studies:

1. (b) (4)
2. (b) (4)
clinical trial evaluating the effect of hepatic impairment on the PK of methylene (b) (4)
3. (b) (4)
A clinical trial evaluating the effect of renal impairment on the PK of methylene (b) (4)
4. (b) (4) Design
and conduct a prospective trial and provide the full final report and data sets to evaluate the safety and efficacy of ProvayBlue for treatment of methemoglobinemia (b) (4)
The minimal efficacy endpoints should include achieving a 50% reduction in methemoglobin within 1 hour of the first dose of ProvayBlue and normalization of the respiratory rate, heart rate and blood pressure within 2 hours of the first dose of ProvayBlue.

To expedite the review, please send me your response via e-mail and officially to your application by **COB March 10, 2016**.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service

Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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/s/

LAURA C WALL
03/08/2016

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Friday, March 04, 2016 7:56 PM
To: 'Clara Li'
Subject: FDA Information Request NDA 204630- Please Respond by March 15, 2016 or sooner

Hello Clara,

Please see the below CMC Information Requests for NDA 204630.

We refer to your Class 2 resubmission from October 9, 2015 for NDA204630 (eCTD sequence number) and have the following questions and comment:

- Testing of (b) (4):
 - You should include a specific test for (b) (4).
 - Provide the Certificate of Analysis and data from your in-house analysis for lots received.
- Testing of (b) (4)
 - Please include assay test with specification range.
 - Provide the Certificate of Analysis and data from your in-house analysis for lots received.
- We refer to the two footnotes in your proposed specifications table in section 3.2.S.4.1, regarding (b) (4)
 - We do not allow (b) (4). So please confirm that every batch will be tested for conformance with all the release test limits.

Please send me a curtesy email copy of the responses followed by a formal submission though the FDA gateway.

Kindly confirm receipt of the email.

Thank you!
Rabiya

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov



From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](#)
Subject: NDA 204630 - FDA Information Request - Please respond by Noon March 4,2016
Date: Wednesday, March 02, 2016 10:56:00 AM

Dear Clara,

The team requests that you respond to the following Information Request:

In your response to our information request from 2/24/2016 you submitted on 2/29/2016 the data file [ex.fda.xpt](#) for Study PVP-2014001. This file is not reviewable. There should be one subject and event per row in such a file. Please see the Study PVP-2014002 [dv.xpt](#) as an example of the correct content and format for such a file. Submit a revised version of DV (protocol deviation) data file in xpt format for Study PVP-2014001.

To expedite the review, please send me the information via e-mail and officially to your application by Noon (EST) Friday, March 4, 2016.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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Phone: 301-796-2237 | laura.wall@fda.hhs.gov

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/s/

LAURA C WALL
03/02/2016

From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](#)
Subject: FDA revisions to NDA 204630 methylene blue PI
Date: Thursday, February 25, 2016 4:41:00 PM
Attachments: [NDA 204630 methylene blue PI 20160225.doc](#)

Dear Clara,

Please refer to the attached labeling revisions to the prescribing information (PI) for NDA 204630 methylene blue. Please note that the sections marked “Pending” are still under review. In addition to the attached labeling revisions to the PI, you will also need to correct the following formatting issues:

-There should be ½ inch margins on all sides and between columns in the HL section, and the Highlights of Prescribing Information at the top should not be indented.

- Please format the PI for letter size paper.

-Please add a space between the last bullet of the USE IN SPECIFIC POPULATION section and the patient counseling information statement.

-There is an extra white space before the WARNINGS AND PRECAUTIONS section, therefore please delete the space.

-The INDICATIONS AND USAGE and WARNINGS AND PRECAUTIONS sections do not provide a reference to the FPI.

-The name of the drug product needs to appear in upper case letters. Only the product should be listed and not the dosage form or strength.

-If a product **does not** have FDA-approved patient labeling:

See 17 for PATIENT COUNSELING INFORMATION

-The revision date needs to be right justified.

-In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, please send me the revised tracked change labeling via e-mail before you make your official submission electronically.

Please send me your response **by 11 a.m. (EST) on Tuesday, March 1, 2016.**

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

13 Pages of Draft Labeling have
been Withheld in Full as b4 (CCI/
TS) immediately following this page

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/s/

LAURA C WALL
02/25/2016

From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](mailto:Wall.Laura)
Subject: NDA 204630 - FDA Information Request - Please respond by Noon Friday, February 26, 2016
Date: Wednesday, February 24, 2016 3:29:00 PM

Dear Clara,

The Clinical and Clinical Pharmacology review teams request that you respond to the following Information Request regarding NDA 204630:

Comments to Sponsor

1. For Study PVP-2014002, please provide any follow-up information on Subject 086517. Did the subject have a subsequent cardiac evaluation, and if so, did that evaluation provide an alternative etiology for the cardiac event?

2. For Study PVP-2014001, please address the following:

a) Submit a DV (protocol deviation) data file in xpt format.

b) In the data file FA (findings), what are the units for oxygen content (FATESTCD=OX_CONT)?

c) The actual dose of study drug administered cannot be determined from the EX data file. Submit an exposure data file in xpt format with at least the following information: Study ID, Unique Subject ID, actual drug administered, dose administered in mg/kg, corrected dose administered in mg/kg (i.e., corrected for the measured amount of methylene blue in the product used in this study), date and time of study drug administration.

3. It was noted during the review of Study PVP-2014001 “A Single-Dose, Parallel, Bioequivalence Study of Methylene Blue Intravenous Injection” that the actual dosing of the reference product was substantially lower than the nominal 2 mg/kg dose. Please provide an explanation for the observed discrepancy in dosing.

To expedite the review, please send me your responses via e-mail and officially to your application by Noon (EST), Friday, February 26, 2016.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361

Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

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LAURA C WALL
02/24/2016



NDA 204630

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Provepharm SAS
c/o Clinipace Worldwide RSD
4840 Pearl East Circle
Suite 201E
Boulder, CO 80301

ATTENTION: Clara Li
Vice President, Regulatory and Strategic Development

Dear Ms. Li:

Please refer to your New Drug Application (NDA) dated and received, October 9, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Methylene Blue Injection, 50 mg/10 mL.

We also refer to:

- your correspondence, dated and received January 11, 2016, requesting review of your proposed proprietary name, ProvayBlue
- your January 18, 2016, amendment, received January 19, 2016, to your request for name review

We have completed our review of the proposed proprietary name, ProvayBlue and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your January 11, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sarah Harris, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4774. For any other information regarding this application, contact Laura Wall, Senior Regulatory Project Manager, in the Office of New Drugs at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
02/22/2016

From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](#)
Subject: NDA 204630 - FDA Information Request - Please respond by COB February 10, 2016
Date: Friday, February 05, 2016 1:45:00 PM

Dear Clara,

The team is requesting that you respond to the following Information Request:

In reference Study PVP-2014001 “A Single-Dose, Parallel, Bioequivalence Study of Methylene Blue Intravenous Injection in Adult Healthy Volunteers”, provide the detailed bioanalytical methods report for the study for both analyses (methylene blue and Azure B) in whole blood as well as plasma.

To expedite the review, please send me the report via e-mail and officially to your application by COB Wednesday, February 10, 2016.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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Phone: 301-796-2237 | laura.wall@fda.hhs.gov

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/s/

LAURA C WALL
02/05/2016

From: Wall, Laura
To: ["Clara Li"](#)
Subject: RE: NDA 204630 Methylene Blue - request (b) (4)
Date: Friday, January 29, 2016 4:56:00 PM

Dear Clara,

I followed up with the team and was told that we cannot (b) (4)
(b) (4) At the time the (b) (4), you can submit an
amendment (pending the action of this NDA) to change the label.

Kindly confirm receipt.

Thank you,

Laura

From: Clara Li [mailto:CLi@clinipace.com]
Sent: Friday, January 29, 2016 1:37 PM
To: Wall, Laura
Subject: RE: NDA 204630 Methylene Blue - request (b) (4)

Dear Laura,

Thank you. I look forward to the team's advice.

Best regards,
Clara

From: Wall, Laura [mailto:Laura.Wall@fda.hhs.gov]
Sent: Friday, January 29, 2016 11:30 AM
To: Clara Li
Subject: RE: NDA 204630 Methylene Blue - request (b) (4)

Dear Clara,
I will have to follow-up with the review team.
Thank you,
Laura

From: Clara Li [mailto:CLi@clinipace.com]
Sent: Thursday, January 28, 2016 7:44 PM
To: Wall, Laura
Subject: NDA 204630 Methylene Blue - request (b) (4)

Dear Laura,

While Provepharm's NDA is under review, Provepharm has also been addressing the USP

monographs for methylene blue drug substance and drug product. As you know, the Provepharm product cannot at this time be called USP because Provepharm's product is 0.5% and the current monograph specifies that the drug product must be 1%. Provepharm has been working with USP to change the definition to a percent range of the target concentration and to revise the monograph specifications to be in line with what the FDA is requiring for the Provepharm NDA.

Assuming approval by the April 9th PDUFA date, Provepharm is planning a product launch in (b) (4)

-
Status of the monographs

New drug substance monograph

- The publication is planned in Second Supplement to USP 39–NF 34 (on June, 1st 2016 with official date of Dec 1, 2016.)

New Injection (drug product) monograph – *pending monograph status*

- Provepharm has notified USP of the April 9th PDUFA date and USP has agreed to apply an accelerated process
- Provepharm will inform USP of the NDA Approval, once received
- USP will ask FDA for a conformity check of the specifications on monograph and NDA
- After FDA confirmation, USP will publish the new monograph as official new 'Injection' monograph on the USP website. USP indicated this should take place in a matter of days.

QUESTION: (b) (4)

(b) (4) ?

- (b) (4)

Best regards,
Clara

.....
Clara Li

Vice-President,
Regulatory & Strategic Development

CLINIPACE

WORLDWIDE

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/s/

LAURA C WALL
01/29/2016

From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](#)
Subject: NDA 204630 - FDA Information Request - Please respond within 1-week of receipt
Date: Friday, January 08, 2016 5:26:00 PM

Dear Clara,

DMEPA recommends the following be implemented prior to approval of NDA 204630:

A. Container label

1. As currently presented there are two barcodes (e.g. linear barcode and internal identification code) on the vial container label. Since the drug barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes is confusing to healthcare providers^[1]. Therefore, we recommend removing the internal barcode if feasible. If it is not feasible to remove the internal barcode, decrease its prominence and increase the prominence of the NDC barcode. Additionally, the barcode containing the NDC number should reorient to a vertical position to improve the scannability of the barcode. From the literature, it has been noted that barcodes placed in a horizontal position may not scan due to vial curvature^[2]. Curvature is an important factor in readability and should be avoided if possible.
2. Consider removing the statement (b) (4) that appears before “Single dose ampule” as this information already appears in the statement of strength (50 mg/10 mL) and contributes to visual clutter.
3. We recommend increasing prominence of the route of administration on the Principal Display Panel (PDP) by bolding, increasing font size, or some other means to help mitigate the risk of administration errors.

B. Carton labeling

1. The proprietary name (b) (4) is presented with all letters capitalized. Words written in all-capital letters are less legible than words written in mixed case letters. Consider capitalizing only the first letter in the proprietary name to improve readability^[3]. Additionally, the display of the proprietary name on the container label should be identical to the carton labeling for consistency.

To expedite the review, please e-mail me your responses and send them officially to your application within 1-week of receipt of this correspondence.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service

Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

[1] Institute for Safe Medication Practices. Safety briefs: More barcodes than needed. ISMP Med Sad Alert Acute Care. 2014; 19(2): 1-3.

[2] Neuenschwander M. et al. Practical guide to barcoding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15; 60(8):768-79.

[3] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ICM349009.pdf>.

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/s/

LAURA C WALL
01/08/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204630

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Provepharm SAS
c/o Clinipace Worldwide RSD
4840 Pearl East Circle
Suite 201E
Boulder, CO 80301

ATTENTION: Clara Li
Vice President, Regulatory and Strategic Development

Dear Ms. Li:

Please refer to your New Drug Application (NDA) dated and received October 9, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Methylene Blue Injection, 50 mg/10 mL.

We also refer to your correspondence, dated and received October 9, 2015, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:



We note that our current findings differ from our previous review of the proposed proprietary name, (b) (4) as communicated in the conditionally acceptable letter dated May 28, 2014. The reason we have reached a different determination regarding the safety of the proposed name is based upon newly identified information we considered. Specifically, (b) (4) may be administered at a dose of 1 mg/kg, which overlaps with the dosing of your proposed product. This information caused us to revisit the Failure Modes and Effects Analysis of the (b) (4) name pair. After further consideration of (b) (4) and (b) (4) product characteristics, the orthographic similarity between these proprietary names and our post-marketing experience, we believe the proposed proprietary name, (b) (4) is vulnerable to confusion with the currently market product, (b) (4).

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sarah Harris, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 240-402-4774. For any other information regarding this application, contact Laura Wall, Regulatory Project Manager in the Office of New Drugs, at 301-796-2237.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
12/22/2015

From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](mailto:Wall.Laura)
Subject: NDA 204630 - FDA Carton and Container Labeling Information Request
Date: Thursday, December 03, 2015 3:17:00 PM

Dear Clara,

Please find the following Information Request with regards to the carton and container labeling:

We recommend the following be implemented prior to approval of this NDA:

A. Container label

1. The presentation of the text on the container label is currently vertical, making it difficult to read. We recommend you revise the presentation of the text to read in a horizontal direction for better readability.
2. The proprietary name (b) (4) is presented with all letters capitalized. Words written in all-capital letters are less legible than words written in mixed case letters. Consider capitalizing only the first letter in the proprietary name to improve readability⁴.
3. Add the “Rx only” statement to the container label per Section 503(b) (4) (A) of the Federal Food, Drug and Cosmetic Act.

B. Carton labeling

1. The drug barcode is hidden inside the folding flap of the carton and will not be visible once the carton is assembled. Please relocate the drug barcode to a visible location on carton labeling as it is often used as an additional verification during the pharmacy procurement process.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Rm 2361
Silver Spring, MD 20993
Phone: 301-796-2237 | laura.wall@fda.hhs.gov

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/s/

LAURA C WALL
12/03/2015

From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](mailto:Wall.Laura)
Subject: NDA 204630 - FDA Information Request - Please respond as soon as possible
Date: Tuesday, November 17, 2015 1:45:00 PM

Dear Clara,

It is requested that you respond to the following two Information Requests:

IR #1: Please identify where in the NDA the following items can be found for Study PVP-2014002:

- a. Annotated CRF
- b. A data definition file which describes the contents of the electronic data sets
- c. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
- d. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
- e. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
- f. Narrative summaries and case report forms for any
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study
- g. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- h. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table (attached)

IR #2: Please submit a complete highlights table.

To expedite the review, please send me your responses via e-mail and officially to your application **as soon as possible**.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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/s/

LAURA C WALL
11/17/2015

From: Wall, Laura
To: [Clara Li \(CLi@cinipace.com\)](mailto:Clara.Li@cinipace.com)
Cc: [Wall, Laura](#)
Subject: NDA 204630 - FDA Information Request - Please respond by Noon Tuesday, November 10, 2015
Date: Tuesday, November 03, 2015 10:37:00 AM

Dear Clara,

The clinical pharmacology review team requests that you respond to the following information request:



To expedite the review, please send me your responses via e-mail and to your application by Noon (EST) Tuesday, November 10, 2015.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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/s/

LAURA C WALL
11/03/2015



NDA 204630

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

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

Dear Ms. Li:

We acknowledge receipt on October 9, 2015, of your October 9, 2015, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for methylene blue injection, solution 0.5% (5 mg/mL).

We consider this a complete, class 2 response to our October 10, 2014 action letter. Therefore, the user fee goal date is April 9, 2016.

If you have any questions, call me at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Laura Wall, MS, APHN, OCN
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

LAURA C WALL
10/30/2015

From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](mailto:Wall.Laura)
Subject: NDA 204630 - FDA Information Request - Please respond by COB Friday, October 30, 2015
Date: Thursday, October 29, 2015 4:05:00 PM

Dear Clara,

The review team requests that you respond to the following Information Request:

Comments to Sponsor:

1. The dataset folder for PVP-2014002 includes only ADAM data files. The data files are in .sas7bdat and .xpt formats, and files with the same name contain different information (for example, adeg.sas7bdat has 7,743 rows, but adeg.xpt has only 107 rows). Please address the following:

a) Please submit the SDTM files for PVP-2014002.

b) Please clarify the difference between the .sas7bdat files and the .xpt files, including why files with the same name have different data. If you are unable to confirm which files are correct, please resubmit the dataset for PVP-2014002.

c) Please submit define files for the PVP-2014002 datasets.

To expedite the review, please send me your responses via e-mail and to your application by **COB, Friday, October 30, 2015**.

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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/s/

LAURA C WALL
10/29/2015

From: Wall, Laura
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Cc: [Wall, Laura](mailto:Wall.Laura)
Subject: NDA 204630 - FDA Information Request - Please respond by COB Wednesday, October 28, 2015
Date: Friday, October 23, 2015 2:07:00 PM

Dear Clara,

The team requests that you respond to the following Information Request:

Comment to Sponsor:

1. Please submit the complete datasets for Study PVP-2014001 and Study PVP2014002.

To expedite the review, please send me the datasets via e-mail and officially to your application **by COB Wednesday, October 28, 2015.**

Kindly confirm receipt.

Thank you,

Laura

Laura Wall, MS, BSN, APHN, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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/s/

LAURA C WALL
10/23/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: April 30, 2014

Application Number: NDA 204630

Product Name: Methylene Blue Injection, 0.5%

Sponsor/Applicant Name: Provepharm SAS

Subject: The need for a biowaiver, a bioequivalence study, and the interaction between Methylene Blue and the urine leukocyte esterase test.

FDA Participants : Ann T. Farrell, MD, Director ; Albert Deisseroth, MD, Ph.D., Clinical Team Leader ; Donna Przepiorka, MD, Ph.D., Clinical Reviewer ; Julie Bullock, PharmD., Clinical Pharmacology Team Leader ; Joseph Grillo, PharmD., Clinical Pharmacology Reviewer ; Minerva Hughes, Ph.D., Biopharmaceutics Reviewer ; Amit Mitra, Ph.D., CMC Reviewer ; Brenda Gehrke, Ph.D., Pharmacology/Toxicology Reviewer ; Carolyn Yancey, MD, OSE Clinical Reviewer ; Kim J. Robertson, Regulatory Health Project Manager

Sponsor/Applicant Participants : Caroline Benkemoun, Regulatory Affairs, Manager ; Michel Féraud, Ph.D., CEO ; Emilie Huyghues des Etages, R&D Manager ; Severine Pelletier, Regulatory Affairs Manager ; Clara Li, Vice President, Regulatory and Strategic Development ; Kip Vought, Vice President, Regulatory and Strategic Development ; (b) (4), BS Pharm, JD, Regulatory Counsel; (b) (4) Consultant; (b) (4), Senior Regulatory Consultant

1.0 BACKGROUND: On March 14, 2014, the Division of Hematology Products held its Mid-Cycle meeting for 505(b)(2) NDA 204630; Methylene Blue Injection, 0.5%. During the Mid-Cycle, the scientific disciplines expressed matters of concern that needed to be addressed with the applicant in anticipation that the applicant could resolve the issues, prior to the NDA's due date. A telecon was held with the applicant to discuss the need for a biowaiver to link their product used in PK trial AA98923 to (b) (4)®, the need for a bioequivalence study of Methylene Blue Injection, USP to (b) (4)® in order to extrapolate pediatric dosing to the (b) (4)® product, and the interaction between Methylene Blue and the urine leukocyte esterase test.

2.0 DISCUSSION: The Agency explained to the sponsor that it cannot grant the biowaiver because there is no listed drug to use as a reference for the waiver. The Agency also stated that it is unlikely that it could to link BA/BE to the literature because the PK information provided by the sponsor for methylene blue injection USP 1% (10 mg/mL) is highly variable due to a combination of assay, formulation and sampling issues. The most comprehensive information is from the Luitpold 2013 trial which was conducted in healthy volunteers by its partner, with right of reference to the sponsor, using the American Reagent's (i.e., Luitpold Pharmaceuticals, Inc.) methylene blue injection USP 1% (10 mg/mL). Unfortunately the results from this non comparative single arm PK trial are not similar to any of the available published PK literature.

The applicant believed their product qualified for a “good clause” waiver, but the Division did not. We recommended the sponsor conduct a bioequivalence (BE) trial to characterize the PK of their product and link BA/BE to the clinical studies that used methylene blue injection USP 1% (10 mg/mL) in the literature. The applicant expressed concern about doing a BA/BE trial against an unapproved product and stated that they didn’t believe they could do a BE study in normal healthy people. The Agency replied that the current application is also extrapolating efficacy from an unapproved product.

The main outcome from the meeting was that the sponsor would conduct a comparative PK study of Provepharm’s methylene blue drug product compared to another commercialized USP Methylene Blue (1%) product available in the US. The Division suggested that the applicant do a single dose, standard pharmacokinetics trial and collect PK samples for both parent and the azure B metabolite. The Agency suggested the sponsor assess the validation issues described in Luitpold 2013 trial report if it intended to use this assay in its trial.

(b) (4)

3.0 ACTION ITEMS: The applicant is to address the Agency’s concerns in writing officially, that were discussed during the telecon. This information was submitted on May 16, 2014.

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/s/

JULIE M BULLOCK
09/24/2014



NDA 204630

GENERAL ADVICE

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

Dear Ms. Clara Li:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylene Blue Injection.

We also refer to our advice sent to you July 1, 2014, and your submission dated July 9, 2014.

(b) (4)

”

We have reviewed the referenced material and have the following comments:

•

(b) (4)

To comply with this requirement, we reiterate our recommendation in the advice sent July 1, 2014 that you include additional ECG samplings around the time of Cmax in your planned PK study in healthy volunteers.

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, M.D.
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
07/17/2014

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, July 09, 2014 11:55 AM
To: Clara Li (CLi@clinipace.com)
Subject: NDA 204630; Methylene Blue--DMEPA/Carton & Container Recommendations

Hello again Clara:

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed Provepharm's revised container label and carton labeling for Methylene Blue Injection to determine if it is acceptable from a medication error perspective. The revised container label and carton labeling are unacceptable from a medication error perspective.

DMEPA identified the following areas of vulnerability to error in the revised container label and carton labeling:

- Both ampule label and carton labeling have the same NDC number and is vulnerable to error because the bed side barcode medication administration (BCMA) system may mistake an ampule for a carton containing 5 ampules or vice versa.
- The total drug quantity (10 mL) is located immediately below the strength (50 mg/10 mL, 5 mg/mL) and competes in prominence with the strength presentation, where "10 mL" may be mistaken as "10 mg".
- The statement "(b) (4)" may increase the risk of confusion (b) (4)
- The manufacturer logo (American Regent) appears more prominent than the proprietary name and the established name.

Therefore, we provide the following recommendations for your consideration, prior to the approval of this NDA:

A. Both container label and carton labeling

- a. As currently presented, it appears that both ampule label and carton labeling have the same NDC number. Since NDC number is often used as an additional verification by the bed side barcode medication administration (BCMA) system prior to drug administration to the patient, it is important that the NDC number for the ampule label be different than the NDC number for the carton labeling. The BCMA may mistake an ampule for a carton containing 5 ampules or vice versa. Therefore, revise the NDC number for the ampule label so that it does not match the NDC number on the carton labeling.

B. Container label

- a. We recommend unbold the statements "10 mL – Single dose ampule – Discard Unused Portion" and "Intravenous use only" to reduce its prominence and

minimize the risk of overlooking important information including proprietary name, established name, and strength.

- b. As currently presented, the statement “10 mL – Single dose ampule – Discard Unused Portion” competes in prominence with the strength presentation, where “10 mL” may be mistaken as “10 mg”. We recommend moving the statement (“10 mL – Single dose ampule – Discard Unused Portion”) further down and below the statement “Intravenous use only” to create sufficient white space between this statement, the route of administration statement, and the strength presentation to improve readability and avoid crowding.

For example:

50 mg/10 mL
(5 mg/mL)

Intravenous use only

10 mL – Single dose ampules –
Discard unused portion

- c. Decrease the font size of the “Manufacturer by CENEXI” and “Distributed by AMERICAN REGENT, INC” statements to create sufficient space to allow recommendation in section B.b to be implemented.

C. Carton labeling

- a. Since the total drug content (10 mL) is already stated below the established name, revise the statement “^{(b) (4)}” to “5 ampules” to minimize the risk of confusion ^{(b) (4)}.
- b. To minimize the risk of the route of administration being overlooked, we recommend move the statement “Intravenous use only – For slow intravenous injection” above the total drug quantity statement (10 mL – Single dose ampule). Ensure that there is sufficient white space between the route of administration statement and the total drug quantity statement to improve readability and avoid crowding.**Error! Bookmark not defined.**
- c. As currently presented, the manufacturer logo (American Regent) appears more prominent than the proprietary name and established name. Minimize the size of the logo so that the logo does not compete in prominence with important information such as proprietary name, established name, and product strength.

Please provide updated Carton and Container information by **Wednesday, July 30, 2014.**

Regards,

Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
07/09/2014

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, July 01, 2014 12:20 PM
To: Clara Li (CLi@clinipace.com)
Subject: NDA 204630; Methylene Blue--QT/IRT Information Request

Importance: High

Hello Clara:

Our Interdisciplinary QT/IRT colleagues, who reviewed the Methylene Blue NDA, has identified some issues with the cardiac studies. Please see the following request for information:

COMMENTS TO PROVEPHARM:

A dedicated thorough QT (TQT) study is required based on the ICH E14 guidance. Refer to the E14 guidance for the trial design. In brief,

- According to the E14 guidance, drugs are expected to receive a clinical electrocardiographic evaluation, beginning early in clinical development, typically including a single trial dedicated to evaluating their effect on cardiac repolarization (“thorough QT/QTc study”). Because Methylene blue can be tested in healthy volunteers and has systemic bioavailability, a TQT study is required.
- The “thorough QT/QTc study” is intended to determine whether the drug has a threshold pharmacologic effect on cardiac repolarization, as detected by QT/QTc prolongation. The threshold level of regulatory concern, discussed further below, is around 5 ms as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms.
- The “thorough QT/QTc study” should be adequate and well-controlled, with mechanisms to deal with potential bias, including use of randomization, appropriate blinding, and concurrent placebo control group. The positive control should have an effect on the mean QT/QTc interval of about 5 ms.
- The timing of the collection of ECGs and the study design (e.g., single or multiple dose, duration) of the “thorough QT/QTc study” should be guided by the available information about the pharmacokinetic profile of the drug. For drugs with short half-lives and no metabolites, a single dose study might be sufficient. Studies should characterize the effect of a drug on the QT/QTc throughout the dosing interval.

While the peak serum concentration does not always correspond to the peak effect on QT/QTc interval, care should be taken to perform ECG recordings at multiple time points around the Cmax.

We recommend that you submit your TQT study protocol to the IND for review prior to conduct of the study.

Please provide a response to this IR no later than Wednesday, July 09, 2014, 3:00pm, EST. Please also provide a plan.

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
07/01/2014

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, June 12, 2014 11:50 AM
To: Clara Li (CLi@clinipace.com)
Subject: NDA 204630--Clinical Pharmacology IR

Importance: High

Hi Clara:

Please see the following request for information from the Clinical Pharmacology Reviewer of NDA 204630:

CLINICAL PHARMACOLOGY INFORMATION REQUEST:

We note that you have provided the revised report BD00196. We find this report incomplete because it does not include the observed raw data used to create the tables and figures you display in the report. For example, table 1 states that the IC50 results are an average yet there is no way to evaluate the range of measurements observed. In addition, you have not justified that [REDACTED]^{(b) (4)} is a sufficiently sensitive inhibitor of CYP 2B6 and 2C19 to be an acceptable positive control in your inhibition study.

Please submit this justification and all observed data from both the inhibitor and inducer investigations in report BD00196 no later than **Monday, June 16, 2014, 3:00PM, EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
06/12/2014

From: Agosto, Teicher
To: [Clara Li \(CLi@clinipace.com\)](mailto:Clara.Li@clinipace.com)
Subject: NDA 204630
Date: Monday, June 02, 2014 12:59:00 PM

Hi Clara,

We have reviewed your proposal regarding designation of starting materials options, dated 05-MAY-2014 discussing timeline and feasibility of (b) (4) in your submission.



If you agree to these terms update the NDA with the recommended modifications and include revised specification sheets for the (b) (4) and methylene blue drug substance. (b) (4)

After reviewing the FDA response, please let me know how you would like to proceed with the teleconference.

Please confirm receipt of this email.

Best Regards,

Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993
Teicher.agosto@fda.hhs.gov
P: (240) 402-3777

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/s/

TEICHER N AGOSTO
06/02/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204630

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Provepharm SAS
c/o Clinipace Worldwide RSD
4840 Pearl East Circle, Suite 201E
Boulder, CO 80301

ATTENTION: Clara Li
Vice President, Regulatory and Strategic Development

Dear Ms. Li:

Please refer to your New Drug Application (NDA) dated September 13, 2013, received September 13, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Methylene Blue Injection, 50 mg/10 mL.

We also refer to your March 13, 2014, correspondence, received March 13, 2014, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your March 13, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Kim Robertson, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
05/28/2014

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, May 27, 2014 4:36 PM
To: Clara Li (CLi@clinipace.com)
Subject: NDA 204630-Methylene Blue--Clinical Pharmacology Information Request

Importance: High

Hi Clara:

With regard to Provepharm's NDA for Methylene Blue, we note your clinical pharmacology summary states "Little to no induction of CYP450 1A2 or 3A4" in Table 6 with the reference as the bd00196a study-Report. We followed this link and do not find information related to enzyme induction in the linked in vitro CYP inhibition trial . Note that we requested a revised copy of this study in a November 5, 2013 information request and were assured it was contained in a previous submission (November 19, 2013 response to IR). We now find this does not appear to be the case. Therefore, provide justification for the statement "Little to no induction of CYP450 1A2 or 3A4" in Table 6 of your clinical pharmacology summary **within 2 business days**.

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
05/27/2014

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, May 21, 2014 1:44 PM
To: Clara Li (CLi@clinipace.com)
Subject: NDA 204630; Meth Blue--Non-Clinical Information Request

Hello Clara:

With regard to NDA 204630 for Methylene Blue Injection, my non-clinical reviewers have the following request for information:

- We could not find the definition of “level” in the study report (Study 36110TSC) when referring to the pathology findings at the injection site. Please define Levels 1, 2, and 3. You use this terminology in several places in the report; see page 56 and pathology tables (pages 649-720).

Please provide us with this information by **Friday May 23, 2014; 3:00pm, EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
05/21/2014

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, May 21, 2014 11:20 AM
To: 'Clara Li'
Subject: RE: Provepharm- request for teleconference

Hi Clara:

Before the Agency considers a teleconference to discuss the Methylene Blue Inj. application in (b) (4) presence, we would first require written permission allowing us to do so. Please provide us with documentation to this affect and *then and only then* can we consider a teleconference with (b) (4) present. While it may be Provepharm's prerogative to debrief with (b) (4), the Agency will not disclose any information it deems confidential to (b) (4), without prior written consent, as they are not the NDA holder.

Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Tuesday, May 20, 2014 12:41 PM
To: Robertson, Kim
Subject: Provepharm- request for teleconference

Hi Kim,

This email is to let you know that we submitted a letter today to NDA 20-4630 (SN0030, May 20, 2014) requesting a teleconference so that Provepharm and (b) (4), can both be on a call together with the Division to answer any outstanding questions about the Provepharm drug. A copy of the letter is enclosed.

(b) (4)
We believe that having all three parties on the call would be the best way to address any outstanding questions.

Best regards,
Clara

=====
Clara Li
VP, Regulatory and Strategic Development

CLINIPACE WORLDWIDE
(formerly Regulus Pharmaceutical Consulting)
4840 Pearl East Circle, Suite 201E
Boulder, CO 80301

(e) cli@clinipace.com
(o) 303-225-0980 x3024
(direct) 720-644-0664
(f) 303-225-0984

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/s/

KIM J ROBERTSON
05/21/2014



NDA 204630

**REVIEW EXTENSION –
MAJOR AMENDMENT**

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 under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Methylene Blue Injection, 0.5%.

On April 30, 2014, we received your April 30, 2014, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 13, 2014.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 15, 2014.

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, M.D.
Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
05/19/2014

Robertson, Kim

From: Robertson, Kim
Sent: Friday, May 09, 2014 4:44 PM
To: Clara Li (CLi@clinipace.com)
Subject: NDA 204630; Meth Blue--Micro Information Request

Hi Clara:

Please see the following, as our microbiology reviewer has the following request for information regarding NDA 204630: Methylene Blue:

MICRO REQUEST FOR INFORMATION:

Please provide English translations of the following information regarding  (b) (4)



 (b) (4)

Please provide responses to these queries by **Friday, May 30, 2014, 2:00pm, EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
05/09/2014

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, May 08, 2014 1:09 PM
To: 'Clara Li'
Subject: RE: NDA 204630; Meth Blue--Information Request

Thank you Clara.
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Thursday, May 08, 2014 1:09 PM
To: Robertson, Kim
Subject: RE: NDA 204630; Meth Blue--Information Request

Hi Kim,

I will get back to you by the due date/time.

Best regards,
Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Thursday, May 08, 2014 11:05 AM
To: Clara Li
Subject: NDA 204630; Meth Blue--Information Request
Importance: High

Hi Clara:

Would you please provide us with the contact information for the following:

1. Email address for the principle clinical investigator of trial AA98923 (Fareeda Hosein, MD)
2. A telephone number and fax number for the analytical site for trial AA98923 [REDACTED] (b) (4) and an email for the Principal Analytical Investigator [REDACTED] (b) (4)

We need this information no later than **Monday, May 12, 2014; 12Noon, EST.**

Thank you,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

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/s/

KIM J ROBERTSON
05/08/2014

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, May 06, 2014 1:05 PM
To: 'Clara Li'
Subject: RE: NDA 204630; Meth Blue--Information Request

Importance: High

Hi Clara:

My QT-IRT colleagues are unable to locate any ECG waveforms in the ECG warehouse. Has Provepharm started the process of submitting them? If not, we are advising them to please submit all related ECG waveforms to the ECG warehouse at www.ecgwarehouse.com

Also, would you please provide me with a quick line notifying me when all of the other items we've requested has been officially submitted to the NDA as well?

Thank you Clara,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Wednesday, April 30, 2014 3:56 PM
To: Robertson, Kim
Subject: RE: NDA 204630; Meth Blue--Information Request

Dear Kim,

Enclosed please find a partial response to your request (responses to Items 1 and Item 3). We are waiting for the response to Item 2 (define.pdf) and expect it May 6th or 7th. I will email that file to you, when received. All of these files are expected to be uploaded on May 7th (as SN0028).

Best regards,
Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, April 23, 2014 6:19 PM
To: Clara Li

Cc: Todd Marshall
Subject: RE: NDA 204630; Meth Blue--Information Request

Welcome back Clara. Thank you for that. My reviewers are standing by for the information, so they may complete their review.

Enjoy your evening,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Wednesday, April 23, 2014 8:16 PM
To: Robertson, Kim
Cc: Todd Marshall
Subject: RE: NDA 204630; Meth Blue--Information Request

Hi Kim,

I'm back from vacation and things over again. Your questions will be forwarded to Provepharm for a response as soon as possible.

Best regards,
Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, April 23, 2014 6:14 PM
To: Todd Marshall
Cc: Clara Li
Subject: RE: NDA 204630; Meth Blue--Information Request

Hello Todd:

After reviewing the submitted materials, the requesting reviewers found a few things missing. Would you please submit the following:

- 1) Eg.xpt is corrupted in EDR after row 193, please resubmit
- 2) Please provide define.pdf for all datasets submitted, including conc.xpt,
- 3) Is the Subject Number (PTNO) in conc.xpt corresponding to the CLIENTID in dm.xpt?

Thank you,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Todd Marshall [<mailto:TMarshall@clinipace.com>]
Sent: Thursday, April 17, 2014 12:24 PM
To: Robertson, Kim
Cc: Clara Li
Subject: RE: NDA 204630; Meth Blue--Information Request

Hello Kim,

I hope that you are enjoying/have enjoyed your vacation. I just wanted to inform you that Provepharma has submitted their responses/documents electronically to their NDA 204630 as Sequence Number 24.

Best regards,

Todd

From: Todd Marshall
Sent: Wednesday, April 16, 2014 2:58 PM
To: 'Robertson, Kim'
Cc: Clara Li
Subject: RE: NDA 204630; Meth Blue--Information Request

Hi Kim,

I sent 3 emails, each containing a Zip file, to you ~ Noon Mountain Time that contained the documents in response to your April 10, 2014 Information Request regarding Provepharm's Study 1MBL120002. I hadn't heard back from you and just wanted to make sure that you received them.

Best regards,

Todd

Todd Marshall
Executive Director, Regulatory Affairs and Strategic Development

CLINIPACE WORLDWIDE
4840 Pearl East Circle, Suite 201E
Boulder, Colorado 80301

(o) 720-644-0662 (Direct) or 303-225-0980 (Main) Ext 3022
(m) (b) (6)
(f) 303-225-0984

Follow us:
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From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Monday, April 14, 2014 5:56 PM
To: Todd Marshall
Cc: Clara Li
Subject: RE: NDA 204630; Meth Blue--Information Request

Hello Todd (please call me Kim).....

That is perfectly fine with me, as I am trying to enjoy my well-earned vacation as well!! ☺ It starts as soon as I respond to your e-mail. I will be coming back online however on Wednesday **ONLY** to receive the information we need from Clara (now you). After that, I will be signing back off to enjoy the rest of my vacation.

Thank you Todd,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Todd Marshall [<mailto:TMarshall@clinipace.com>]
Sent: Monday, April 14, 2014 7:53 PM
To: Robertson, Kim
Cc: Clara Li
Subject: RE: NDA 204630; Meth Blue--Information Request

Dear Ms Robertson,

I will be providing the response on the 16th on behalf of Clara so she is able to enjoy her well-earned vacation.

Todd

Todd Marshall
Executive Director, Regulatory Affairs and Strategic Development

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(m) (b) (6)
(f) 303-225-0984

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From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Thursday, April 10, 2014 1:41 PM
To: Clara Li
Subject: RE: NDA 204630; Meth Blue--Information Request

Sure Clara. Via e-mail is perfectly fine. That will actually expedite the process of me getting what I need by the 16th, so my reviewers can have what they need. The official submission can certainly arrive a few days later.

Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Thursday, April 10, 2014 2:41 PM
To: Robertson, Kim
Subject: RE: NDA 204630; Meth Blue--Information Request

Hi Kim,

I don't know if we will need to do this, but if it becomes a time crunch, can I send the response by email and then have the official upload to the NDA completed within a couple of days after that?

Best regards,
Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Thursday, April 10, 2014 12:01 PM
To: Clara Li
Subject: RE: NDA 204630; Meth Blue--Information Request

OK.....I will be looking for a response for my reviewers by Apr. 16th.

Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products

Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Thursday, April 10, 2014 1:54 PM
To: Robertson, Kim
Subject: RE: NDA 204630; Meth Blue--Information Request

Hi Kim,

I will get back to you as soon as possible.

Best regards,
Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Thursday, April 10, 2014 11:18 AM
To: Clara Li
Subject: NDA 204630; Meth Blue--Information Request
Importance: High

Hi Clara:

In order for my reviewers to complete their review, they will need Provepharma to provide us with the following information, as it relates to Study 1MBL12002:

- a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
- b. Electronic or hard copy of the Investigator's Brochure
- c. Annotated CRF
- d. A data definition file which describes the contents of the electronic data sets
- e. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
- f. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)

- g. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
- h. Narrative summaries and case report forms for any
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study
- i. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com). If you use Holter recording and select 10-second segments to measure, submit either the entire Holter recording or at least the entire analysis windows.
- j. A completed Highlights of Clinical Pharmacology Table (attached)

Please provide this information to us no later than **Wednesday, April 16, 2014**.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

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/s/

KIM J ROBERTSON
05/06/2014

Robertson, Kim

From: Robertson, Kim
Sent: Sunday, May 04, 2014 10:59 PM
To: 'Clara Li'
Subject: RE: NDA 204630; Methylene Blue--Clinical Pharmacology Information Request

Thank you Clara.
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Friday, May 02, 2014 8:38 PM
To: Robertson, Kim
Subject: RE: NDA 204630; Methylene Blue--Clinical Pharmacology Information Request

Hi Kim,

I will email you the letter by the due date/time. At the same time we will prepare the letter for submission to the NDA.

Best regards,
Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Thursday, May 01, 2014 3:10 PM
To: Clara Li
Subject: NDA 204630; Methylene Blue--Clinical Pharmacology Information Request
Importance: High

Hi Clara:

In light of comments made at our April 30, 2014 teleconference regarding your NDA application, please provide the right of cross reference document for the PK trial AA98923 and related bioassay by **Tuesday, May 06, 2014, 1:00pm, EST.** If this document was already submitted, please identify the location in the eCTD.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

*Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
05/06/2014

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, April 23, 2014 8:19 PM
To: 'Clara Li'
Cc: Todd Marshall
Subject: RE: NDA 204630; Meth Blue--Information Request

Welcome back Clara. Thank you for that. My reviewers are standing by for the information, so they may complete their review.

Enjoy your evening,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Wednesday, April 23, 2014 8:16 PM
To: Robertson, Kim
Cc: Todd Marshall
Subject: RE: NDA 204630; Meth Blue--Information Request

Hi Kim,

I'm back from vacation and things over again. Your questions will be forwarded to Provepharm for a response as soon as possible.

Best regards,
Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, April 23, 2014 6:14 PM
To: Todd Marshall
Cc: Clara Li
Subject: RE: NDA 204630; Meth Blue--Information Request

Hello Todd:

After reviewing the submitted materials, the requesting reviewers found a few things missing. Would you please submit the following:

- 1) Eg.xpt is corrupted in EDR after row 193, please resubmit

- 2) Please provide define.pdf for all datasets submitted, including conc.xpt,
- 3) Is the Subject Number (PTNO) in conc.xpt corresponding to the CLIENTID in dm.xpt?

Thank you,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Todd Marshall [<mailto:TMarshall@clinipace.com>]
Sent: Thursday, April 17, 2014 12:24 PM
To: Robertson, Kim
Cc: Clara Li
Subject: RE: NDA 204630; Meth Blue--Information Request

Hello Kim,

I hope that you are enjoying/have enjoyed your vacation. I just wanted to inform you that Provepharma has submitted their responses/documents electronically to their NDA 204630 as Sequence Number 24.

Best regards,

Todd

From: Todd Marshall
Sent: Wednesday, April 16, 2014 2:58 PM
To: 'Robertson, Kim'
Cc: Clara Li
Subject: RE: NDA 204630; Meth Blue--Information Request

Hi Kim,

I sent 3 emails, each containing a Zip file, to you ~ Noon Mountain Time that contained the documents in response to your April 10, 2014 Information Request regarding Provepharm's Study 1MBL120002. I hadn't heard back from you and just wanted to make sure that you received them.

Best regards,

Todd

Todd Marshall
Executive Director, Regulatory Affairs and Strategic Development

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Boulder, Colorado 80301

(o) 720-644-0662 (Direct) or 303-225-0980 (Main) Ext 3022

(m) (b) (6)

(f) 303-225-0984

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From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]

Sent: Monday, April 14, 2014 5:56 PM

To: Todd Marshall

Cc: Clara Li

Subject: RE: NDA 204630; Meth Blue--Information Request

Hello Todd (please call me Kim).....

That is perfectly fine with me, as I am trying to enjoy my well-earned vacation as well!! ☺ It starts as soon as I respond to your e-mail. I will be coming back online however on Wednesday **ONLY** to receive the information we need from Clara (now you). After that, I will be signing back off to enjoy the rest of my vacation.

Thank you Todd,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Todd Marshall [<mailto:TMarshall@clinipace.com>]

Sent: Monday, April 14, 2014 7:53 PM

To: Robertson, Kim

Cc: Clara Li

Subject: RE: NDA 204630; Meth Blue--Information Request

Dear Ms Robertson,

I will be providing the response on the 16th on behalf of Clara so she is able to enjoy her well-earned vacation.

Todd

Todd Marshall

Executive Director, Regulatory Affairs and Strategic Development

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(m) (b) (6)

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From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]

Sent: Thursday, April 10, 2014 1:41 PM

To: Clara Li

Subject: RE: NDA 204630; Meth Blue--Information Request

Sure Clara. Via e-mail is perfectly fine. That will actually expedite the process of me getting what I need by the 16th, so my reviewers can have what they need. The official submission can certainly arrive a few days later.

Kim

Kim J. Robertson

Regulatory Health Project Manager

Office of Hematology and Oncology Products

Division of Oncology Products 1

E-mail: kim.robertson@fda.hhs.gov

Phone: (301) 796-1441

Fax: (301) 796-9845

From: Clara Li [<mailto:CLi@clinipace.com>]

Sent: Thursday, April 10, 2014 2:41 PM

To: Robertson, Kim

Subject: RE: NDA 204630; Meth Blue--Information Request

Hi Kim,

I don't know if we will need to do this, but if it becomes a time crunch, can I send the response by email and then have the official upload to the NDA completed within a couple of days after that?

Best regards,

Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]

Sent: Thursday, April 10, 2014 12:01 PM

To: Clara Li

Subject: RE: NDA 204630; Meth Blue--Information Request

OK.....I will be looking for a response for my reviewers by Apr. 16th.

Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Thursday, April 10, 2014 1:54 PM
To: Robertson, Kim
Subject: RE: NDA 204630; Meth Blue--Information Request

Hi Kim,

I will get back to you as soon as possible.

Best regards,
Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Thursday, April 10, 2014 11:18 AM
To: Clara Li
Subject: NDA 204630; Meth Blue--Information Request
Importance: High

Hi Clara:

In order for my reviewers to complete their review, they will need Provepharma to provide us with the following information, as it relates to Study 1MBL12002:

- a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
- b. Electronic or hard copy of the Investigator's Brochure
- c. Annotated CRF
- d. A data definition file which describes the contents of the electronic data sets
- e. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses

- f. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
- g. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
- h. Narrative summaries and case report forms for any
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study
- i. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com). If you use Holter recording and select 10-second segments to measure, submit either the entire Holter recording or at least the entire analysis windows.
- j. A completed Highlights of Clinical Pharmacology Table (attached)

Please provide this information to us no later than **Wednesday, April 16, 2014.**

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

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/s/

KIM J ROBERTSON
05/06/2014

From: Agosto, Teicher
To: ["Clara Li"](#)
Subject: RE: USE THIS ONE: Provepharm - summary notes for FDA NDA 20-4630
Date: Tuesday, April 15, 2014 1:32:00 PM

Dear Clara,

We reviewed your proposed (b) (4). We do not agree with your proposal (b) (4) for the following reasons:



If you have any questions, please feel free to contact me.

Best Regards,
Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993
Teicher.agosto@fda.hhs.gov
P: (240) 402-3777

From: Clara Li [mailto:CLi@clinipace.com]
Sent: Thursday, April 03, 2014 3:43 AM
To: Agosto, Teicher
Subject: USE THIS ONE: Provepharm - summary notes for FDA NDA 20-4630

Dear Teicher,

Please use this version of the email as Provepharm's official response. I sent the previous one by my phone and the format got garbled. Thank you.

As promised, here are a bulleted summary of Tuesday's teleconference with the ONDQA. This lists what Provepharm believes to be action items resulting from the call. We request FDA feedback regarding the last item listed under Question 1.

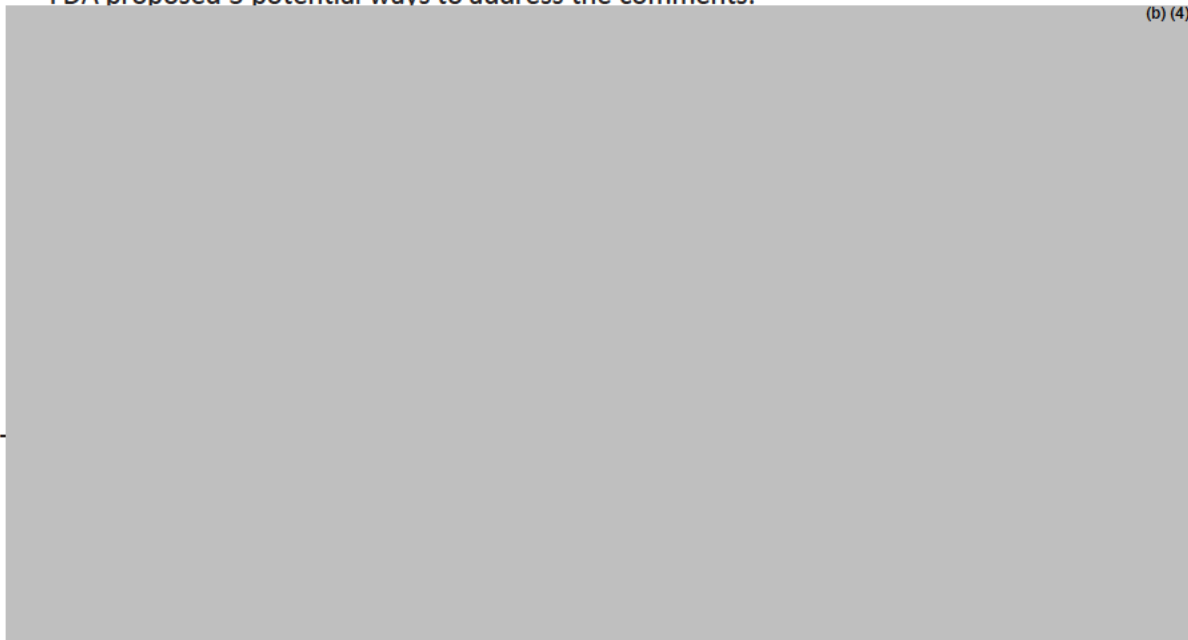
Provepharm will provide information in future submissions. Please let me know if these items are captured correctly.

Question 2

- FDA requested that the validation of the container-closure integrity test be provided and that Provepharm notify ONDQA of when this submission will be made.
- POST MEETING NOTE: Provepharm spoke with Cenexi after the meeting. The submission of the requested information is targeted for April 25th, 2014. Provepharm already plans to submit follow-up CMC data on that date in reply to the February 18th, 2014 Information Request [response submitted March 4th, 2014 (SN0021)] and March 19th, 2014 Information Request [Responses due for 4th April (SN0023)], so all of the CMC information will be compiled into one submission.

Question 1

- FDA proposed 3 potential ways to address the comments.



The results of these investigations will be shared and discussed with the FDA as soon as they are available.

Best regards,
Clara

=====
Clara Li
VP, Regulatory and Strategic Development

CLINIPACE WORLDWIDE
(formerly Regulus Pharmaceutical Consulting)
4840 Pearl East Circle, Suite 201E
Boulder, CO 80301

(e) cli@clinipace.com
(o) 303-225-0980 x3024
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(f) 303-225-0984

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/s/

TEICHER N AGOSTO
04/15/2014

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, April 10, 2014 2:01 PM
To: 'Clara Li'
Subject: RE: NDA 204630; Meth Blue--Information Request

OK.....I will be looking for a response for my reviewers by Apr. 16th.

Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Thursday, April 10, 2014 1:54 PM
To: Robertson, Kim
Subject: RE: NDA 204630; Meth Blue--Information Request

Hi Kim,

I will get back to you as soon as possible.

Best regards,
Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Thursday, April 10, 2014 11:18 AM
To: Clara Li
Subject: NDA 204630; Meth Blue--Information Request
Importance: High

Hi Clara:

In order for my reviewers to complete their review, they will need Provepharma to provide us with the following information, as it relates to Study 1MBL12002:

- a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
- b. Electronic or hard copy of the Investigator's Brochure
- c. Annotated CRF

- d. A data definition file which describes the contents of the electronic data sets
- e. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
- f. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
- g. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
- h. Narrative summaries and case report forms for any
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study
- i. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com). If you use Holter recording and select 10-second segments to measure, submit either the entire Holter recording or at least the entire analysis windows.
- j. A completed Highlights of Clinical Pharmacology Table (attached)

Please provide this information to us no later than **Wednesday, April 16, 2014**.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

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/s/

KIM J ROBERTSON
05/06/2014

Executive CAC

Date of Meeting: March 18, 2014

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Adebayo Lanionu, Ph.D., DMIP, Alternate Member
Haleh Saber, Ph.D., DHOT, Team Leader
Brenda J. Gehrke, Ph.D., DHOT, Presenting Reviewer

Author of Draft: Brenda J. Gehrke, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 204630

Drug Name: Proposed drug is methylene blue injection; methylene blue trihydrate was used in carcinogenicity studies conducted by the National Toxicology Program (NTP) using the oral gavage route.

Applicant: Provepharma SAS

Background:

Provepharma SAS is developing an intravenous methylene blue product for the treatment of acquired methemoglobinemia and has submitted NDA 204630. Methylene blue is a thiazine dye that promotes a non-enzymatic redox conversion of methemoglobin to hemoglobin. To support NDA 204630, toxicology studies conducted by NTP with methylene blue trihydrate were submitted including 2-year carcinogenicity studies in rats and mice. Methylene blue trihydrate was mutagenic in the Ames test. In *in vitro* tests in Chinese hamster ovary (CHO) cells, methylene blue trihydrate induced sister chromatid exchanges and was clastogenic by inducing chromosomal aberrations. Methylene blue trihydrate was not genotoxic in an *in vivo* mouse micronucleus study.

Rat Carcinogenicity Study:

To assess the carcinogenic potential of methylene blue, F344/N rats were administered oral doses of 5, 25, or 50 mg/kg/day methylene blue trihydrate once daily, 5 days per week for 2 years. The vehicle control consisted of 0.5% aqueous methylcellulose. Survival in the methylene blue-treated groups was similar to that of controls. Body weights were lower in males and females treated with 25 and 50 mg/kg/day methylene blue compared to controls, with mean weights 9-13% lower than controls at Week 101. Toxicities included drug-related hematological responses of anemia and methemoglobinemia at 25 and 50 mg/kg/day doses, as well as dose-related hyperplasia in pancreatic islets in males at 25 and 50 mg/kg/day. The incidences of adenoma and adenoma or carcinoma (combined) in the pancreatic islets were increased in males treated with methylene blue and were above the historical control. Adenoma or carcinoma (combined) in pancreatic islets was observed in 9/50 (18%), 14/50 (28%), and 8/50 (16%) males in the 5, 25, and 50 mg/kg methylene blue-treated groups, respectively. The neoplasm was observed in 4/50

(8%) males in the concurrent control group. According to the historical incidence for all routes of administration provided in the NTP report, adenoma or carcinoma in pancreatic islets has been observed in 92/1,448 (6.4%) of controls, with a mean of 6.8% and a range of 0-14%.

Mouse Carcinogenicity Study:

To assess the carcinogenic potential of methylene blue, B6C3F₁ mice were administered oral gavage doses of 2.5, 12.5, or 25 mg/kg/day methylene blue trihydrate once daily, 5 days per week for 2 years. The vehicle control consisted of 0.5% aqueous methylcellulose. Survival in the methylene blue-treated groups was similar to that of controls. Toxicities observed included lower body weights (5-9%) in females treated with 25 mg/kg/day compared to controls during weeks 45 through 73 and drug-related anemia in males at 25 mg/kg/day and methemoglobinemia at 12.5 (females only) and 25 mg/kg/day. There were no statistically significant neoplastic findings in mice using the FDA criteria for drug-related tumors. The incidences of carcinoma and adenoma or carcinoma (combined) in the small intestine were increased in males administered methylene blue. Adenoma or carcinoma combined in the small intestine was observed in 6/50 (12%) males administered the high dose of methylene blue compared with 1/50 (2%) control males. In addition to not being statistically significant, this incidence was only slightly above the historical control (12% at high dose and 10% in historical control).

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee concurred that the study was acceptable, although daily dosing would have been more representative of any future chronic usage.
- The Committee concurred that pancreatic islet adenomas or carcinomas (combined) in the males were drug related because the incidence exceeded the historical control, particularly in the mid dose group. Furthermore, it was noted that the animals were not dosed on weekends (and thus had time to recover from drug-related effects). The terminal half-life of the drug is reported to be around 5 hours.

Mouse:

- The Committee concurred that the study was acceptable.
- The Committee concurred that there were no drug-related neoplasms in the study.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DHP
/HSaber, DHOT
/BGehrke, DHOT
/KRobertson, DOP1 for DHP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
03/20/2014

DAVID JACOBSON KRAM
03/20/2014



NDA 204630

INFORMATION REQUEST

Provepharm SAS
c/o Clinipace Worldwide RSD
Attention: Clara Li
Vice President, Regulatory & Strategic Development
4840 Pearl East Circle
Suite #201 E
Boulder, CO 80301

Dear Ms. Li:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylene Blue Injection, 5 mg/mL.

We also refer to your September 13, 2013, submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response by April 4, 2014, in order to continue our evaluation of your NDA.

Drug Substance:

[REDACTED] (b) (4)

2. Adopt a separate identification test for [REDACTED] (b) (4) for the drug substance; otherwise, justify.
3. Justify the [REDACTED] (b) (4) acceptance criteria based on batch analyses data and the fact that the drug substance [REDACTED] (b) (4)
4. The assay acceptance criteria [REDACTED] (b) (4) justification is not acceptable since it is not supported by the batch analyses/stability data under the proposed storage conditions or the current USP (98-103%) or Ph.Eur (95-101%) acceptance criteria standards. Revise the assay acceptance criteria to at least comply with the current USP specification.

5. Provide the following items as parts of the system suitability for “The assay of Methylene Blue and the impurities and degradation products by HPLC according to the description (b) (4) [redacted]”
6. For the reference standards, provide comparative HPLC purity results of methylene blue, specified impurities and related substances of the compendial reference standards versus your working standards for methylene blue, specified impurities, related substances and degradation products.
7. For the container/closure system, provide your acceptance specification for the (b) (4) [redacted] used for primary and secondary packaging for those items including the test methods and acceptance criteria. Also, include a letter of authorization for appropriate DMFs for primary packaging with components/composition and its suitability description for (b) (4) [redacted] otherwise, you may provide that information as an amendment to the NDA.

Drug Product:

1. Include appropriate excess volume to (b) (4) [redacted] Injection Product (0.5%) to comply with USP General Information <1151> Pharmaceutical Dosage Forms.
2. You reported in the “Compatibility” section that three experiments were performed. However, only two results from these experiments were provided. Please explain the discrepancy.
3. In the method of “HPLC assay for the determination of Methylene Blue, impurity (b) (4) [redacted] and unspecified impurity in (b) (4) [redacted] Injection, 0.5%”, two standard solutions is required to be prepared to ensure the weight accuracy of the standard used for the quantitation.
4. In the section of 3.2.P.5.3, the total mass balance is around (b) (4) [redacted] of (b) (4) [redacted] which is more than (b) (4) [redacted] % under (b) (4) [redacted]. Please explain.
5. Provide English translation of Figures 5a, 5b, 5c, 5d, 5e, 5f, 5g, 5h, 5i, 8a, 8b, 8c, 9a, 9b, 9c, 10a, 10b, 10c in section of 3.2.P.7.

If you have any questions, call Teicher Agosto, Regulatory Project Manager, at (240) 402-3777.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
03/19/2014



NDA 204630

INFORMATION REQUEST

Provepharm SAS
c/o Clinipace Worldwide RSD
Attention: Clara Li
Vice President, Regulatory & Strategic Development
4840 Pearl East Circle
Suite #201 E
Boulder, CO 80301

Dear Ms. Li:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylene Blue Injection, 5 mg/mL.

We also refer to your September 13, 2013, submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by March 4, 2014, in order to continue our evaluation of your NDA.

1. We do not agree with the (b) (4)
(b) (4)
(b) (4) Once an (b) (4) has been selected, provide the following information:

- a. In-house acceptance criteria and Vendor's Certificate of Analysis.
- b. Supplier information and a brief description of synthetic scheme and method of manufacture and reaction controls.
- c. Impurity profile.
- d. Detailed discussion on carry-forward impurities.
- e. Controls and analytical methods to separate and measure appropriate impurities.

- f. Detailed discussion on purging studies using impurities to demonstrate the ability of the manufacturing process to remove and control the impurities to desired levels.
- g. Change of control strategies for any potential revisions to the manufacture of proposed starting materials including the vendor's reporting of any changes in starting material specification or control.

2. Provide a brief description of the HPLC analytical method (b) (4)

(b) (4)
[Redacted]

3. (b) (4)
[Redacted]

4. (b) (4)
[Redacted]

5. (b) (4)
[Redacted]

6. Were (b) (4) placed inside the ampoules of drug product? If not, provide a comparison of the (b) (4) of the (b) (4) in the drug product and the master solution.

If you have any questions, please contact Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

JANICE T BROWN

02/18/2014

Janice Brown for Ali Al-Hakim, Ph.D.

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, February 05, 2014 4:25 PM
To: 'Clara Li'
Subject: RE: NDA 204630 – Request guidance on FDA information request

You're most welcome Clara.
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Wednesday, February 05, 2014 4:22 PM
To: Robertson, Kim
Subject: RE: NDA 204630 – Request guidance on FDA information request

Dear Kim,

Thank you for this quick reply.

Best regards,
Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, February 05, 2014 2:21 PM
To: Clara Li
Subject: RE: NDA 204630 – Request guidance on FDA information request
Importance: High

Hello Clara:

With regard to Clinipace's "Request Guidance on FDA Information Request" to the Division re: NDA 204630; Methylene Blue Injection, please see the following containing our responses:

(b) (4)



(b) (4) Does the
Division agree to this approach?

FDA Response: No. (b) (4) would not be viewed favorably. We do not recommend this approach.

We have reviewed your timeline, and it appears that you will be able to submit complete datasets for all 12 subjects by **30 April 2014**. Therefore, we will be extending the deadline to that date.

2. (b) (4)
This will
b ed to
FDA. Does the Division agree to this approach?

FDA Response: No. See response to question 1.

If you have any further questions, or concerns, please do not hesitate to let us know.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Tuesday, February 04, 2014 8:31 PM
To: Robertson, Kim
Subject: RE: NDA 204630 – Request guidance on FDA information request

Thank you.

Best regards,
Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Tuesday, February 04, 2014 2:58 PM
To: Clara Li
Subject: RE: NDA 204630 – Request guidance on FDA information request

Hello Clara:

We are in receipt of your questions and we will prepare responses for Clinipace very soon.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Friday, January 31, 2014 1:34 PM
To: Robertson, Kim
Subject: NDA 204630 – Request guidance on FDA information request

Dear Kim,

Reference is made to the teleconference held with the Division (Dr. Przepiorka, Dr. Deisseroth, Ms. Robertson) on December 11, 2013 to discuss clinical comments. Reference is also made to the Information Request received from the Division on December 20, 2013 summarizing the December 11 discussion (email enclosed). Provepharm has been working diligently to respond to the information request, however, we have encountered difficulty in meeting one of the Division's requests and need further guidance.

In Item Number 4 of the December 20 Information Request, the Division requested the following:

4. In your response to comment #3, you indicated that the CRFs from hospitals in Taiwan were incomplete, and in your response to comment #4, you indicated that due to "time constraints," an older version of the CRF was used to collect data in Taiwan. This omission of data is a potential source of bias that may invalidate any conclusions drawn from analyses of results from your protocol. Please submit complete data from all clinical sites, including the sites in Taiwan.

BACKGROUND TO PROVEPHARM QUESTIONS

- On September 28, 2011: Proveblue® Injection (European marketed product) was imported by Taiwan upon the request of the Taiwan National Poison Center (TNPC) [REDACTED] (b) (4). [REDACTED] The product was imported under a special license from the Ministry of Health to stock approximately 60 hospitals.
- December 18, 2012: Following a meeting with FDA, Provepharm contacted the TNPC to determine whether Proveblue® Injection had been used to treat cases of methemoglobinemia and to collect available information on these patients.
- February 6, 2013: The TNPC informed Provepharm that they had 3 cases reported of treatment with Proveblue® Injection since the import. The information provided by the Poison center was very brief (eg: age, total dose, AE).
- March 28, 2013: Provepharm forwarded the information provided by the TNPC to FDA (pre-IND meeting package). Provepharm also sent CRFs (version 1) to the TNPC for collection of additional information.
- September 13, 2013 (SN0008): The NDA was resubmitted to include data for the 3 Taiwanese patients (information originally provided by the TNPC) and data for the 9 French patients (provided on CRF version 1).
- October 4, 2013: FDA asked Provepharm to revise the CRFs template to include more details (CRF version 2).
- Provepharm asked the Director of the TNPC to collect information using CRF version 2, however the Version 1 was already completed, signed, and data verified (according to the monitoring plan). Provepharm received the data (collected on CRF Version 1) on October 22, 2013. The Director did not have time to collect additional

information. Data collection was made through the TNPC in Taipei which is empowered to monitor all poisoning cases in Taiwan, including methemoglobinemia cases. The TNPC has access to a certain amount of patient information without IRB approval.

- November 4, 2013 (NDA SN0011): Provepharm submitted the monitoring plan followed by the TNPC and the signed Taiwanese CRFs (Version 1) to FDA (SN0011).
- December 20, 2013: FDA asked Provepharm to collect the data for the 3 Taiwanese patients using CRF version 2 and submit the additional information and analyses by February 17, 2014.
- In order to collect the additional information requested by FDA, monitors would have to visit each of the 3 Taiwanese hospitals that treated the patients. Provepharm engaged a CRO to conduct monitoring visits. However, it was confirmed on January 22, 2014 that a formal IRB review and approval are required prior to any data access at hospitals by the CRO.
- IRB approval would take approximately 2 months. Additional weeks would also be needed for monitoring visits, data entry, analyses, and updating the clinical report.

QUESTIONS TO FDA

As summarized above, Provepharm will be unable to collect the additional Taiwanese data within the specified timeline. Provepharm is on track to submit a response regarding the other requested items from the FDA December 20 email by February 17.

- In order not to delay the review of the clinical data, Provepharm proposes [REDACTED] (b) (4)
[REDACTED]
Does the Division agree to this approach?
- [REDACTED] (b) (4)
[REDACTED] his will be provided as a separate, brief summary of the information previously provided to FDA. Does the Division agree to this approach?

Please let me know if I could provide additional information to aid in the response to these questions.

Best regards,
Clara

=====
Clara Li
VP, Regulatory and Strategic Development

CLINIPACE WORLDWIDE
(formerly Regulus Pharmaceutical Consulting)
4840 Pearl East Circle, Suite 201E
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/s/

KIM J ROBERTSON
02/05/2014

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, February 04, 2014 8:08 PM
To: Clara Li (CLi@clinipace.com)
Subject: NDA 204630; Methylene Blue Inj.--DMEPA Comments

Importance: High

Hello Clara:

During the Division of Medication Error Prevention and Analysis (DMEPA)'s review of Provepharm's newly submitted NDA for Methylene Blue Injection, the primary reviewer has ascertained the following comments that we recommend Provepharm addresses, prior to us taking an action on this application:

A. Ampule container label:

a. We recommend the labels and labeling should conform with the United States Pharmacopeia (USP) General Chapter <1> Injections. Revise the statement of strength to increase the prominence of the statement of total drug content in terms of total strength per total amount of milliliters on the principal display panel followed in close proximity by strength per milliliter enclosed by parentheses. The total drug content should appear immediately underneath dosage form of the product.

50 mg/10 mL
(5 mg/mL)

Additionally, please delete all concentration expression as a percentage (e.g. 5%). Expressing the concentration as a percentage is error-prone because not all health care professionals are familiar or adept at calculating doses in mg for drugs with concentrations expressed in percentage.⁷

b. We recommend revising the statement [REDACTED] ^{(b) (4)} to "Single dose ampule – Discard unused portion".

c. Decrease the prominence of manufacturer and distributor information on the principal display panel as it competes for prominence with information located at the top half of the principal display panel. Only the most important information such as name of the product, strength, and route of administration should be the most prominent information on the principal display panel.⁸

B. Carton labeling:

a. See section A.a. through A.b.

b. English is a predominant language in the United States. Therefore, it is an important safety feature that all parts of the label and labeling should be in English. Therefore, we request you revising the statement [REDACTED] ^{(b) (4)} to "5 Ampules" as required per 21 CFR 201.15 (c)(1).

c. Increase the prominence of the statement "Intravenous use only – For slow intravenous injection" to minimize wrong route of administration errors.

- d. Remove manufacturer information from the principal display panel to reduce information crowding as it competes for prominence with the name of the product, strength, and route of administration. Only the most important information such as name of the product, strength, and route of administration should be the most prominent information on the principal display panel.
- e. Re-locate the statement “Rx only” to the bottom 1/3 of the principal display panel as it competes for prominence with the name of the product, strength, and route of administration.
- f. As currently presented, it appears that the drug barcode is hidden inside the folding flap of the carton and will not be visible once the carton is constructed. The drug barcode is often used as an additional verification during the pharmacy procurement process; therefore it is an important safety feature that should be visible on the labeling.
- g. On the back panel, please revise the statement “(b) (4)” to “For single dose only” to be consistent with the statement “single dose ampule” on the principal display panel.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

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/s/

KIM J ROBERTSON
02/04/2014

Robertson, Kim

From: Robertson, Kim
Sent: Friday, December 20, 2013 12:03 PM
To: Clara Li (CLi@clinipace.com)
Subject: NDA 204630; Methylene Blue--Information Request

Importance: High

Hello again Clara:

With regard to Provepharm's NDA for Methylene Blue, we have the following request for information:

PHARMACOLOGY/TOXICOLOGY INFORMATION REQUEST:

- The NTP report for the evaluation of the effects of methylene blue on embryo-fetal development in rats (TER-92-124 1993) that was submitted to the NDA is a laboratory supplement that does not contain the results of the study. Please provide the NTP technical report that contains the complete set of results for study TER-92-124 1993. Additionally, please ensure that results for NTP studies for the effects of methylene blue on embryo-fetal development in rabbits, genetic toxicology, and general toxicology have been submitted to the NDA or submit them.

Please provide us with a response to this IR no later than Tuesday, January 07, 2014.

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
12/20/2013

Robertson, Kim

From: Robertson, Kim
Sent: Friday, December 20, 2013 11:55 AM
To: Clara Li (CLi@clinipace.com)
Subject: NDA 204630; Methylene Blue--Information Request

Importance: High

Hello Clara:

With regards to Provepharm's NDA for Methylene Blue, we have the following request for information:

1. There is no data dictionary for the datasets submitted for protocol 1MBL12002. Please submit a define file for the datasets for this protocol.

Regarding the materials submitted 11/5/2013 to our IR from 10/3/2013:

2. In your response to comment #6, you indicated that there was no oversight by an IRB or IEC for Protocol PVP-2013001, and indicated in the response to comment #7 that no waiver of any regulation is requested. Further, you submitted an exemption granted by a Committee for the Protection of Persons. Please submit a request to waive the requirement for review by an IRB or IEC, and to support the waiver request, describe the Committee for the Protection of Persons and how its operation is consistent with the principle of the regulations being waived.

3. You have submitted copies of the completed case report forms (CRF) with the word "CONFIDENTIAL" in large bold type across the face of each page, obscuring the data entered onto the CRF. Please provide copies of the CRFs with no such images obscuring the pages.

4. In your response to comment #3, you indicated that the CRFs from hospitals in Taiwan were incomplete, and in your response to comment #4, you indicated that due to "time constraints," an older version of the CRF was used to collect data in Taiwan. This omission of data is a potential source of bias that may invalidate any conclusions drawn from analyses of results from your protocol. Please submit complete data from all clinical sites, including the sites in Taiwan.

5. In response to comment #4, you indicated that there were no adverse events after administration of [REDACTED] (b) (4). You also submitted translated versions of partial patient records (Appendix 2). cursory review of these records show that adverse events were

observed and documented. We recommend that you re-examine these records as well as any other notations by the healthcare providers, and collect complete information on adverse events. We caution you that any regular pattern of discrepancy between your submission and the findings of the FDA inspector with regard to adverse events may invalidate any conclusions you draw regarding safety of your product.

6. In Appendix 16.4 of the revised Clinical Study Report for Protocol PVP-2013001, you submitted data listings without use of groups or domains. Further, prpdata.sas7bdat, the only dataset submitted for Protocol PVP2013001, appears to be a analysis dataset with limited baseline and outcome information. An analysis of safety and efficacy cannot be performed with the data as presented.

a) Please submit tabulation datasets for all collected data elements. These should include at least adverse events, concomitant medications, demographics, disposition, exposure to (b) (4) laboratory results, medical history, physical examination results (positive or negative), and vital signs.

We note that in you case report forms, date and time are in separate fields. However, timeline for activities in your study cover hours to days, so intervals will likely be calculated in hours, and to accomplish this, date field must be in the ISO8601 <date>T<time> format YYYY-MM-DDThh:mm.

For additional information, please see the FDA web site “Study Data Standard Resources” to assist in the development of electronic datasets that would be acceptable for submission in an NDA. This web site is available at:

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

b) In the reviewer guide, please identify the dataset with the reason for methemoglobinemia and the results of testing for methemoglobin.

c) Please confirm that all analyses in the Clinical Study Report were based on the single analysis file prpdata.sas7bdat.

d) Please provide a define file for all tabulation and analysis datasets.

Please provide us with responses to these requests no later than Monday, February 17, 2014.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

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/s/

KIM J ROBERTSON
12/20/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204630

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Provepharm SAS
c/o Clinipace Worldwide RSD
4840 Pearl East Circle
Suite #201 E
Boulder, CO 80301

ATTENTION: Clara Li
Vice President, Regulatory & Strategic Development

Dear Ms. Li:

Please refer to your New Drug Application (NDA) dated September 13, 2013, received September 13, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Methylene Blue Injection, 5 mg/mL.

We also refer to your October 31, 2013, correspondence, received October 31, 2013, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed

proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact CDR Sonny Saini, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0532. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Kim Robertson at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
12/06/2013



NDA 204630

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Provepharm SAS
Clinipace Worldwide RSD
Attention: Clara Li, Vice President, Regulatory Strategic Development
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 under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (b) (4) (methylene blue) Injection, 0.5% (5 mg/mL).

We also refer to your amendments dated October 27 and 31, 2013; November 06, 11, 13, 19, and 25, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 13, 2014.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. NDA information and horizontal lines are in the header of the PI; please remove
2. The product name is larger than 12-point font
3. Avoid having white space following your 'Contraindications' Section of the PI

4. Lack of use of command language in the PI; excessive use of passive language (i.e., “Should be avoided in patients” instead of “Avoid in patients”)
5. Remove spacing between Headings and information
6. Remove spacing between sub-headings and information
7. Sub-heading titles are not aligned
8. Lack of indentation of the first sentence of each paragraph under sub-headings
9. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns. Ensure that the top, right, left, and center margins are ½ inch in length
10. The Highlights Section must be one-half page or less. Attempt to decrease the length of this section
11. All headings in HL must be bolded and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column. The headings should be in UPPER CASE letters
12. White space should be present before each major heading in HL
13. The verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”
14. In the TOC, all subsection headings must be indented and not bolded. Please pay specific attention to sub-sections 2.1, 2.2, and 5.3 of your Table of Contents. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)]
15. In the TOC, when a section or subsection is omitted, the numbering must not change. Correct your numbering in Section 8; Use in Specific Population is correct
16. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see Warnings and Precautions (5.2)]” or “[see Warnings and Precautions (5.2)]”. Cross-references should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)] and italicized
17. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:
“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

For further assistance with Physician’s Labeling Rule (PLR) formatting, we strongly encourage you to refer to 21CFR201.56-57 (for PLR-format labels) and FDA’s PLR Internet page: <http://www.fda.gov/cder/regulatory/physLabel/default.htm>.

We request that you resubmit labeling that addresses these issues by December 11, 2013.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list

each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

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.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Hematology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

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, M.D.
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KIM J ROBERTSON
11/27/2013

Robertson, Kim

From: Robertson, Kim
Sent: Monday, November 18, 2013 11:35 AM
To: 'Clara Li'
Subject: RE: NDA 204630; Methylene Blue Injection--Clinical Pharmacology Comments
Importance: High

Hello Clara:

My reviewers are still telling me that they cannot access the files, whether it's the files attached in the e-mail, or the files in the Gateway submission. Apparently, they appear to be CPORT files. We do not accept those. Please re-format the files; preferably one dataset per file in XPORT, rather than CPORT.

Thank you,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Clara Li [mailto:CLi@clinipace.com]
Sent: Tuesday, November 12, 2013 12:24 AM
To: Robertson, Kim
Subject: RE: NDA 204630; Methylene Blue Injection--Clinical Pharmacology Comments

Dear Kim,

The requested file was uploaded to the NDA today (SN0013, November 11, 2013).

The provided XPT file is physically identical to the one submitted in SN0011 (same MD5 hash sum). We were unable to identify any technical issues with the file because our Statistician was able to open the file without problem. The file includes adverse event data. The file content has also been included in this email. The SAS codes are provided below.

(b) (4)



Best regards,
Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Friday, November 08, 2013 1:56 PM
To: Clara Li
Subject: RE: NDA 204630; Methylene Blue Injection--Clinical Pharmacology Comments

Many thanks Clara.

Have a wonderful weekend,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Friday, November 08, 2013 3:55 PM
To: Robertson, Kim
Subject: RE: NDA 204630; Methylene Blue Injection--Clinical Pharmacology Comments

Dear Kim,

We will fix and resend as soon as possible.

Best regards,
Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Friday, November 08, 2013 1:53 PM
To: Clara Li
Subject: FW: NDA 204630; Methylene Blue Injection--Clinical Pharmacology Comments
Importance: High

Hi Clara:

With regard to Clinipace's November 05, 2013 submission, please note that there is a "taa98923.xpt" file that will not open. Please re-submit this as an amendment to the NDA right away.

Regards,
Kim

Kim J. Robertson

*Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Robertson, Kim
Sent: Tuesday, November 05, 2013 11:07 AM
To: Clara Li (CLi@clinipace.com)
Subject: NDA 204630; Methylene Blue Injection--Clinical Pharmacology Comments

Hello Clara:

With regard to Clinipace's re-submitted NDA for Methylene Blue Injection, our Clinical Pharmacology discipline has the following comments:

CLINICAL PHARMACOLOGY COMMENTS:

1.  (b) (4)
 - a.
 - b.
2. Regarding the trial AA98923: "A One-Period, Single-Dose, Safety, Tolerability, and Pharmacokinetic Study of Methylene Blue Injection USP Following a 1 mg/kg Intravenous Dose in Healthy Adult Volunteers provide the following within 10 business days
 - c. It appears that the methylene blue product used in this trial was not your  (b) (4) formulation. Please confirm this and if true please explain how this trial supports the approvability of  (b) (4).
 - d. We note that the final study document reports PK parameters as arithmetic mean (SD) only and the linear time concentrations plot provided is a mean plots without variability. Update the final study report results such that summary statistics for the PK parameters are reported in terms of arithmetic mean, SD, CV, geometric mean, geometric CV, median, range. Time concentration plots should be plotted using both linear and semilog scales and include appropriate variability.
 - e. Provide a PK Analytical report that includes the raw concentration data by subject, calculated PK parameters by subject, the model reports from your NCA analysis (such that your analysis may be reproduced by the Agency) and individual concentration time plots both methylene blue and its metabolite using linear and semilog scales.

- f. Provide complete electronic datasets for this trial in SAS transport file format (*.xpt). Provide all concentration-time and derived PK parameter datasets. In addition, datasets for all other domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included.
- g. Provide a complete bioanalytical report to justify the validation of the assay used to quantify methylene blue and the Azure B metabolite
3. We note that you have not addressed the comments we provided to you previously regarding conflicting PK results in the literature, justification of your proposed pediatric dose, further in vivo evaluation of CYP inhibition, evaluation of the potential for CYP induction, evaluation of the potential as a substrate, inhibitor, or inducer or transporter systems, and the potential QT/QTc interval prolongation. These will not be accepted for review as part of this submission after the filing date.

Please provide us with responses to these comments within 10 business days.

Regards,

Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
11/18/2013

Robertson, Kim

From: Robertson, Kim
Sent: Friday, November 08, 2013 3:56 PM
To: 'Clara Li'
Subject: RE: NDA 204630; Methylene Blue Injection--Clinical Pharmacology Comments

Many thanks Clara.

Have a wonderful weekend,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Friday, November 08, 2013 3:55 PM
To: Robertson, Kim
Subject: RE: NDA 204630; Methylene Blue Injection--Clinical Pharmacology Comments

Dear Kim,

We will fix and resend as soon as possible.

Best regards,
Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Friday, November 08, 2013 1:53 PM
To: Clara Li
Subject: FW: NDA 204630; Methylene Blue Injection--Clinical Pharmacology Comments
Importance: High

Hi Clara:

With regard to Clinipace's November 05, 2013 submission, please note that there is a "taa98923.xpt" file that will not open. Please re-submit this as an amendment to the NDA right away.

Regards,
Kim

Kim J. Robertson

*Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Robertson, Kim
Sent: Tuesday, November 05, 2013 11:07 AM
To: Clara Li (CLi@clinipace.com)
Subject: NDA 204630; Methylene Blue Injection--Clinical Pharmacology Comments

Hello Clara:

With regard to Clinipace's re-submitted NDA for Methylene Blue Injection, our Clinical Pharmacology discipline has the following comments:

CLINICAL PHARMACOLOGY COMMENTS:

1.  (b) (4)
 - a.
 - b.
2. Regarding the trial AA98923: "A One-Period, Single-Dose, Safety, Tolerability, and Pharmacokinetic Study of Methylene Blue Injection USP Following a 1 mg/kg Intravenous Dose in Healthy Adult Volunteers provide the following within 10 business days
 - c. It appears that the methylene blue product used in this trial was not your  (b) (4) formulation. Please confirm this and if true please explain how this trial supports the approvability of  (b) (4).
 - d. We note that the final study document reports PK parameters as arithmetic mean (SD) only and the linear time concentrations plot provided is a mean plots without variability. Update the final study report results such that summary statistics for the PK parameters are reported in terms of arithmetic mean, SD, CV, geometric mean, geometric CV, median, range. Time concentration plots should be plotted using both linear and semilog scales and include appropriate variability.
 - e. Provide a PK Analytical report that includes the raw concentration data by subject, calculated PK parameters by subject, the model reports from your NCA analysis (such that your analysis may be reproduced by the Agency) and individual concentration time plots both methylene blue and its metabolite using linear and semilog scales.
 - f. Provide complete electronic datasets for this trial in SAS transport file format (*.xpt). Provide all concentration-time and derived PK parameter datasets. In addition, datasets for all other domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included.

- g. Provide a complete bioanalytical report to justify the validation of the assay used to quantify methylene blue and the Azure B metabolite
3. We note that you have not addressed the comments we provided to you previously regarding conflicting PK results in the literature, justification of your proposed pediatric dose, further in vivo evaluation of CYP inhibition, evaluation of the potential for CYP induction, evaluation of the potential as a substrate, inhibitor, or inducer or transporter systems, and the potential QT/QTc interval prolongation. These will not be accepted for review as part of this submission after the filing date.

Please provide us with responses to these comments within 10 business days.

Regards,

Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
11/12/2013

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, November 05, 2013 11:07 AM
To: Clara Li (CLi@clinipace.com)
Subject: NDA 204630; Methylene Blue Injection--Clinical Pharmacology Comments

Hello Clara:

With regard to Clinipace's re-submitted NDA for Methylene Blue Injection, our Clinical Pharmacology discipline has the following comments:

CLINICAL PHARMACOLOGY COMMENTS:

1.

[Redacted content] (b) (4)

2.

Pharmacokinetic Study of Methylene Blue Injection USP Following a 1 mg/kg Intravenous Dose in Healthy Adult Volunteers provide the following within 10 business days

- a. It appears that the methylene blue product used in this trial was not your [Redacted] (b) (4) formulation. Please confirm this and if true please explain how this trial supports the approvability of [Redacted] (b) (4).
- b. We note that the final study document reports PK parameters as arithmetic mean (SD) only and the linear time concentrations plot provided is a mean plots without variability. Update the final study report results such that summary statistics for the PK parameters are reported in terms of arithmetic mean, SD, CV, geometric mean, geometric CV, median, range. Time concentration plots should be plotted using both linear and semilog scales and include appropriate variability.
- c. Provide a PK Analytical report that includes the raw concentration data by subject, calculated PK parameters by subject, the model reports from your NCA analysis (such that your analysis may be reproduced by the Agency) and individual concentration time plots both methylene blue and its metabolite using linear and semilog scales.
- d. Provide complete electronic datasets for this trial in SAS transport file format (*.xpt). Provide all concentration-time and derived PK parameter datasets. In addition, datasets for all other domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included.
- e. Provide a complete bioanalytical report to justify the validation of the assay used to quantify methylene blue and the Azure B metabolite

3. We note that you have not addressed the comments we provided to you previously regarding conflicting PK results in the literature, justification of your proposed pediatric dose, further in vivo

evaluation of CYP inhibition, evaluation of the potential for CYP induction, evaluation of the potential as a substrate, inhibitor, or inducer or transporter systems, and the potential QT/QTc interval prolongation. These will not be accepted for review as part of this submission after the filing date.

Please provide us with responses to these comments within 10 business days.

Regards,

Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
11/05/2013

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, October 15, 2013 11:42 AM
To: Clara Li (CLi@clinipace.com)
Subject: NDA 204630; Methylene Blue--CMC Info. Request

Importance: High

Hello Clara:

With regard to Provepharm's NDA for Methylene Blue Injection, my CMC discipline has the following request for information:

CMC INFORMATION REQUEST:

International Conference on Harmonization (ICH) Q1A (R2) states "long term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission". Your NDA included only 3 months of drug substance stability data that included testing for all attributes. Submit available drug substance stability data for batches 25002129, 25002132 and 25002134.

Please submit this information no later than **Wednesday, November 06, 2013.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
10/15/2013

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, October 10, 2013 5:16 PM
To: 'Clara Li'
Subject: RE: NDA 204630; Methylene Blue Injection--CMC IR

Thank you Clara.
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Clara Li [<mailto:CLi@clinipace.com>]
Sent: Thursday, October 10, 2013 5:16 PM
To: Robertson, Kim
Subject: RE: NDA 204630; Methylene Blue Injection--CMC IR

Hi Kim,

I will respond to this as soon as possible.

Best regards,
Clara

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Thursday, October 10, 2013 3:11 PM
To: Clara Li
Subject: NDA 204630; Methylene Blue Injection--CMC IR
Importance: High

Hi Clara:

The CMC reviewers of Provepharm's NDA for Methylene Blue Injection wanted to inquire as to whether or not the following components are actually cross referenced to the Original NDA submission. Listed below in **red** are the components that we do not see in the September, 2013 re-submission:

P DRUG PRODUCT

1 Description and Composition of the Drug Product - Included in the NDA

P.2 Pharmaceutical Development

P.2.1 Components of the Drug Product

- P.2.1.1** *Drug Substance*
- P.2.1.2** *Excipients*
- P.2.2** *Drug Product*
- P.2.2.1** *Formulation Development*
- P.2.2.2** *Overages*
- P.2.2.3** *Physicochemical and Biological Properties*
- P.2.3** *Manufacturing Process Development*
- P.2.4** *Container Closure System*
- P.2.5** *Microbiological Attributes*
- P.2.6** *Compatibility*
- P.3** **Manufacture**
- P.3.1** *Manufacturers*
- P.3.2** *Batch Formula*
- P.3.3** *Description of Manufacturing Process and Process Controls*
- P.3.4** *Controls of Critical Steps and Intermediates*
- P.3.5** *Process Validation and/or Evaluation - Included in the NDA*
- P.4** **Control of Excipients**
- P.4.1** *Specifications*
- P.4.2** *Analytical Procedures*
- P.4.3** *Validation of Analytical Procedures*
- P.4.4** *Justification of Specifications*
- P.4.5** *Excipients of Human or Animal Origin*
- P.4.6** *Novel Excipients*
- P.5** **Control of Drug Product [name, dosage form]**
- P.5.1** *Specification(s)*
- P.5.2** *Analytical Procedures*
- P.5.3** *Validation of Analytical Procedures- Included in the NDA*
- P.5.4** *Batch Analyses – Included in the NDA*
- P.5.5** *Characterization of Impurities*
- P.5.6** *Justification of Specification(s)*
- P.6** **Reference Standards or Materials**
- P.7** **Container Closure System**
- P.8** **Stability – Included in the NDA**
- P.8.1** *Stability Summary and Conclusion*
- P.8.2** *Postapproval Stability Protocol and Stability Commitment*
- P.8.3** *Stability Data*

Perhaps this is what Provepharm wants us to do..... cross reference the Original NDA, but did not ask us to do so? Please also remember to submit Attachment 1, as referenced in the cover letter.

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441*

Fax: (301) 796-9845

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/s/

KIM J ROBERTSON
10/15/2013



NDA 204630

INFORMATION REQUEST

Provepharm SAS
Attention: Clara C. Li
Vice President, Regulatory & 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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) Injection (Methylene Blue Injection), 0.5%.

We also refer to your September 13, 2013 submission, containing addressed deficiencies summarized in the Refuse to File letter of October 11, 2012 which relate to pharmacokinetics of methylene blue by accessing a study conducted by Luitpold and by developing a bridge between the Luitpold product and your product.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

You had submitted on August 13, 2012 NDA 204630 under the 505(b)(2) pathway which allows Applicants to rely on FDA determinations or information from the literature. The original application was not found to be acceptable for filing (see Refuse to File Letter from Dr. Ann Farrell on October 11, 2012) because you had not established that reliance on the clinical studies that you cited from the literature was scientifically appropriate. Specifically, the NDA did not include any adequate and well-controlled clinical trials using your product. In the 505(b)(2) pathway, if the determinations of the FDA or literature do not answer the questions regarding the drug's efficacy and safety, the Applicant will need to fill in this information by conducting new studies.

In addition, you have attempted to utilize the clinical experience gained by the treatment of 12 patients with methemoglobinemia with the Provepharm product by a retrospective review of this clinical experience. In previous meetings with the FDA, the endpoints for efficacy were clearly stated: a 50% reduction in methemoglobin percentage, and a change in physical signs associated with methemoglobinemia (e.g. respiratory rate and heart rate) as evidence of efficacy. In addition, the FDA emphasized that the Applicant should provide evidence on the safety of the

Provepharm product by reporting on the adverse events (both clinical and laboratory) observed in the immediate post treatment period (Type B meeting May 24, 2013).

The FDA standard for a “new trial” is that the data from the primary source documentation (clinical notes of medical staff attending the patients during the treatment period, vital signs and other clinical observations recorded in the hospital chart, and a comprehensive listing of all laboratory test during the immediate post treatment period) be verified directly by the Applicant (or a CRO representing the Applicant), and the primary data elements for all 12 patients be listed and sent to the FDA for analysis. In the SCE and SCS, (as well as the ISE and ISS), the Applicant will summarize and analyze the data. But it is the primary responsibility of the Applicant to provide the FDA with the primary data lists for FDA analysis.

In the amended NDA submitted on September 13, 2013, the Applicant has submitted summary tables derived from reports of pharmacists in the hospitals in which the patients were treated. What will be required to bring the amended NDA to the standard of being “Fileable” is for the Applicant to examine the hospital records of the admissions of all 12 patients in the retrospective patient study to verify that all required data elements listed above relevant to the determination of the efficacy and safety of the Provepharm Methylene Blue from the primary source documents (hospital charts, records, laboratory reports) have been collected accurately, so that these data can be submitted to the FDA for FDA analysis, and so that the Applicant can produce its own analysis and submit it one week before the filing deadline of November 12, 2013.

Please submit the following:

1. Your cover letter refers to a descriptive listing of the content of the revised NDA in Attachment 1, but there is no such attachment in the NDA. Please submit Attachment 1 to the cover letter.
2. Please provide a tabular listing of the Module 5 clinical studies in Section 5.2. These are the clinical studies that address your product specifically.
3. You stated in Section 9.6 of the Clinical Study Report for Protocol PVP-2013001 that data were handled according to SOPs based on Good Clinical Practice (GCP). Please describe the plan you followed for monitoring and auditing clinical sites for this protocol. Please provide copies of all reports of audits of the clinical sites.
4. The Clinical Study Report for Protocol PVP-2013001 does not address several critical analyses needed to assess safety. Please provide analyses and your conclusions for the following:
 - a) All adverse events that occurred in the study subjects.
 - b) All vital signs for the study subjects.
 - c) All laboratory data for the study subjects.

5. Please provide the datasets for the clinical studies in Module 5 Section 5. The datasets should be in SAS transport format (.xpt). For additional information about data files for NDA submissions, please see:

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

As per our discussion 10/4/2013, we will accept .xls data sets for a small clinical study. The .xpt format would be preferred for the PK and ECG study in healthy volunteers.

6. You stated in Section 5.1 of the Clinical Study Report for Protocol PVP-2013001 that there was no IRB oversight for this protocol, and in Section 5.2 you stated that the Declaration of Helsinki governed this activity. Paragraph 25 of the Declaration of Helsinki requires consideration and approval by a research ethics committee for medical research using human material or data. Please provide the documentation of review and approval of Protocol PVP-2013001 by a research ethics committee. This documentation should also be submitted with your request to waive the IRB approval required under 21 CFR 314.106 as described in 21 CFR 312.120.

7. 21 CFR 312.120 describes the information required for acceptance of foreign clinical trial data in a New Drug Application under 21 CFR 314.106. Please clarify where in the NDA each of the required elements is located.

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

Sincerely,

{See appended electronic signature page}

Kim J. Robertson
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluations and Research

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/s/

KIM J ROBERTSON
10/04/2013



NDA 204630

**ACKNOWLEDGE RESUBMISSION
AFTER REFUSE-TO-FILE**

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

Dear Ms. Clara Li:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act in response to our October 11, 2012, refusal to file letter for the following:

Name of Drug Product: Methylene Blue Injection

Date of Application: September 13, 2013

Date of Receipt: September 13, 2013

Our Reference Number: NDA 204630

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 12, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the 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>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was

amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 204630** submitted on September 13, 2013, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3691.

Sincerely,

{See appended electronic signature page}

Ebla Ali Ibrahim, M.S.
Lead Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

EBLA ALI IBRAHIM
09/27/2013



PIND 118156

MEETING MINUTES

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

Dear Ms. Li:

Please refer to your Pre-Investigational New Drug Application (PIND) file for methylene blue injection.

We also refer to the teleconference between representatives of your firm and the FDA on May 24, 2013. The purpose of the meeting was to discuss the prospective collection and analysis plan for retrospective data and your planned New Drug Application.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Sherry Stewart, Regulatory Project Manager at (301) 796-9618.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-IND

Meeting Date and Time: May 24, 2013, 11:00 AM to 12:00 PM EST
Meeting Location: Teleconference

Application Number: Pre-IND 118156
Product Name: Methylene blue injection

Indication: Treatment of acquired methemoglobinemia
Sponsor/Applicant Name: Provepharm

Meeting Chair: Albert Deisseroth, MD, PhD
Meeting Recorder: Sherry Stewart, PharmD

FDA ATTENDEES

OFFICE OF NEW DRUGS

Sally Loewke, MD, Director for Guidance and Policy (Acting)

OFFICE OF NEW DRUGS/OFFICE OF HEMATOLOGY AND ONCOLOGY
PRODUCTS/DIVISION OF HEMATOLOGY PRODUCTS

Ann T. Farrell, MD, Director

Albert Deisseroth, MD, PhD, Clinical Team Leader

Donna Przepiorka, MD, PhD, Clinical Reviewer

Sherry Stewart, PharmD, Regulatory Project Manager

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL
PHARMACOLOGY/ DIVISION OF CLINICAL PHARMACOLOGY 5

Julie Bullock, PharmD, Clinical Pharmacology Team Leader

Rachelle Lubin, PharmD, Clinical Pharmacology Reviewer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF BIOSTATISTICS/
DIVISION OF BIOMETRICS V

Mark D. Rothmann, PhD, Biostatistics Team Leader

Kallapa Koti, PhD, Biostatistics Reviewer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL
PHARMACOLOGY/DIVISION OF PHARMACOMETRICS

Kevin Krudys, PhD, Clinical Pharmacology Reviewer

OFFICE OF COMPLIANCE/OFFICE OF UNAPPROVED DRUGS AND LABELING
COMPLIANCE/DIVISION OF PRESCRIPTION DRUGS

Barbara Wise, PhD, RN, CPNP, Team Leader, Marketed Unapproved Drugs Enforcement Team

Kathleen Joyce, Reviewer, Marketed Unapproved Drugs Enforcement Team

SPONSOR ATTENDEES

PROVEPHARM

Michel Féraud, PhD, CEO

Emilie Huyghues des Etages, R& D Manager

Caroline Benkemoun, Regulatory Affairs Manager

Severine Pelletier, Regulatory Affairs Manager

Consultants:

[REDACTED] (b) (4)

Clara Li, MS, Vice President, Regulatory Strategic Development, Clinipace

[REDACTED] (b) (4)

1.0 BACKGROUND

On August 13, 2012, Clinipace, the US Agent for Provepharm, submitted a 505(b)(2) New Drug Application, NDA 204630, for methylene blue injection for the treatment of methemoglobinemia. On October 11, 2012, after a preliminary review, the Food and Drug Administration (FDA) refused to file the application based on clinical and clinical pharmacology issues. On November 6, 2012, Clinipace/Provepharm requested a formal meeting to discuss the issues cited in the Refuse to File letter. A Type A meeting was held on December 18, 2012. On March 21, 2013 Clinipace/Provepharm requested a second meeting under NDA 204630. FDA requested that Clinipace/Provepharm open a pre-Investigational New Drug (PIND) application for their proposed drug product and submit the meeting request to that application. PIND 118156 was established on March 28, 2013 with Clinipace/Provepharm's request for a Type B PIND meeting for the purpose of discussing the prospective collection and analysis plan for retrospective data and Provepharm's planned NDA. The meeting between Clinipace/Provepharm was held on May 24, 2013 via teleconference.

2.0 DISCUSSION

Question 1

Provepharm has designed a clinical protocol for the prospective collection and analysis of retrospective data from the patients listed in Table 3.1 who received [REDACTED] (b) (4) Injection, 0.5% for the treatment of acquired methemoglobinemia (see Appendix 8.1). In addition to the available data from the literature, Provepharm believes that the data collected with this protocol

(presented in the briefing package) are adequate to address the Division's RTF comments regarding:

- the establishment of an endpoint to predict a clinical benefit or clinically meaningful treatment effect,
- the establishment of the incidence and severity of risks,
- the definition of a protocol of administration of (b) (4) Injection, 0.5%, and
- the use of these data to support the development of the package insert.

Does FDA agree that the data prospectively collected on (b) (4) Injection, 0.5% with the proposed protocol, will likely address the RTF comments?

FDA Preliminary Response: No. We have identified several deficiencies and other concerns regarding the current version of the protocol.

- a) Please provide a description of how you have protected against bias in ascertaining these cases. It is appropriate to consider all patients accrued to the compassionate use protocol for treatment of acquired methemoglobinemia in France, but the strategy to select other cases on the basis of a literature search would suffer from publication bias, i.e., only success stories are published, thereby potentially over estimating the treatment effect. Please discuss why you did not send a request for numbers of patients treated with your drug at all hospitals to which your drug was distributed. Quantification of responses to this request would greatly facilitate an understanding of potential biases in your study.
- b) You have not identified an endpoint that denotes clinical benefit in the treatment of acquired methemoglobinemia. We refer you to the publications of Guay (Anesth Analg.2009;108:837) and Bucarechi et al (J Pediatr (Rio J) 2000;76:290) which show that if the inciting agent is discontinued, methemoglobin levels fall with supportive care alone. Consequently, one could not infer that there was a treatment effect by the observation that the methemoglobin level normalized at some time after treatment with your drug. We recommend that the primary endpoint be the proportion of subjects with at least a 50% decrease in methemoglobin at one hour after infusion of your drug. We also recommend that you identify as secondary endpoints the change in the key clinical signs that trigger the intervention (e.g., tachypnea, tachycardia, altered mental status). The protocol should also include a more detailed plan for statistical analyses of these endpoint and the statistical basis for any inferences to be made.
- c) Please clarify how adverse events will be graded. We recommend categorization by WHO or NCI CTCAE criteria.
- d) It does not appear that the case report form will allow for collection of adequate details regarding the treatment and treatment outcomes. Please clarify how you will collect the details of adverse events, including grade, relation to study drug, and seriousness. Please clarify where the methodology used for measurement of methemoglobin levels is identified. Regarding all demographic, treatment, clinical, safety and laboratory data, we refer you to "Study Data Standard Resources" to assist in the development of electronic datasets that would be acceptable for submission in an NDA. This web site is available at:

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

- e) Please describe how you confirm and document that your drug was used for treatment of the proposed patients for the study.

Discussion:

- a) Provepharm clarified that they have contacted as many hospitals as possible to identify patients that have been treated with (b) (4).
- b) Provepharm agreed to change the primary endpoint and that secondary endpoints will be added. It is not necessary to include cyanosis as a secondary endpoint.
- c) and d) FDA encouraged Provepharm to grade the events as mild, moderate and severe. Provepharm agreed.
- e) The compassionate use program in France is strictly regulated and the cases are clearly documented as using (b) (4). Regarding the cases in Taiwan, the product was provided by Provepharm to the Taiwan Poison Center.

Question 2

Data on cardiac conduction issues were missing in the submitted NDA. Thus, Provepharm searched for more information to address the FDA concerns with the following result.

Cardiac effects have been monitored at least:

- during the treatment of methemoglobinemia of 10 patients with (b) (4) Injection, 0.5% in France, and
- in the Cosmo Pharmaceuticals clinical study to evaluate in healthy volunteers the safety and the bioavailability in 22 patients with (b) (4) drug visualization (indication: chromoendoscopy). No adverse cardiac conduction effects were observed. Data will be presented in the briefing package.

Does FDA agree that this data will likely address the QT/QTc interval questions raised in the RTF letter?

FDA Preliminary Response:

No, these data will not address the potential of your drug to prolong the QT/QTc interval because the ECGs are not available for the patients treated in France and the ECGs collected in the Cosmo Pharmaceuticals clinical study are collected at a time (Day 5) when systemic concentration of methylene blue is minimal or nonexistent.

Discussion:

FDA stated that the requirement to characterize QT risk must be met. FDA recommended a single study to characterize the QT risk and PK study to characterize the bioavailability of the product in healthy volunteers. This is an important study to establish the safety of the product.

Question 3

Provepharm intends to write study reports for the new data on the use of (b) (4) following, as much as possible, the ICH GCP requirements for Clinical Study Reports (ICH Guideline E6(R1), 1996). The following report will be provided in the NDA:

- Summary Report on the Use of (b) (4) Injection, 0.5% for the Treatment of Methemoglobinemia (13 cases from France and Taiwan). Other relevant information will be summarized in Module 2.5 and 2.7 of the NDA.

Does FDA agree that this approach is appropriate?

FDA Preliminary Response: See the response to Question 1.

No discussion occurred.

Question 4

Provepharm has information on a recent study performed by Cosmo Pharmaceuticals (see Table 3.4) with (b) (4) drug substance used in the manufacture of modified release tablets in comparison to methylene blue injection USP 1%.

This PK study entitled "An open labeled, randomized study to evaluate in healthy volunteers the bioavailability of methylene blue MMX 200 mg modified release tablets administered as single ascending doses in comparison to methylene blue 1% vials administered as a single IV dose of 100mg" was conducted where the PK criteria for evaluation were Tmax, Cmax, AUC0-t, AUC0-∞, t1/2 (terminal elimination half-life), MRT, Fabs, XU0-t and %XU0-t of blood and urine.

This information is provided in the Briefing Package.

Provepharm believes this data will adequately address the Division's comments regarding methylene blue PK and that no other PK data would be needed.

Does FDA agree that this PK data will address FDA's concerns identified in the RTF letter?

FDA Preliminary Response: No. Although you have provided PK parameter results following the administration of methylene blue 1% IV (Repici et al), this does not resolve the observed discrepancy of PK data seen from other publications (Peter et al, Walter-Sack et al). We continue to recommend that you characterize the PK of your product using validated methods and submit the full study report with your NDA.

Discussion:

Since the drug product used in literature cannot be identified, that information will be viewed as supportive only. A biowaiver will need to be submitted to waive an in vivo bioequivalence study between Methylene Blue USP and (b) (4)

Question 5

Safety data have been collected from 291 patients:

- 40 patients exposed to (b) (4) Injection, 0.5% in France and Taiwan (see Table 3.3).
- 251 patients exposed to (b) (4) drug substance (see Table 3.4).

Provepharm intends to submit this safety data to demonstrate that (b) (4) safety profile is comparable to the known profiles of other methylene blue products. Therefore, Provepharm believes that we may adopt the defined safety profiles from these case reports, clinical studies, publications, and other public data on methylene blue.

Does FDA agree that this safety data will likely address FDA's concerns identified in the RTF letter?

FDA Preliminary Response: See the response to Question 1.

No discussion occurred.

Additional Clinical Comments:

1. Please clarify under what authority (b) (4) was used in Taiwan (investigational or marketed product).
2. Please confirm that the sites from which you collected data will be available for inspection.

Discussion:

Provepharm said that these sites would be available for inspection.

3. In section 8.1 of the protocol you indicate that no ethical consideration is required for the proposed protocol. If the results of this study are to be submitted to support an NDA, 21 CFR 50.3(c) requiring IRB oversight will apply. You may consider requesting a waiver of the IRB requirements, but this is generally not approved unless there is an alternate acceptable mechanism for ensuring protection of the rights and welfare of the subjects, such as review and approval by an ethics committee that operates in accordance with GCP.

3.0 PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

5.0 ATTACHMENTS AND HANDOUTS

No attachments were used or distributed at this meeting.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHERRY A STEWART
05/29/2013

ALBERT B DEISSEROTH
05/29/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204630

MEETING MINUTES

Provepharm SAS
Attention: Clara C.Li
VP Regulatory & Strategic Development
Clinipace Worldwide RSD, US Agent for Provepharm SAS
4840 Pearl East Circle, Suite 201E
Boulder, CO 80301

Dear Ms. Li:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylene Blue.

We also refer to the meeting between representatives of your firm and the FDA on December 18, 2012. The purpose of the meeting was to discuss the refusal to file issues and additional Agency comments provided in the refuse to file letter.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Sherry Stewart, Regulatory Project Manager at (301) 796-9618.

Sincerely,

(See appended electronic signature page.)

Albert Deisseroth, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Guidance
Meeting Date and Time: December 18, 2012
Meeting Location: FDA, White Oak Campus, Building 22, Room 1417
Application Number: NDA 204630
Product Name: Methylene blue
Indication: Acquired methemoglobinemia
Sponsor/Applicant Name: Provepharm SAS
Meeting Chair: Albert Deisseroth, MD
Meeting Recorder: Sherry Stewart, PharmD

FDA ATTENDEES

OFFICE OF NEW DRUGS

Sally Loewke, MD, Director for Guidance and Policy (Acting)

OFFICE OF NEW DRUGS/OFFICE OF HEMATOLOGY AND ONCOLOGY
PRODUCTS/DIVISION OF HEMATOLOGY PRODUCTS

Ann T. Farrell, MD, Director
Albert Deisseroth, MD, Clinical Team Leader
Donna Przepiorka, MD, Clinical Reviewer
Sherry Stewart, PharmD, Regulatory Project Manager

OFFICE OF ORPHAN PRODUCTS DEVELOPMENT

Jeff Fritsch, RPh, Drug Designation Team

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

Cristina Makela, Regulatory Project Manager

NDA 204630
Meeting Minutes
Products
Type A Meeting

Office of Hematology and Oncology Products
Division of Hematology

OFFICE OF PHARMACEUTICAL SCIENCE/OFFICE OF NEW DRUG
QUALITY ASSESSMENT/DIVISION OF NEW DRUG QUALITY
ASSESSMENT I

Janice Brown, PhD, Chemistry Reviewer

OFFICE OF PHARMACEUTICAL SCIENCE/OFFICE OF NEW DRUG
QUALITY ASSESSMENT/DIVISION OF NEW DRUG QUALITY
ASSESSMENT I/BRANCH III

Ted Chang, PhD, Chemistry Reviewer

SPONSOR ATTENDEES

PROVEPHARM SAS

Michel Feraud, PhD, CEO, Provepharm

Emilie Huyghues des Etages, R&D Manager, Provepharm

Caroline Benkemoun, Regulatory Affairs Manager, Provepharm

Clara Li, Vice President, Regulatory and Strategic Development, Clinipace

(b) (4) Consultant, (b) (4)

(b) (4), Senior Regulatory consultant, (b) (4)

(b) (4)

(b) (4) Regulatory Attorney, (b) (4)

1.0 BACKGROUND

On August 13, Provepharm submitted a New Drug Application (NDA) under section 505 (b)(2) of the Federal Food, Drug and Cosmetic Act for (b)(4) (methylene blue) Injection 0.5%, for the treatment of acquired methemoglobinemia.

On October 11, 2012, after a preliminary review, the Food and Drug Administration (FDA) sent Provepharm a Refusal To File (RTF) letter under 21 CFR 314.101(d) based on clinical issues. P

Provepharm requested a meeting on November 5, 2012. A Type A meeting was scheduled for December 18, 2012 to discuss the issues cited in the RTF letter.

2.0 DISCUSSION

Preamble:

In response to your comments regarding the best regulatory path forward for your NDA, you have several options:

- *You may resubmit your NDA to the same NDA file using the same NDA number. The cover letter of your resubmission should state: "Resubmission after Refuse to File". This is the preferred approach. In addition, after consultation with User fee staff, if you applied for a small business waiver, you would only be eligible to request another waiver if you resubmitted your application to the original application that was Refuse to file.*
- *You may withdraw your NDA and submit a new NDA.*
- *You may request to File the application over protest after the Informal Conference per 21 CFR 314.101(a)(3).*

Clinical Questions

1. Provepharm has demonstrated through chemical/PK comparisons and through nonclinical studies that (b)(4) Injection may be considered to be equivalent to other methylene blue injections currently on the market. Therefore, Provepharm believes that we may adopt the defined safety and efficacy profiles from the publications and other public data on methylene blue. (See discussion in Section 3.1.2)

Does FDA agree?

***Preliminary Response:** No. There are no methylene blue products approved for a marketing indication to treat patients. Your proposal is to market a 0.5% solution of methylene blue. The publications you provided did not identify the source of the Methylene Blue used in the clinical studies. Second, most if not all of the literature references did not identify the percent solution used. You would have to justify that*

your 0.5% methylene blue product is safe and effective based on the literature and therefore, there would be no need for a clinical study.

Discussion: *The applicant stated that the reason for using the 0.5% concentration is due*

(b) (4)

FDA stressed the need for establishing a link between the scientific literature that the company has provided and their product. FDA recommended a prospectively defined retrospective study looking at AAPCC data. The sponsor spoke about the 150 year history of empirical usage of the product giving the assumption of safety and efficacy. FDA discussed the need for the applicant to provide the agency with clinical data that would be necessary to develop a label that provides clinical guidance to practitioners on the use of the drug including repeat dosing, and the need to demonstrate clinical benefit. The company will provide information on the products that were used to treat patients in the databases used to support the application. The applicant offered to provide the agency with a report on a compassionate use trial of their product that was given to patients with acquired and congenital methemoglobinemia in France.

The QT issue will need to be addressed. The sponsor noted there was no evidence in the literature to indicate cardiac issues with methylene blue. FDA noted that there was also nothing in the literature to demonstrate that there are no cardiac issues associated with the drug.

FDA recommended that the sponsor develop a proposal and submit it for Agency review.

2. Methemoglobinemia is an orphan indication and may be considered an "ultra-orphan". Provepharm believes it is not possible to conduct a prospectively designed, adequate and well-controlled study because of the rarity of the patient population. (See discussion in Section 3.1.4.2).

Does FDA agree?

Preliminary Response: *No. The Agency believes that the collection of efficacy and safety data from a single arm trial using your product may be sufficient to support submission of an NDA. You may wish to consider Alexion's approach which enabled marketing for Soliris for atypical Hemolytic Uremic Syndrome.*

3. Provepharm has presented prospective and retrospective data from children, adults, and from the American Association of Poison Control Centers (AAPCC) (see discussions in Sections 3.1.4.3). Provepharm also cites the guidance entitled "Guidance for FDA Staff and Industry, Marketed Unapproved Drugs—Compliance Policy Guide" (CPG) related to The Unapproved Drugs Initiative. Section C, Special Circumstances – Newly Approved (see Section 3.1.4.5).

Provepharm believes the data provided in the literature and from the AAPCC adequately address FDA comments regarding requiring adequate and well-controlled trials.

Does FDA agree?

Preliminary Response: *No. As we stated in the Refuse to File letter, we do not believe that the analysis of the reports to the American Association of Poison Control Centers and the four publications submitted are adequate and conform to the requirements as described in 21.CFR. 314.126. See also the response to Question 1 above.*

4. Provepharm believes the information presented in Section 3.2.1 adequately addresses the FDA's RTF comment 2a regarding the establishment of an endpoint to predict a clinical benefit or clinically meaningful treatment effect.

Does FDA agree?

Preliminary Response: *No, you have not provided an adequate rationale for your dosing schedule and a quantifiable outcome that reflects a clinical benefit. We recommend that you consider a decrease in methemoglobin of at least 50% and concurrent reduction in clinical signs of methemoglobinemia.*

5. Provepharm believes the information presented in Section 3.2.2 adequately addresses the FDA's RTF comment 2b regarding the establishment of the incidence and severity of risks.

Does FDA agree?

Preliminary Response: *No. You need to provide data to support the quantification of safety risks. A prospective trial will enable a better understanding of the efficacy and safety of your product.*

6. Provepharm has provided responses to the FDA's non-RTF Additional Comments and the FDA's PreNDA Submission Meeting Minutes Clinical Pharmacology Comments in Section 4 and Section 5, respectively, of this document.

Does FDA have any comments?

Preliminary Response:

- *You have not adequately addressed the QT/QTc interval prolongation potential of your product in humans. We recommend submitting your overall QT risk evaluation plan, along with cardiac safety data for FDA review to determine whether a QT study is needed. For more information, refer to the Guidance for Industry entitled E14 Clinical Evaluation of QT/QTc Interval Prolongation.*
- *Studies (b)(4) submitted in Appendices 1 and 2 are not adequate. Full study reports must be included with the revised NDA.*
- *You have proposed labeling recommendations (b)(4) This is not acceptable. A clinical study needs to be conducted to support recommending (b)(4) in labeling.*

- *You have acknowledged that conflicting pharmacokinetic (PK) data (e.g. half-life, analytical methods) exist in published literature. Whether these findings can be associated with your product is yet to be determined and will be a review issue. We continue to recommend that you characterize the PK of your product using validated methods and submit the full study report with your NDA.*
- (b) (4)
[REDACTED]
We encourage you to simulate the expected exposure for doses in children by incorporating known significant covariates (e.g., the organ maturation, the body weight, etc). Since your product is renally eliminated, younger children with immature renal function may have higher exposure seen in adults. An indication in pediatric patients without pediatric efficacy or pediatric PK data will be unlikely.
- *Your product has been shown to inhibit CYP1A2, 2B6, 2C9 and 2C19 in-vitro. The clinical impact will need to be addressed. We recommend performing in-vivo studies or PBPK modeling.*
- *Provide in-vitro CYP induction results with your revised NDA.*

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our November 13, 2012 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>

4.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts were used at this meeting

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALBERT B DEISSEROTH
01/03/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND113942

MEETING MINUTES

Regulus Pharmaceutical Consulting, Inc. – U.S. Agent for Provepharm SAS.
Attention: Alyssa Carter
Senior Manager Regulatory Affairs
4840 Pearl East Circle, Suite 201E
Boulder, CO 80301

Dear Ms. Carter:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Methylene Blue Injection.

We also refer to the teleconference between representatives of your firm and the FDA on January 30, 2012. The purpose of the meeting was to gain FDA agreement on content of complete application, including data to accept the NDA filing for review, and data for an approvable NDA.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lara Akinsanya, Regulatory Project Manager at (301) 796- 9634.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, M.D., Ph.D.
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

Reference ID: 3080022

Reference ID: 3918487



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-IND
Meeting Date and Time: January 30, 2012; 12:00PM – 1:00PM ET
Meeting Location: White Oak Building 22, Conference Room: 1313
Application Number: 113942
Product Name: Methylene Blue Injection
Indication: For the treatment of methemoglobinemia
Sponsor/Applicant Name: Provepharm (Regulus Pharmaceutical – US Agent)

Meeting Chair: Kathy Robie Suh, M.D., Ph.D.
Meeting Recorder: Lara Akinsanya, M.S.

FDA ATTENDEES

Division of Hematology Products (DHP)

Ann Farrell, M.D., Acting Division Director
Kathy Robie-Suh, MD, Clinical Team Leader
George Shashaty, M.D., Medical Officer
Haleh Saber, Ph.D., Supervisory, Pharmacologist
Brenda Gehrke, Ph.D., Toxicologist
Lara Akinsanya, M.S., Regulatory Health Project Manager

Office of Clinical Pharmacology (OCP)

Julie Bullock, PharmD, Clinical Pharmacology Team Leader
Joseph A. Grillo, Pharm.D., Clinical Pharmacology Reviewer

Office of New Drug Quality Assessment (ONDQA)

Janice Brown, Ph.D, Chemistry Manufacturing & Controls Lead

Office of Biostatistics, Division of Biometrics V (DBV)

Qing Xu, Ph.D., Statistician

Division of Data Management Services & Solutions

Valerie Gooding, Regulatory Information Specialist

Division of Medication Error Prevention and Analysis

Kimberly DeFronzo, R.Ph., M.S., MBA, Safety Evaluator

IND 113942
Meeting Minutes
Type B/PIND
January 30, 2012

Office of Hematology and Oncology Products
Division of Hematology Products

SPONSOR ATTENDEES

Name	Title	Discipline	Affiliation
Jeff Kaufman	R & D Director	CMC	Provepharm SAS
S��verine Pelletier	Project Manager / Regulatory Affairs	Clinical	Provepharm SAS
(b) (4)	Senior Consultant	Clinical	(b) (4)
(b) (4)	Principal Consultant	Nonclinical	(b) (4)
(b) (4)	Affiliate Consultant	Regulatory	(b) (4)
(b) (4)	Regulatory Consultant	CMC	(b) (4)
Alyssa Carter	Regulatory Consultant / US Agent	Regulatory	Regulus Pharmaceutical Consulting

1.0 BACKGROUND

Provepharm requested a type B, Pre-BLA meeting with FDA on November 17, 2011, to gain FDA agreement on content of complete application, including data to accept the NDA filing for review, and data for an approvable NDA. On December 1, 2011, FDA granted Provepharm's meeting request.

On January 26, 2012, FDA emailed Provepharm preliminary responses to the question contained in the meeting information package dated December 22, 2011.

On January 29, 2012, Provepharm provided the following written response to FDA preliminary responses received for (b) (4).



Labeling of Methylene Blue injection (“(b) (4) injection”)

The Sponsor requests (b) (4)
The FDA has responded by stating;

“You have not adequately justified your proposed (b) (4)

”

(b) (4)

(b) (4)

(b) (4)

The above Sponsor’s written responses were discussed at the teleconference on January 30, 2012.

2. DISCUSSION

2.1. Administrative

Question 1:

There are currently no methylene blue products approved by FDA or listed in the Orange Book as a reference product. The Sponsor intends to submit a 505(b)(2) application using literature to support the proposed indication, but will not have a reference listed product for the application. Does the Agency agree with this proposed filing strategy?

FDA Response to Administrative Question 1:

A 505(b)(2) application appears to be appropriate because intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval (other than for a few nonclinical studies that you have performed).

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrtms/dockets/dailys/03/oct03/162303/01p-0323-pdn0001-vol1.pdf>).

You also must establish that reliance on the studies described in the literature is scientifically appropriate. You should consider that your application must include all the substantial information needed to adequately direct the safe use of your product for the desired indication. This includes, but is not limited to, justification and support for recommended dose and administration (including any repeated dosing), justification and support for each desired specific indication, identification of adverse drug reactions, and evaluation of potentially important drug interactions. Data to support efficacy and safety should be derived from adequate and well-controlled studies. Primary data to support efficacy and safety claims are desirable. The submission should include an integrated analysis and discussion of the supporting information.

Note that the information in your background package does not appear to adequately address the need for information to guide dosing in particular clinical settings.

Also, all required CMC information for a NDA should be submitted in the application.

Adequacy of the submitted information to support approval of the application for the indication is a review issue. Note that you must submit all publications on which you intend to rely and not just summaries of the literature.

Discussion:

The FDA reiterated its response to this question emphasizing the need for evidence of efficacy and safety from adequate and well-controlled studies and that the adequacy of what is submitted will be a review issue. The sponsor indicated that it understood.

Question 2:

The 505(b)(2) application will be filed with a reference to study literature for the non-clinical and clinical data for the application. Does the Agency agree with this proposed plan?

FDA Response to Administrative Question 2:

See FDA Response to Administrative Question 1.

Also see FDA Response to Nonclinical Question 1.

Discussion:

No discussion occurred.

Question 3:

The Sponsor plans to submit the NDA using the electronic Common Technical Document (eCTD) format with all specifications that are stated on the CDER eCTD specifications website. Does the Agency concur with the proposed plan for electronic submission of the NDA?

FDA Response to Administrative Question 3:

Yes. However, we recommend that if you have never submitted an eCTD application, you should submit an eCTD sample prior to submitting an actual eCTD application. To submit an eCTD sample, please follow the instructions stated on the eCTD sample website, located at:-

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>. Also, when providing hypertext links in documents, it can be designated by rectangles using thin lines or by blue text. A consistent method of designating links in a document, avoids confusion.

Best Available
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Discussion:

No discussion occurred.

Question 4:

Sections for a 505(b)(2) application that are not relevant to this product will be included in the eCTD to show that they were considered but are not applicable. Does the Agency agree with this proposal to include sections that are not relevant?

FDA Response to Administrative Question 4:

No. It is not necessary to include sections that are not applicable when submitting in eCTD format.

Discussion:

No discussion occurred.

Question 5:

The non-clinical and clinical literature referenced in the 502(b)(2) application will be located in Modules 4.3 and 5.4 Literature, as study tagging files are not relevant for reference based reports. Does the Agency agree with this proposal for placement of the references?

FDA Response to Administrative Question 5:

Yes. Modules 4.3 and 5.4 are designated for nonclinical and clinical literature references without the use of study tagging files.

However, in Module 5, where the clinical evidence for efficacy and safety is presented, you should provide links to the specific pages in data/reports/papers, etc. that are being used to support your findings and desired claims for efficacy and safety.

Also you should hyperlink non-clinical summaries in Module 2 to the references located in Module 4.3 or to the study reports in Module 4.

Discussion:

No discussion occurred.

2.2. Labeling

Question 1:

[REDACTED] (b) (4)

FDA Response to Labeling Question 1:

No. [REDACTED] (b) (4)

Discussion:

No discussion occurred.

Question 2:

[REDACTED] (b) (4)

FDA Response to Labeling Question 2:

It is premature to discuss [REDACTED] (b) (4) for [REDACTED] (b) (4) until after a decision is made on the approval of your [REDACTED] (b) (4) NDA application.

Discussion:

No discussion occurred.

Question 3:

[REDACTED] (b) (4)
[REDACTED] Does the Agency agree that the dosage and administration is appropriate?

FDA Response to Labeling Question 3:

Support for your proposed dosing and administration should be included in your application as described in the response to Administrative Question 1. Acceptability will be a review issue.

Additionally:

(b) (4)

- You have not adequately addressed dosing of Methylene Blue in the presence of systemic disease that may affect drug exposure (e.g., renal impairment).

Your submission should include your proposed labeling in PLR format as specified in 21 CFR 201.56(d) and 201.57. You should include a clean version (pdf and Word) and an annotated version providing references to the location of the supporting information in the application for each labeling statement.

Discussion:

(b) (4)

Upon submission of the NDA, the pediatric information/data in the application would be discussed with the Agency's Pediatric team as well as within the review division during the review.

2.3. Chemistry Manufacturing and Controls (CMC)

Question 1:

Are the tests and methods outlined in the drug substance specification adequate for the control of Methylene Blue, USP?

FDA Response to CMC Question 1:

The specification includes acceptance criteria and analytical methods. Those items including the analytical methods validation are review issue and will be reviewed when the NDA is received.

Discussion:

No discussion occurred.

Question 2:

Are the tests and methods outlined in the drug product specification adequate for the control of (b) (4) Injection, 0.5%?

FDA Response to CMC Question 2:

The specification includes acceptance criteria and analytical methods. Those items including the analytical methods validation are review issue and will be reviewed when the NDA is received.

Discussion:

No discussion occurred.

Question 3:

The current USP monograph for methylene blue allows for uncontrolled levels of (b) (4) and certain unidentified impurities, which are typically present in commercially available Methylene Blue, USP drug substance.

The drug substance manufacturing process by Provepharm provides for a (b) (4) that confers a much safer drug substance that is in conformance with the current Ph .Eur. monograph and ICH requirements. (b) (4). Furthermore, Provepharm has confirmed the ability to manufacture this product commercially.

(b) (4)

(b) (4)

FDA Response to CMC Question 3:

ONDQA will make an assessment on the level of the (b) (4) based on the drug product quality; i.e., batch data on level of (b) (4), and safety information available at the time of the NDA submission. ONDQA does not advocate for or against Sponsor-initiated changes to USP. ONDQA makes recommendations to USP based on the specific scientific and regulatory merits of each case.

Discussion:

No discussion occurred.

Question 4:

Are there any other comments or recommendations relative to the proposed CMC data package intended to be submitted in the NDA?

FDA Response to CMC Question 4:

All the required items based on CFR and CMC guidance should be followed for the NDA submission. Clarify whether you intend to submit a DMF with drug substance CMC information or provide the drug substance information in the NDA.

Discussion:

No discussion occurred.

2.4. Nonclinical

Question 1:

The Sponsor will submit a data package containing, amongst others, a summary of the literature, NTP study reports and the following Provepharm-sponsored study reports to supplement the available literature data:

- *in vitro bacterial reverse mutation studies*
- *MTD and 4 week dog toxicity studies*
- *zebrafish acute toxicity embryo-fetal development screen*
- *in vitro mitochondrial study.*

Does the Agency agree that the non-clinical study reports and literature that will be provided are sufficient to fulfill the requirement for NDA approval?

FDA Response to Nonclinical Question 1:

The non-clinical study reports and literature appear sufficient. However, the final decision on the adequacy of the study reports and literature to support the NDA will be a review issue.

In the literature there appears to be evidence that methylene blue produces developmental toxicity, however, developmental toxicity was not observed in the NTP studies. Provide a justification for the doses used in the embryo-fetal development studies based on the comparison of these doses/exposures to the human dose/exposure

or based on other criteria (e.g. a maximum feasible dose, an MTD, etc). As stated under our response to Administrative Question 1, you must submit all publications on which you intend to rely and not just summaries of the literature.

Discussion:

No discussion occurred.

2.5. Clinical Development and safety

Question 1:

[REDACTED] (b) (4)

(b) (4) Does the Agency agree that a pediatric data package from the literature is sufficient and that no additional pediatric studies are warranted?

FDA Response to Clinical Question 1:

It appears probable that the pediatric population will be significant target for the clinical use [REDACTED] (b) (4). 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.

[REDACTED] (b) (4)
[REDACTED] (b) (4)
[REDACTED] (b) (4)

Note also FDA response to Labeling Question 3. The sufficiency of the data provided in the NDA submission to determine the efficacy and safety of the use of [REDACTED] (b) (4) in pediatric patients is a review issue.

If you wish to request for a waiver for pediatric studies (for part or all of the pediatric age range) your request should be submitted with the NDA. Whether or not a waiver for pediatric studies will be granted depends on the justification and supporting data submitted.

Discussion:

Please see discussion for Labeling Question 3 above.

Question 2:

The Sponsor will submit a data package containing a summary of the literature. Does the Agency agree that the literature that will be provided in Module 5 is sufficient to fulfill the requirement for NDA approval?

FDA Response to Clinical Question 2:

See FDA Response to Administrative Question 1. The sufficiency of the data to be provided in the NDA submission to determine the efficacy and safety of (b) (4) is a review issue.

Also, it appears from the submitted information/data that methylene blue is a narrow therapeutic index drug that may be associated with a number of adverse reactions and may increase, rather than decrease, the concentration of methemoglobin. In addition, the dose range in the submitted tables is broad. Therefore, close scrutiny will be paid to the recommended dosing.

See FDA Response to Labeling Question 3 and the following:

- The conflicting results from the literature references you provided regarding the adult pharmacokinetics and urinary elimination of methylene blue will make a regulatory determination unlikely without additional confirmatory information. A carefully designed mass balance study that includes an analysis of the PK profile (b) (4) in healthy adult volunteers may provide this confirmation.
- Sufficient detail regarding the design and results of your in vitro CYP inhibition study was not provided to FDA. We note your general comment that your in vitro CYP inhibition study shows that your product is a potent inhibitor of CYP 1A2, 2B6, 2C9 and 2C19. Based on your assessment, additional in vivo interaction studies may be required pursuant to our guidance for Industry titled "Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling." This can be found at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf>
- Sufficient detail regarding the design and results of your in vitro CYP induction study was not provided to FDA. Please verify whether or not (b) (4) induced the CYP pathways studied.
- You have not adequately addressed the potential for your drug to inhibit the P-gp transporter system.

- You have not adequately addressed the potential QT/QTc interval prolongation (see ICH E14) by your drug.

Discussion:

No discussion occurred.

Question 3:

The Sponsor will mitigate any risk to the patients with detailed dosing instructions and safety information to be provided in the labeling. Therefore the Sponsor does not believe any further REMS strategy is necessary for this product. Does the Agency agree?

FDA Response to Clinical Question 3:

At this time, the Agency has insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

We remind you that a proposed REMS will not be approved as a REMS unless and until the FDA determines that it is required to ensure that the benefits of the drug outweigh the risks and that it meets the FDAAA criteria.

Discussion:

No discussion occurred.

2.6. Additional Comment

We encourage you to submit your requests for FDA review of your proposed proprietary name during the IND phase of your drug development program. The content requirements for such a submission can be found in the draft Guidance for Industry, entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>). Please note that such a request can be made as early as at the end of phase 2 of the IND review process.

Discussion:

No discussion occurred.

3.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

5.0 ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

6.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

7.0 ISSUES REQUIRING FURTHER DISCUSSION

None

8.0 ACTION ITEMS

None

9.0 ATTACHMENTS AND HANDOUTS

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHY M ROBIE SUH
01/31/2012

Reference ID: 3080022

Reference ID: 3918487