CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204630Orig1s000

CHEMISTRY REVIEW(S)

Recommendation:
NDA: Approval

NDA 204630
Review #2

Drug Name/Dosage Form	Methylene Blue Injection/ Injection, solution
Strength	0.5% (mg/mL)
Route of Administration	IV
Rx/OTC Dispensed	Rx
Applicant	Provepharm SAS
US agent, if applicable	Clara Li

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sithamalli Chandramouli	
Drug Product	Anamitro Banerjee	CDER/OPQ/ONDP/DNDP I/Branch II
Process	Sung Kim	
Microbiology	Jonathan Swoboda, PhD, RAC Dupeh Palmer, PhD	DMA/Branch 3
Facility	Rebecca Dombrowski	
Biopharmaceutics	Banu Zolnik/Angelica Dorantes	Biopharmaceutics/Branch 1
Regulatory Business Process Manager	Rabiya Laiq	CDER/OPQ/OPRO/B1
Application Technical Lead	Anamitro Banerjee	CDER/OPQ/ONDP/DNDP I/Branch II
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	N/A	

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: None

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	(b) (4)
IND	(b) (4)	(b) (4)

2. CONSULTS: None

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC point of view. No outstanding CMC deficiencies are identified at this time.

1. Summary of Complete Response issues:
   None

2. Action letter language, related to critical issues such as expiration date:
   The applicant has provided 18 month stability data under long term storage conditions. The applicant requested (b) (4) months shelf life. However, 30 month shelf life was found acceptable at the time as per ICH Q1E guidelines. As the applicant did not provide any additional drug product stability data in this resubmission, a shelf life of 30 months may granted at this time.

3. Benefit/Risk Considerations:
   None

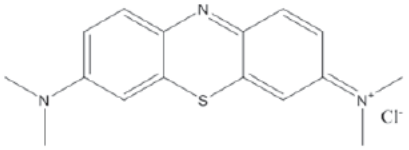
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

1. Chemical Name or IUPAC Name/Structure: 3,7 – bis(Dimethylamino)-phenazathionium chloride



2. Properties/CQAs Relevant to Drug Product Quality: The drug substance prepared using the described route in this Class 2 resubmission, is (b) (4) . As a consequence, (b) (4)

3. List of starting materials: (b) (4)

4. Suppliers of starting materials (site): (b) (4)

(b) (4)

(b) (4)

7. Container Closure: No new information was provided in this resubmission. Information submitted in the NDA and subsequent amendments has been found acceptable.
   Retest Period & Storage Conditions: The drug substance will be stored (b) (4), and the retest period is (b) (4) months.

B. Drug Product [Established Name] Quality Summary

1. Strength: 0.5%, is available in 10 mL ampules. Each ampule contains 50 mg of methylene blue (5mg/mL).
2. Description/Commercial Image: 0.5% (methylene blue) is a sterile solution intended for intravenous administration. The product is (b) (4) into ampoules and (b) (4)

(b) (4)

[redacted]

3. List of Excipients: Water for injection [redacted] (b) (4)
4. Process Selection (Unit Operations Summary):
   a. Sterilization processes of the drug product, as applicable
      The Division of Microbiology Assessment has reviewed the sterilization processes used in the commercial production of the subject, sterile drug product. This submission is recommended for approval on the basis of sterility assurance.

5. Container Closure: The primary container consists of 10 mL [redacted] (b) (4) Type I USP glass ampule. The ampules are labelled with transparent labels which report, besides the Regulatory Health Authorities approved artwork and text, also the batch number and expiry date of the batches.
   The secondary packaging container is a [redacted] (b) (4) box containing tray with 5 ampules and one Patient Information Leaflet. The secondary container is printed with all information required by the current directives
6. Expiration Date & Storage Conditions: A shelf life of 30 months may be provided based on the data submitted in the original submission. The applicant did not submit updated stability data in this review cycle. The product may be stored at [redacted] (b) (4) to 25°C (USP controlled Room Temperature)
7. List of co-packaged components:
   None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	ProvayBlue
Non Proprietary Name of the Drug Product	Methylene Blue Injection
Non Proprietary Name of the Drug Substance	Methylene Blue
Proposed Indication(s) including Intended Patient Population	treatment of pediatric and adult patients with acquired methemoglobinemia
Duration of Treatment	1 mg/kg over 5-30 minutes. Repeat dose of 1 mg/kg (if necessary)
Maximum Daily Dose	Not determined
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

- **BCS Classification:**
  - Drug Substance:

  The Applicant did not identify the BCS classification.
  - Drug Product:

  The Applicant did not identify the BCS classification.

- **Biowaivers/Biostudies**
  - **Biowaiver Requests**

  There is no biowaiver request since the Applicant conducted the PK study.
  - **PK studies**

  The Applicant conducted a single-dose, parallel BE study of methylene blue intravenous injection conducted in healthy volunteers. The Office of Clinical Pharmacology will review this study.
  - **IVIVC**

  The proposed drug product is solution for injection therefore there is no IVIVC established.

E. Novel Approaches

None

F. Any Special Product Quality Labeling Recommendations

None

G. Life Cycle Knowledge Information (see Attachment A)

None

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Anamitro Banerjee -S

Digitally signed by Anamitro Banerjee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000423276, cn=Anamitro Banerjee -S
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(b) (4)

[redacted]

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

OPQ/OPF/DIA: An inspection at Cenexi was recommended and performed 3/29-4/06/2016. Results of the inspection support approval of this site under this application-resubmission. All other sites are recommended for approval based on file/site review.

Date: 04/06/2016
Rebecca Dombrowski

Secondary Review Comments and Concurrence:

Concur with inspection findings based on expedited review of the field recommendation and a t-con with the inspection team.

Recommendation: **APPROVE**

Derek Smith, Ph.D., 4/6/2016

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

This Class 2-Resubmission of 505(b)(2) NDA 20460 for (b) (4) Methylene Blue solution, 0.5% for IV Injection, provides the Applicant's responses to the deficiencies listed in the FDA's Complete Response Letter dated 10/10/2014 for this NDA. The proposed indication for methylene blue is for the treatment of acquired methemoglobinemmia.

The NDA's resubmission includes the following studies:

1) a single-dose, parallel BE study of methylene blue intravenous injection conducted in healthy volunteers.
2) Phase 1 Study –A Single Center, Randomized, Placebo and Positive Controlled, Cross-over Thorough QT Study to Assess the Effect of a Single Intravenous Dose of (b) (4) on QTc Interval in Healthy Subjects and
3) A prospectively defined retrospective study on patients treated with (b) (4) injection for methemoglobinemia.

The resubmission also included a pediatric PK extrapolation from adult information study and in vitro drug-drug interaction studies to evaluate the proposed drug product's plasma protein binding, interaction with CYP P450 enzymes, and transporters.

18. **Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?**

The proposed drug product is a solution; therefore, a dissolution test is not needed for assuring the drug product quality

19. **Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?**

No

Reviewer's Assessment:

The provided BA/BE study will be evaluated by the Office of Clinical Pharmacology. Therefore, the resubmission of NDA 204630 does not require further assessment from the Division of Biopharmaceutics.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

The Division of Biopharmaceutics defers the approvability decision on this NDA to the other review disciplines.

Banu Sizanli Zolnik, Ph. D 1/25/2016
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Review Comments and Concurrence:

I concur.

Angelica Dorantes, Ph.D. 1/26/2016
Acting Biopharmaceutics Branch Chief
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

20. Are the tests and proposed acceptance criteria for sterility and endotoxins limit adequate for assuring the microbial quality of the drug product?

Control of Drug Product

Specifications

The drug product is to be sterile (USP <71>) and will contain no more than (b) (4) EU/mL.

Analytical Procedures

- Endotoxin –

(b) (4)

- Sterility –
  The results of sterility testing validation studies were provided in the method validation report titled "Sterility Test Method Validation on Methylene Blue Ampoules." Validation testing was conducted according to the methodology specified in the current editions of the USP and Eur. Ph. The results of the validation studies were provided in the method validation report and met the requirements of USP <71>.

Reviewer's Assessment: Adequate

The applicant has provided successful results verifying sterility and endotoxins testing per USP<71> and USP<85>, respectively.

2.3.P.7 Container/Closure System

21. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

- Description of container closure system –
  The drug product will be packaged in a 10 mL (b) (4) Type I glass ampoule (manufactured by (b) (4)).

- Container-Closure and Package integrity –
  100% container closure integrity testing is conducted using a (b) (4) The validation procedure was provided in section 3.2.P.3.5 of the application. (b) (4) All control vials were rejected and all validation acceptance criteria were met.

Reviewer's Assessment: Adequate
The applicant has provided sufficient results demonstrating the integrity of the container-closure as a microbial barrier.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

22. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: N/A

Reviewer's Assessment:
None of the materials used for the manufacture of the drug product are of biological origin or derived from biological sources.

23. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: N/A

Reviewer's Assessment:
See Reviewer's Assessment for Question 42.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
The Division of Microbiology Assessment has reviewed NDA 204630 for methylene blue for injection, and found the microbiology information adequate. From a microbiology perspective, NDA 204630 is recommended for **APPROVAL.**

Jonathan G. Swoboda, PhD, signed 25 January 2016
Microbiology Reviewer
OPQ/OPF/Division of Microbiology Assessment Branch 3

Secondary Review Comments and Concurrence:
I concur with the microbiology assessment. NDA 204630 is recommended for **APPROVAL.**

Dupeh Palmer, PhD, signed 25 January 2016
Senior Microbiology Reviewer
OPQ/OPF/Division of Microbiology Assessment Branch 3

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The Applicant claimed categorical exclusion for EA per 21 CFR 25.5(c) and 21 CFR 25.31(a) in the original submission. No new information submitted in this resubmission.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

The CMC sections of the PI were reviewed and recommended changes were made by the applicant.

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	**PROVAYBLUE™** (methylene blue)	
Dosage form, route of administration	Injection	
Controlled drug substance symbol (if applicable)	N.A.	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	50 mg/10 mL (5 mg/mL) single-dose ampule.	

Conclusion:
Acceptable

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Injection:	
Strengths: in metric system	50 mg/10 mL (5 mg/mL) in single-dose ampules	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	clear dark blue solution	

Conclusion:
Acceptable

#11: Description (21CFR 201.57(c)(12))

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	PROVAYBLUE™ (methylene blue)	
Dosage form and route of administration	Sterile solution intended for intravenous administration	
Active moiety expression of strength with equivalence statement for salt (if applicable)	10 mL ampule contains 50 mg Proveblue® methylene blue	
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Each mL of solution contains 5 mg methylene blue and water for injection q.s.	
Statement of being sterile (if applicable)	It is a sterile solution	
Pharmacological/ therapeutic class	oxidation-reduction agent	
Chemical name, structural formula, molecular weight	3,7-bis(dimethylamino)phenothiazin-5-ium, chloride. The molecular formula of methylene blue is $C_{16}H_{18}ClN_3S$ and its molecular weight is 319.86 g/mol	
If radioactive, statement of important nuclear characteristics.	N.A.	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Clear dark blue solution with a pH value between 3.0 and 4.5. The osmolality is between 10 and 15 mOsm/kg	

Conclusion:
Acceptable

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Each 10 mL ampule contains 50 mg of methylene blue	
Available units (e.g., bottles of 100 tablets)	A box contains five ampules placed in a tray.	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	A clear dark blue solution. NDC 0517-0374-05	
Special handling (e.g., protect from light, do not freeze)	Do not refrigerate or freeze. Keep the ampule in the original package to protect from light.	
Storage conditions	Store at 20°C to 25°C (68°F to 77°F).	

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured by: CENEXI 52 rue Marcel et Jacques Gaucher 94120 Fontenay sous Bois, FRANCE	

Conclusion:
Acceptable

2. Container and Carton Labeling

1) Immediate Container Label

(b) (4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Information provided is acceptable.	
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Provided: Acceptable	
Route of administration 21.CFR 201.100(b)(3))	Provided: Acceptable	
Net contents* (21 CFR 201.51(a))	Provided: Acceptable	
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Provided: Acceptable	
Lot number per 21 CFR 201.18	Provided: Acceptable	
Expiration date per 21 CFR 201.17	Provided: Acceptable	
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided: Acceptable	
Storage (not required)		
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided: Acceptable	
Bar Code per 21 CFR 201.25(c)(2)***	Provided: Acceptable	
Name of manufacturer/distributor (21 CFR 201.1)	Provided: Acceptable	
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:
Acceptable

2) **Carton Labeling**

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Provided: Acceptable	
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Provided: Acceptable	
Net contents (21 CFR 201.51(a))	Provided: Acceptable	
Lot number per 21 CFR 201.18	Provided: Acceptable	
Expiration date per 21 CFR 201.17	Provided: Acceptable	
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Provided: Acceptable	
Sterility Information (if applicable)		
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Provided: Acceptable	
Storage Conditions	Provided: Acceptable	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided: Acceptable	
Bar Code per 21 CFR 201.25(c)(2)**	Provided: Acceptable	
Name of manufacturer/distributor	Provided: Acceptable	
"See package insert for dosage information" (21 CFR 201.55)	Provided: Acceptable	
"Keep out of reach of children" (optional for Rx, required for OTC)		
Route of Administration (not	Provided: Acceptable	

required for oral, 21 CFR 201.100(d)(1) and (d)(2))		

Conclusion:
Acceptable

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
Anamitro Banerjee
OPQ/ONDP/DNDP I/Branch II
April 06, 2016

Secondary Review Comments and Concurrence:

II. List of Deficiencies To Be Communicated

N.A.

III. Attachments

A. Lifecycle Knowledge Management
N.A.

NDA 204630

Ptoveblue® (Methylene Blue) Injection

Provepharm SAS

Review of Drug Product Sections

Z. Jean Tang

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II

Chemistry, Manufacturing, and Controls (CMC)
Team Review of Original NDA
For the Division of Drug Oncology Products 2

Table of Contents

CMC Review Data Sheet

1. NDA 204630

2. REVIEW #: 1

3. REVIEW DATE: 18-Jan-2014

4. REVIEWER: Z. Jean Tang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND (b) (4) submission	18-Nov-2011
Original IND (b) (4) CMC review	N/A*
CMC-only pre-NDA type B meeting preliminary comments	26-Jan-2012
CMC-only pre-NDA type B meeting	31-Jan-2012
Original NDA Submission	13-AUG-2012
Refuse to file	11-Oct-2012

*: IND submission is only for meeting request.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	13-Aug-2012	13-AUG-2012
Resubmission/After Refusal to File	9	13-Sep-2013	13-Sep-2013
Amendment	24	04-Apr-2014	04-Apr-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Provepharm SAS
Address:	Hôtel Technologique, Technopôle de Château-Gombert, 45 rue Frédéric Joliot-Curie, 13013 Marseille, France
Representative:	Clara Li, Clinipace Worldwide RSD
Authorized U.S. agent	4840 Pearl East Circle, Suite 201E, Boulder, CO 80301
Telephone / email:	303-225-0980 ext. 3024 / cli@clinipace.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4) Injection
b) Non-Proprietary Name: Methylene Blue Injection

c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: Type 5
- Submission Priority: Standard

(b) (4)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of acquired methemoglobinemia

11. DOSAGE FORM: Injections

12. STRENGTH/POTENCY: 0.5% (5mg/mL) in 10 ml

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
__√__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical structure (b) (4)

Molecular formula	$C_{16}H_{18}ClN_3O_3S$, (b) (4)
Molecular weight	319.85 g/mol for anhydrous form
United States Adopted Name (USAN)	Methylene blue
International Nonproprietary Name (INN)	Methylthioninium chloride
CAS Chemical (IUPAC) name	3,7-bis(Dimethylamino)-phenazathionium chloride
Chemical Abstracts Service (CAS) registry number	(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	N/A	N/A	LOA provide enough information
	III			4	N/A	N/A	LOA provide enough information
	III			4	N/A	N/A	LOA provide enough information,.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A	N/A	N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	22-Sep-2013	Vipul Dholakia
Pharm/Tox	Acceptable	27-May-2014	Brenda Gehrke
Biopharm	Not acceptable	05-Sep-2014	Minerva Hughes
Methods Validation	N/A		
DMEPA**	N/A		
EA	Categorical exclusion (see review)	Date of this review	Jean Tang
Microbiology	Acceptable	17-Jun-2014	Stephen Langille

*LNC: Labeling and Nomenclature Committee
**DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 204630

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Originally, ONDQA agreed on a post-approval commitment [redacted] However, the Clinical Division is recommending a Complete Response. Therefore, the post-approval commitments (see below) would be pre-mature. In case, the Agency chooses to propose a Complete Response for non-CMC reasons, convey the following to sponsor: We acknowledge the post-marketing commitment made between the ONDQA and applicant. You can submit all the agreed upon results from your post marketing commitments in the response to the Complete Response letter instead of submitting that in a Prior Approval Supplemen [redacted]. In the submission you are recommended to include all pertinent CMC information due to the process change.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no PMCs from Drug Product. Refer to Dr. Amit Mitra's review for the PMCs of drug substance.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

Refer to Dr. Amit Mitra's review for drug substance.

(2) Drug Product

[redacted] Injection, 0.5% (methylene blue) is a sterile solution intended for intravenous administration. The product is [redacted] filled into ampoules and [redacted]. Each [redacted] Injection, 0.5%, 10 mL ampule contains 50 mg Proveblue methylene blue (USP) and water for injection. The drug product is extremely hypotonic and [redacted] be diluted in 50 mL [redacted] (5%) solution for injection prior to intravenous administration.

The a [redacted] mitted stability data up to 18 months for six batches of commercial scal [redacted] Methylene Blue) Injection, 0.5% drug product. Three batches were manufactured [redacted] and three batches were manufactured in Cenexi site. All the stability data up to 18 months under the long term storage condition and 6 months

under the accelerated st ge condition are well within the specification. The applicant proposed a shelf life of (b) (4) months. However, only 30 months shell life is granted according to ICH guid e Q1E.

As of the date of this review, the Office of Compliance has not issued an overall recommendation for the inspection of the drug product manufacturing site (Attachment I).

B. Description of How the Drug Product is Intended to be Used

Methylene Blue (MB) is able to reduce the heme from methemoglobin (MetHb) to hemoglobin, as it acts as a co-factor of NADPH reductase, which reduces MB to leucomethylene blue (LMB); this reaction is catalyzed by NADPH reductase.

(b) (4) Injection, 0.5% belongs to the pharmacotherapeutic group of antidotes (ATC code: V03AB17). The proposed indication for (b) (4) Injection, 0.5% is the treatment of acquired methemoglobinemia.

The recommended dose for adults and children (b) (4) is 1 mg/kg (b) (4) intravenously over a period of 5 minutes. If methemoglobin level remains > 30 % or if clinical symptoms persist, a repeat dose of up to 1 mg/kg (b) (4) may be given one hour after the first dose.

C. Basis for Approvability or Not-Approval Recommendation

In order for this NDA to be recommended for Approval from a Chemistry, Manufacturing, and Controls standpoint, the starting material for the manufacture of the drug substance is recommended to be redefined (see drug substance review). Pertinent CMC information is recommended in a Complete Response amendment.

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

Zhe Jean Tang, Ph.D, Reviewer, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Ali Al Hakim, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

ZHE J TANG
09/22/2014

ALI H AL HAKIM
09/22/2014

NDA 204-630

[redacted] (b) (4) (methylene blue) Injection, 0.5%

Provepharm, SAS

Office of New Drug Quality Assessment
Reviewed for the Division of Hematology Products (DHP)

CMC Review Team:
Amit Mitra, Ph.D (Drug Substance)
Jean Tang, Ph.D (Drug Product)
Stephen Langile (Microbiology)

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Chemistry Review Data Sheet

1. NDA 204-630

2. REVIEW #1

3. REVIEW DATE: 30-AUG-2014

4. REVIEWER/S: Amit Mitra, Ph.D (Drug Substance)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA submission	13-AUG-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission	13-SEP-2013
Amendment	06-NOV-2013
Amendment	04-APR-2014
Amendment	05-MAY-2014
Amendment	16-JUN-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Provepharm, SAS
Address:	Hôtel Technologique, Technopôle de Château-Gombert, 45 rue Frédéric Joliot-Curie, 13013 Marseille, France
Representative:	Clara Li, Clinipace Worldwide RSD, 4840 Pearl East Circle, Suite 201E, Boulder, CO 80301 phone 303-225-0980 ext. 3024, fax 303-225-0984, email: cli@clinipace.com
Telephone:	303-225-0980 ext. 3024

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4) Injection
b) Non-Proprietary Name (USAN): Methylene blue injection.
c) Code Name/# (ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)2

10. PHARMACOL. CATEGORY: (b) (4) is indicated for treatment of acquired methemoglobinemia

11. DOSAGE FORM: Injections

12. STRENGTH/POTENCY: 0.5%/ 50 mg/10 ml.

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(b) (4)

(1) (b) (4).
Comment: (b) (4)
(b) (4)

$C_{16}H_{18}ClN_3S$. (b) (4)

Chemistry Review Data Sheet

Molecular weight: 319.85 g/ml [redacted]

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
[redacted]	III	[redacted]	[redacted]	7			The DMF has been reviewed by several reviewers (CMC and Pharm-Tox reviewers). The last reviewed by Toxicology reviewer for [redacted] and found adequate by Dr. T.Robison on [redacted]. Subsequent annual reports and amendments are minor in nature and does not need to be reviewed.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Not applicable

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	[redacted]	[redacted]	Cross reference to the IND is authorized
IND	[redacted]	[redacted]	Cross reference to the IND is authorized

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE	STATUS/	COMMENTS

Chemistry Review Data Sheet

		FORWARDED	REVIEWER	
Biometrics	N/A			
EES	Site inspections			Acceptable, 04-JUN-2013
Pharm/Tox	Drug substance, impurity qualification (organic and inorganic)	27-MAY-2014	Dr. B. Gehrke	Satisfactory, 27-MAY-2014
Biopharm	N/A			Will submit separate review
ODS/DMETS	Labeling consult			Pending as of 20-MAY-2014.
Methods Validation	N/A			
EA	N/A	N/A		Not applicable for drug substance
Microbiology			Dr. S. Langille	Acceptable, 17-JUN-2014

The Chemistry Review for NDA 204-630

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Originally, ONDQA agreed on a post-approval commitment for (b) (4) . However, the Clinical Division is recommending a Complete Response. Therefore, the post-approval commitments (see below) would be premature. However, if the Clinical Division chooses to propose a Complete Response for non-CMC reasons, the following should be conveyed to the sponsor: We acknowledge the post-marketing commitment made between the ONDQA and applicant. You can submit all the agreed upon results from your post marketing commitments in the response to the Complete Response letter instead of submitting that in a Prior Approval Supplement (b) (4) In the submission, you should include all pertinent CMC information due to the process change.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The following risk management strategies were agreed upon by the Agency and the applicant (b) (4) The applicant made the following commitments (b) (4) and has proposed to submit the CMC information in a prior approval supplement, post approval. For details see Section S.2.2 of the review.

(b) (4)

(b) (4)

Since a Complete Response will be issued for this submission. There is no need to send the post-marketing commitment (PMC) to the applicant; however, the Agency may want to acknowledge the PMC in the Complete Response letter.

II. Summary of Chemistry Assessment

A. Description of the Drug Substance(s) and Drug Product

Drug Substance (methylene blue)
Methylene blue is a New Chemical Entity with a chemical name: 3, 7-Bis(dimethylamino)-phenazathionium chloride. It is a non-hygroscopic, white to off-white powder which possesses a solubility of 1.33 mg/ml in water. The structure of methylene blue is presented on the next page. There are no definable pKa values reported to be within the ranges of 0 to 1.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The applicant has conducted 6 months satisfactory long term stability studies at the proposed storage condition (b) (4) C) for 3 lots. Based on the stability data the applicant is proposing a retest period of (b) (4) months. A retest period of (b) (4) months may be granted since the applicant has adequately tightened the assay and related substances acceptance criteria including Azure B and other genotoxic impurities (see the comments in the specification section). Similarly, 6 months satisfactory stability data were presented under accelerated conditions (b) (4) Therefore, a retest period of (b) (4) months may be granted. The applicant also provided supporting stability data for additional lots.

B. Description of How the Drug Product is Intended to be Used

See the Drug Product Review by Dr. Jean Tang.

C. Basis for Approvability or Not-Approval Recommendation

In order for this NDA to be recommended for Approval from a Chemistry, Manufacturing, and Controls standpoint, the starting material for the manufacture of the drug substance is recommended to be redefined. Pertinent CMC information is recommended in a Complete Response amendment.

III. Administrative

This NDA was submitted electronically as a 505(b)(2) application. A Quality Overall Summary is included in the application.

The CMC section of this application was reviewed by a team. The review team members selected for the quality assessment and their individual responsibilities are listed below:

Review Team	Assessment Responsibility

CHEMISTRY REVIEW

Chemistry Assessment

Amit K. Mitra, Ph.D.	Drug Substance
Jean Tang, Ph.D	Drug Product (separate review)
Steve Langille, Ph.D.	Microbiology Evaluation (separate review)

A. Reviewer's Signature

See electronic signature

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/s/

AMIT K MITRA
09/11/2014

ALI H AL HAKIM
09/11/2014

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: 07-Aug-2014

From: Janice Brown, M.S.
CMC Lead
DNDQA I/ONDQA

Through: Ali Al-Hakim, Ph.D.
Chief, Branch II
New Drug Quality Assessment Division II
ONDQA

To: NDA 204630
Methylene Blue Injection

Subject: Risk Assessment

As per a new policy, each NDA with GRMP dates on or after August 1, 2014 will include a risk assessment in the Executive summary. This will be based on an initial risk assessment that would be captured in all IQAs written for NDAs received on or after June 1, 2014. It was decided that the CMC Lead would perform a retrospective risk assessment for those NDAs received prior to June 1, 2014 that had GRMP dates after August 1, 2014.

The following IQA template was provided:

ONDQA Risk Assessment Template for Initial Quality Assessments of Original NDAs

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment

In an email dated 30-May-2014, Dr. Ramesh Sood provided follow-up guidance on how to fill out the required IQA template that is used to populate the NDA template. The guidance provided templates for the most common dosage forms.

This memo captures both the table that would normally be in the IQA and populates the first three columns of the NDA template that will be filled in by the primary CMC reviewer.

IQA RISK ASSESSMENT

Product attribute/ CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment	Risk
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	4	5 (IV)	5	100		H
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	2	4	4	32		M
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	4 (Poorly stable drug)	2	1	8	Poorly Stable Drug: No single impurity > 0.5%; Total impurities > 2.0%	L
Uniformity of Dose (Fill Volume/ Deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	2	4 (HRD)	2	16	Applicant does not perform a density determination prior to filling and meets the USP <1151> excess volume recommendation (10.5 mL)	L
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	3 (SVP)	5	30	No osmolality testing is performed.	M
pH- (High)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	2	2	1	4		L
pH- (Low)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	3	4	1	12		L
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	3	5 (IV)	3	45		M
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	2	4	3	24		L
Appearance (Color/turbidity)	• Formulation • Raw Materials • Process parameters • Scale/equipment • Site	3	3	1	9		L

The evaluation from the IQA table was transferred to the following NDA table that can be used by the primary reviewer as a part of the NDA review.

NDA RISK ASSESSMENT TABLE

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations / Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	H			
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	M			
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L			
Uniformity of Dose (Fill Volume/ Deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L			
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M			
pH- (High)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L			
pH- (Low)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L			
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	M			
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L			
Appearance (Color/turbidity)	• Formulation • Raw Materials • Process parameters • Scale/equipment • Site	L			

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/s/

JANICE T BROWN
08/18/2014

ALI H AL HAKIM
08/18/2014

Memorandum

To: NDA 204-630

CC:

From: Amit K. Mitra, Ph.D

Through: Ali Al Hakim, Ph.D

Date: 6/2/2014

Re: Applicant's proposal on designation of starting material

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

(b) (4)

; therefore, options 3 or 4 could be explored. However, you are requested a commitment to submit prior approval supplement/s with options 3 & 4 with firm dates. (b) (4)

If you agree to these terms, update the NDA with the recommended modifications and include revised specification sheets for the (b) (4) Also, include a commitment to submit a prior approval supplement with firm dates with a detailed description of options 3 and 4.

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/s/

AMIT K MITRA
06/02/2014

ALI H AL HAKIM
06/02/2014

FILING REVIEW and INITIAL QUALITY ASSESSMENT

FILING REVIEW – NDA 204630

NDA Number:	**Supplement Number and Type:**	**Established/Proper Name:**
204630	000	Methylene Blue Injection
Applicant:	**Letter Date:**	**Stamp Date:**
Provepharm SAS	11-Sep-2013	11-Sep-2013

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			N.A.

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			N.A.

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?			N.A.
23.	Have any biowaivers been requested?	X		
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?		X	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	

Filing Letter Comments to the NDA applicant:

Janice Brown, M.S., CMC Lead
Division 1, Branch 2
Office of New Drug Quality Assessment
(See electronic signature stamp)

Ali Al Hakim, Ph.D., Chief Branch 2
Division 1, Branch 2
Office of New Drug Quality Assessment
(See electronic signature stamp)

Initial Quality Assessment

1. NEW DRUG APPLICATION NUMBER: 204630

2. DATES AND GOALS:

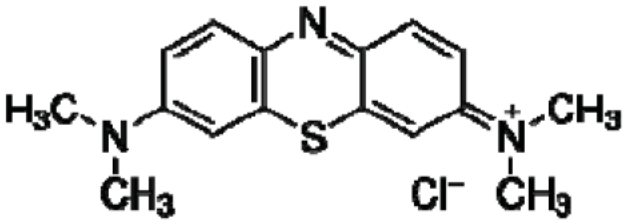
Letter Date: 11-Sep-2013	Submission Received Date : 13-Sep-2013
PDUFA Goal Date: 13-Jul-2014	

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	[redacted] (b) (4) Injection
Established or Non-Proprietary Name (USAN):	Methylene Blue Injection
Dosage Form:	Solution
Route of Administration	IV
Strength/Potency	0.5% (5 mg/mL)
Rx/OTC Dispensed:	Rx

4. INDICATION: Treatment of acquired methemoglobinemia

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



[redacted] (b) (4)

Empirical Formula: $C_{16}H_{18}ClN_3S$, [redacted] (b) (4)
Formula Weight: 319.85 g/mol [redacted] (b) (4)

6. NAME OF APPLICANT: Provepharm SAS

7. SUBMISSION PROPERTIES:

Review Classification:	Standard
Submission Classification (Chemical Classification Code):	Type 7 NCE
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	OHOP/DHP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		Entered on 03-Oct-2013
Pharmacology/Toxicology			Determined by the primary reviewer
Methods Validation	X		Not required per IQP 5105
Environmental Assessment	X		
CDRH		X	
Other		X	

9. REVIEW TEAM

Reviewer	Name
CMC	Jean Tang (Drug Product) and Amit Mitra (Drug Substance)
Biopharmaceutics	Minerva Hughes
Microbiology	Stephen Langille
CMC Lead	Janice Brown
Chief, Branch II	Ali Al Hakim

10. DMFs

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III	(b) (4)		12-23-2011	None
	III			1-2-2012	None
	III			7-18-2012	None

SUMMARY

Methylene Blue Injection, 0.5% antidote indicated for the treatment of acquired methemoglobinemia. Methemoglobinemia is caused by an abnormal increase in blood concentration of an altered form of hemoglobin, MetHb, where one or more iron molecules have been oxidized to the ferric state (Fe3+), instead of the normal ferrous form (Fe2+). Following this change of state, the heme group is unable to bind to a molecule of oxygen. In addition, the change in conformation of the MetHb structure increases the oxygen affinity with the remaining ferrous hemes, further reducing the oxygen delivery to tissues. For the treatment of methemoglobinemia, methylene blue acts to reduce the heme group from methemoglobin (MetHb) to hemoglobin.

Since there is no FDA approved Methylene Blue (MB) product, this 505(b)(2) application does not have complete comparative CMC studies using a listed drug. The applicant for this 505(b)(2) NDA is relying upon information in the public domain (published studies) to support nonclinical sections for the labeling for the new Methylene Blue injection product.

The applicant has provided comparative impurity analysis of a several commercial methylene blue products that are not intended for medical use. The analysis of methylene blue products were obtained from (b) (4) None of the commercial products meet USP or Ph. Eur. assay requirements for Methylene Blue Injection. The methylene blue described in this NDA also does not meet the USP Assay (b) (4) requirements for Methylene Blue.

Methylene blue drug substance (b) (4)
(b) (4)

(b) (4) Injection, 0.5% (methylene blue) is a sterile solution intended for intravenous administration. The product is (b) (4) into ampoules and (b) (4). Each (b) (4) Injection, 0.5%, 10 mL ampule contains 50 mg Proveblue methylene blue (USP) and water for injection. The drug product is extremely hypotonic and should be diluted in 50 mL (b) (4) (5%) solution for injection prior to intravenous administration.

The applicant is requesting a priority review for this NDA.

DRUG SUBSTANCE

1.0 There was no agreement on the starting material classification of (b) (4)
(b) (4)

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9.0 DRUG SUBSTANCE SPECIFICATION - The Methylene blue drug substance specification is appended as attachment 2. (b) (4)

10.0 CONTAINER – CLOSURE - (b) (4) (b) (4)

11.0 STABILITY – The following RTF deficiency was sent to the applicant on October 15, 2013: ***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.***

The applicant has replaced the original drug substance batches (25002129, 25002132 and 25002134) submitted in the initial NDA with batches 27000760, 27000761, and 27000766/A as primary stability batches. The applicant has stated that the batches were manufactured using the commercial process. Submitted stability data includes (b) (4) (b) (4)

11.1 Provepharm is categorizing batches 25002129, 25002132, and 25002134 as supportive data in order to qualify the following: (b) (4)

A summary of the supportive stability batches is shown in table 5. A retest period of (b) (4) months at (b) (4) C is proposed for (b) (4) Methylene Blue drug substance.

Table 5: Stability Batches

Batch number	25002129	25002132	25002134
Date of manufacture	(b) (4)		
Manufacturing site			

Scale	(b) (4)
Batch size	

- The applicant submitted (b) (4) stability data for 3 batches of drug substance (batches 25002129, 25002132 and 25002134) manufactured at commercial scale at the proposed (b) (4) commercial site. The applicant requested a (b) (4) month retest date when drug substance is stored (b) (4).

- Long term stability data met the proposed drug substance specification at all test stations.

- (b) (4) ICH Q1A(R2) states that if a significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed re-test period should be based on the real time data available at the long term storage condition.

- Forced Degradation Studies - The applicant performed drug substance forced degradation studies under conditions listed in table 6. (b) (4)

Table 6: Solutions preparation for forced degradation

Solution to be stressed	Stress	Duration	Methylene blue content (%)	Percent of degradation (%)	Batch
S1	(b) (4)				
S2					
S3					
S4					
S5					
S6					

DRUG PRODUCT

12.0 (b) (4) Injection, (methylene blue) is a 5mg/mL sterile solution for intravenous ion. Each mL of solution contains 5 mg methylene blue and water for

injection [redacted] njection, 0.5% is a clear dark blue solution with a pH value between

13.0 The composition of the Methylene blue 10 are reproduced in table 7. The drug product is a sterile, clear blue solution for injection in 10 mL glass type I ampoules.

Table 7: Composition of the 10mL/ampule (5mg/mL)

Name Of Ingredient	**Quantity/ 10ml Ampoule**	**Quantity/Ml**	**Function**	**Reference To Standard**
Methylene blue	50.0 mg	5.0 mg	Drug substance	In-house
Water for injection	q. s. 10 mL	q. s. 1.0 mL	[redacted]	USP

14.0 The drug product osmolality is between 10 and 15 milliosmoles per kilogram (mOsm/kg) which is extremely hypotonic and may cause phlebitis. Normal blood values range from 275 to 295 mOsm/kg. Proposed label states that, [redacted] Injection, 0.5% is hypotonic and may be diluted before use in a solution of [redacted] (5%) in order to avoid local pain, particularly in the pediatric population". Whether the labeling requires revision should be discussed with the clinical reviewer. Suggested labeling change: [redacted] Injection, 0.5% is hypotonic and [redacted] be diluted before use in a solution of [redacted] in order to avoid local pain, particularly in the pediatric population."

In NaCl 0.9%, the applicant has stated that precipitation of Methylene Blue is possible. The proposed labeling [redacted]

15.0 Methylene blue injection manufacturing flow diagram and drug product specification are reproduced in attachments 3 and 4, respectively. The drug product is [redacted] into ampoules and [redacted].

16.0 IMPURITIES - [redacted]

17.0 CONTAINER CLOSURE – The primary container is a [redacted] 10 mL [redacted] Type I USP glass ampule. The applicant did not provide any labeling recommendations in the event that glass fragments enter the drug product when the ampule is opened. Refer to http://www.safeinfusiontherapy.com/documents/Products/Particulate_Contamination_M.

pdf. Suggest that the labeling be revised to include the use of an in-line filter and/or a filter needle.

18.0 DRUG PRODUCT STABILITY STUDIES – The applicant submitted stability data for three (b) (4) commercial size batches 1215, 1216 and 1217 and three Cenexi commercial size batches F0001, F0002 and F0003 under accelerated conditions: 6 months at 40°C/75%RH, intermediate conditions: 18 months at 30°C/65%RH and long term conditions: 18 months at 25°C/60%RH. Tables 8 and 9 include a summary of the primary stability studies and data to support the proposed (b) (4) month shelf life.

Table 8: Stability batches

Product		Batch no.	Batch size	Manufacturing date	Manufacturing Site
(b) (4)	Injection, 0.5%	1215	(b) (4)	27 June 2011	(b) (4)
	Injection, 0.5%	1216		29 June 2011	
	Injection, 0.5%	1217		29 June 2011	
	Injection, 0.5%	F0001		25 May 2011	Cenexi, Fontenay
	Injection, 0.5%	F0002		8 June 2011	Cenexi, Fontenay
	Injection, 0.5%	F0003		14 June 2011	Cenexi, Fontenay

Table 9 - Drug Product Stability Summary

Batch No.	Manufacturing Site	Storage conditions	Amount of data	Results
1215	(b) (4)	25 °C/60 % RH	18 months	Pass
		30 °C/65 % RH	18 months	Pass
		40 °C/75 % RH	6 months	Pass
1216		25 °C/60 % RH	18 months	Pass
		30 °C/65 % RH	18 months	Pass
		40 °C/75 % RH	6 months	Pass
1217		25 °C/60 % RH	18 months	Pass
		30 °C/65 % RH	18 months	Pass
		40 °C/75 % RH	6 months	Pass
F0001	Cenexi, Fontenay	25 °C/60 % RH	18 months	Pass
		30 °C/65 % RH	18 months	Pass
		40 °C/75 % RH	6 months	Pass
F0002	Cenexi, Fontenay	25 °C/60 % RH	18 months	Pass
		30 °C/65 % RH	18 months	Pass
		40 °C/75 % RH	6 months	Pass

18.1 PHOTOSTABILITY – The drug product is not photo sensitive.

19.0 Environmental Assessment: The applicant has submitted a claim for categorical exclusion under 25.31(a) which states that use of this product will not does not increase the use of the active moiety and has been determined not to significantly affect the quality of the human environment.

CRITICAL ISSUES FOR REVIEW

1. [redacted] (b) (4)

2. Information intended to establish suitability of the container closure for the drug substance was not provided. This includes information on the identification of the materials of construction (i.e., plastics, elastomers, and other such materials) should be identified by a specific product designation (code name and/or code number) and the source (name of the manufacturer). Alternatively, it may be provided in a drug master file and a letter of authorization (LOA) to the DMF submitted in the application. Either submit suitability information or provide a LOA from the manufacturer for the drug substance container closure system.

3. The applicant is proposing [redacted] (b) (4) genotoxic impurities for the [redacted] (b) (4)

4. The applicant describes [redacted] (b) (4); however, no evaluation was performed to evaluate the effect on product quality. Recommend requesting additional information to support the [redacted] (b) (4)

5. The drug product is extremely hypotonic (see item #14 in this review). Whether the labeling requires revision should be discussed with the clinical reviewer. Suggested labeling change: "[redacted] (b) (4) Injection, 0.5% is hypotonic and [redacted] (b) (4) be diluted before use in a solution of glucose 50 mg/mL (5%) in order to avoid local pain, particularly in the pediatric population.

   In NaCl 0.9%, precipitation of Methylene Blue is observed. The proposed labeling [redacted] (b) (4).

6. The product is filled in a glass ampule. The applicant did not provide any labeling recommendations in the event that glass fragments enter the drug product when the ampule is opened. Refer to http://www.safeinfusiontherapy.com/documents/Products/Particulate_Contamination_M.pdf. Suggest that the labeling be revised to include the use of an in-line filter and/or a filter needle.

[redacted] 6 Pages has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JANICE T BROWN
11/13/2013

RAMESH K SOOD
11/13/2013