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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Office / Division	Office of Hematology and Oncology Products / Division of Hematology Products
Primary Reviewer	Donna Przepiorka, MD, PhD
Team Leader	Albert Deisseroth, MD, PhD
Established Name	Methylene blue
Trade Name	ProvayBlue
Therapeutic Class	Antidote
Applicant	Provepharm SAS
Formulation	Injection, solution (50 mg/10 mL single-dose ampule)
Dosing Regimen	1 mg/kg intravenously over 5-30 minutes with repeat after 1 hour if needed
Indication	Treatment of acquired methemoglobinemia

Note: For the purposes of this review, “ProvayBlue” refers to the drug under review, “Methylene Blue USP 1%” refers to formulations stated to comply with the USP monograph, and “methylene blue class products” refers to any therapeutic methylene blue formulation, including those of unknown provenance.

Table of Contents

CLINICAL REVIEW	1
TABLE OF CONTENTS	2
TABLE OF TABLES.....	5
TABLE OF FIGURES.....	5
TABLE OF ABBREVIATIONS.....	6
1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT.....	7
1.1 Recommendation on Regulatory Action	7
1.2 Basis of the Recommendation	7
1.3 Recommendations for Labeling.....	12
1.4 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies.....	12
1.5 Recommendations for Postmarket Requirements and Commitments	12
2 INTRODUCTION AND REGULATORY BACKGROUND.....	13
2.1 Product Information.....	13
2.2 Currently Available Treatments for Proposed Indication.....	13
2.3 Availability of Proposed Active Ingredient in the United States	13
2.4 Important Issues with Consideration to Related Drugs	14
2.5 Summary of Presubmission Regulatory Activity Related to Submission	14
2.6 Other Relevant Background Information	15
2.7 Compliance with the Pediatric Research Equity Act.....	16
3 ETHICS AND GOOD CLINICAL PRACTICES	17
3.1 Submission Quality and Integrity	17
3.2 Compliance with Good Clinical Practices.....	17
3.3 Financial Disclosures.....	17
4 SIGNIFICANT ISSUES RELATED TO OTHER REVIEW DISCIPLINES	17
4.1 Product.....	17
4.2 Preclinical Pharmacology/Toxicology	17
4.3 Clinical Pharmacology	18
4.4 Interdisciplinary Review Team (IRT)	19
4.5 Pharmacovigilance.....	20
5 SOURCES OF CLINICAL DATA.....	20
5.1 Tables of Studies/Clinical Trials	20
5.2 Review Strategy.....	21
5.3 Discussion of Individual Studies/Clinical Trials	21
5.3.1 Protocol PVP-2013001	21
5.3.2 Protocol PVP-2013002	25
5.3.3 Protocol PVP-2014001	26
5.3.4 Protocol PVP-2014002	28

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

5.3.5 Protocol 1MBL12002 (AA98923).....	29
6 REVIEW OF EFFICACY	30
6.1 Treatment of Acquired Methemoglobinemia	30
6.1.1 Methods	30
6.1.2 Demographics.....	31
6.1.3 Treatment and Disposition	31
6.1.4 Primary Efficacy Endpoint.....	31
6.1.5 Subpopulations	32
6.1.6 Analysis of Supporting Efficacy Endpoints	33
6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations	34
6.1.8 Discussion of Lack of Efficacy	36
7 REVIEW OF SAFETY	38
7.1 Methods	38
7.1.1 Studies/Clinical Trials Used to Evaluate Safety.....	38
7.1.2 Categorization of Adverse Events	38
7.1.3 Pooling of Data.....	38
7.2 Adequacy of Safety Assessments	38
7.2.1 Safety Population	38
7.2.2 Explorations for Dose Toxicity Relationship	39
7.2.3 Special Animal and/or In Vitro Testing	40
7.2.4 Routine Clinical Testing.....	40
7.2.5 Metabolic, Clearance, and Interaction Workup.....	40
7.2.6 Adverse Events of Special Interest.....	40
7.3 Major Safety Results	40
7.3.1 Deaths.....	40
7.3.2 Serious Adverse Events.....	41
7.3.3 Dropouts and/or Discontinuations.....	41
7.3.4 Significant Adverse Events	41
7.4 Supportive Safety Results.....	42
7.4.1 Common Adverse Events.....	42
7.4.2 Dose Dependency for Adverse Events.....	47
7.4.3 Time Dependency for Adverse Events.....	49
7.4.4 Literature Review – Common Adverse Events.....	50
7.5 Results of Safety Tests	51
7.5.1 Laboratory Findings	51
7.5.2 Vital Signs	51
7.5.3 Electrocardiograms (ECGs)	52
7.6 Safety in Special Populations	53
7.6.1 Safety in Pediatric Patients.....	53
7.6.2 Safety in Geriatric Patients.....	53
7.6.3 Drug-Demographic Interactions.....	53
7.6.4 Safety with Organ Impairment	55
7.6.5 Drug-Drug Interactions	55

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

7.7	Additional Safety Evaluations	56
7.7.1	Human Carcinogenicity	56
7.7.2	Human Reproduction and Pregnancy Data	56
7.7.3	Pediatrics and Assessment of Effects on Growth.....	56
7.7.4	Overdose.....	56
7.7.5	Drug Abuse Potential, Withdrawal and Rebound	57
7.7.6	Effects on Instrumental Activities of Daily Living	57
7.8	Additional Submissions / Safety Issues.....	58
7.8.1	Serotonin Syndrome	58
7.8.2	Hypersensitivity.....	58
7.8.3	Hemolytic Anemia	58
7.8.4	Interference with In Vivo Monitoring Devices	59
7.8.5	Infusion Site Reactions and Extravasation.....	60
7.8.6	Phototoxicity	60
7.8.7	Paradoxical Methemoglobinemia.....	61
8	POSTMARKET EXPERIENCE.....	61
9	APPENDICES.....	63
9.1	Advisory Committee Meeting	63
9.2	Case Reports of Treatment with Methylene Blue	63
9.3	References	64

Table of Tables

Table 1: Benefit-Risk Framework	7
Table 2: Signs And Symptoms By Methemoglobin Concentration.....	16
Table 3: Clinical Trials/Studies	20
Table 4: PVP-2013001 - Patient Characteristics	22
Table 5: PVP-2013001 - Methemoglobin Levels After Dose 1 of ProvayBlue	23
Table 6: Adverse Events in Protocol PVP-2013001	25
Table 7: PVP-2014001 - Schedule of Assessments.....	26
Table 8: PVP-2014001 - PK Equivalence Analyses for ProvayBlue vs Comparator.....	27
Table 9: PVP-2014002 - Schedule of Assessments.....	28
Table 10: 1MBL12002 - Schedule of Assessments.....	29
Table 11: Efficacy Population Demographics	31
Table 12: Methemoglobin Levels After Dose 1 of ProvayBlue or Methylene Blue USP 1%.....	32
Table 13: Pooled Population – Subgroup Analysis of Response.....	33
Table 14: Pooled Population – Subgroup Analysis of Percentage Methemoglobin Reduction ...	34
Table 15: Pooled Population – Efficacy Outcomes by First Dose.....	35
Table 16: Preterm Neonates – Efficacy Outcomes by First Dose	36
Table 17: Examples of Lack of Efficacy of Methylene Blue Class Products.....	37
Table 18: Healthy Volunteers – Demographics.....	39
Table 19: Protocol PVP2014001 – Injection Site Reaction Assessments	42
Table 20: TEAE by SOC in Healthy Volunteers Treated with ProvayBlue 2 mg/kg.....	43
Table 21: TEAE by PT in Healthy Volunteers Treated with ProvayBlue 2 mg/kg.....	44
Table 22: Common TEAE in Healthy Volunteers by Study.....	45
Table 23: Moderate-to-Severe TEAE in Healthy Volunteers by Study	47
Table 24: Common TEAE in Healthy Volunteers by Methylene Blue Dose	48
Table 25: Common TEAE in Healthy Volunteers by Methylene Blue Cmax.....	49
Table 26: Additional Intravenous Methylene Blue Class Adverse Reactions.....	50
Table 27: Key Laboratory Abnormalities in Healthy Volunteers by Study	51
Table 28: ECG Outliers in Healthy Volunteers by Study	53
Table 29: TEAE by Age in Healthy Volunteers Treated with ProvayBlue 2 mg/kg.....	54
Table 30: TEAE by Gender in Healthy Volunteers Treated with ProvayBlue 2 mg/kg.....	54
Table 31: TEAE by Race/Ethnicity in Healthy Volunteers Treated with ProvayBlue 2 mg/kg...	54
Table 32: TEAE by Weight in Healthy Volunteers Treated with ProvayBlue 2 mg/kg.....	55
Table 33: Characterization of Key Neurological TEAE in Healthy Volunteer Studies ^a	58
Table 34: Cumulative Summary of Postmarket Safety Reports	62
Table 35: Methemoglobin Reduction Using A Methylene Blue Class Product	63

Table of Figures

Figure 1: PVP-2013001- Residual Methemoglobin After Treatment with ProvayBlue.....	24
Figure 2: PVP-2014001- Methylene Blue and Azure B Concentration-Time Profiles	27
Figure 3: PVP-2014002 - Vital Signs	52

Table of Abbreviations

AE	Adverse event
AERS	Adverse Event Reporting System
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
CFR	Code of Federal Regulations
CI	Confidence interval
CK	Creatinine kinase
C _{max}	Maximum concentration
CNS	Central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCTD	Electronic Common Technical Document
EMA	European Medicines Agency
G6PD	Glucose-6-phosphate dehydrogenase
IRB	Institutional review board
IRT	Interdisciplinary Review Team
LDH	Lactate dehydrogenase
LED	Light-emitting diode
MAO	Monoamine oxidase inhibitor
MB	Methylene blue
MedDRA	Medical Dictionary for Regulatory Activities
MetHb	Methemoglobin
NADPH	Nicotinamide adenine dinucleotide phosphate
NDC	National Drug Code
PB	ProvayBlue
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
PT	Preferred Term
REMS	Risk evaluation and mitigation strategy
RTF	Refuse-To-File
SMQN	Standardized MedDRA Query Narrow
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
USP	United States Pharmacopoeia

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This supplement under NDA 204630 was submitted to address the Complete Response letter issued 10/10/2014. The clinical deficiencies cited in the Complete Response letter included a lack of substantial evidence of effectiveness, and inadequate information on which to base the safety profile. The Agency recommended that the applicant submit either a prospective trial of their product for treatment of acquired methemoglobinemia, or data, such as from a bioequivalence trial, to establish that reliance on published outcomes with Methylene Blue USP 1% is scientifically valid.

This reviewer recommends approval of ProvayBlue under 21 CFR 314 Subpart H for the treatment of adults and children with acquired methemoglobinemia. Approval is based on the finding that all 6 (100%) patients with acquired methemoglobinemia in a case series had a decrease in methemoglobin by at least 50% within 1 hour after treatment with ProvayBlue or a bioequivalent formulation. This conclusion was strengthened by documented responses in the same endpoint for 37 (90%) of 41 patients in published reports treated with a methylene blue class product. The clinical benefit of ProvayBlue remains to be confirmed in a postmarketing study.

1.2 Basis of the Recommendation

Table 1: Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Methemoglobinemia occurs in individuals exposed to oxidizing drugs, chemicals and toxins. • Methemoglobin does not release oxygen to the tissues as easily as reduced hemoglobin. • Cardiac, pulmonary and neurological symptoms occur when methemoglobin levels are > 30%, and levels > 70% may be fatal.	• Methemoglobinemia at high levels may cause symptomatic or fatal multiorgan dysfunction.
Unmet Medical Need	• There are no therapeutics approved for treatment of acquired methemoglobinemia.	• Treatment of acquired methemoglobinemia is an unmet need.
Clinical Benefit	• A reduction in methemoglobin by at least 50% within 1 hour after treatment (“response”) is reasonably likely to predict an improvement in clinical symptoms • In a case series, all 6 (100%) patients with methemoglobinemia had a response after the first dose of ProvayBlue or a bioequivalent formulation. • In a series of published cases, 37/41 (90%) had a response after treatment with another methylene blue class product. • The response rate was similar for 1 or 2 mg/kg.	• A single dose of ProvayBlue 1 mg/kg was active in the reduction of methemoglobin levels, but the effect on clinical measures has not been quantitated. • The efficacy experience is limited, and it is likely that a 100% response rate will not occur in practice.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

Table 1: Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risks	• In healthy volunteers who received a single dose of 2 mg/kg ProvayBlue, the most common ($\geq 10\%$) TEAE were pain in extremity, chromaturia, dysgeusia, feeling hot, dizziness, hyperhidrosis, nausea, skin discoloration, and headache. • The potential for neurological toxicity with therapeutic doses was not emphasized previously. • There were no differences in safety by demographic subgroup, but there were no data for subjects with organ impairment. • There was a trend for a dose-toxicity relationship. • The literature review revealed: - There were numerous other adverse reactions identified. - Serious and potentially fatal adverse reactions reported included serotonin syndrome, anaphylaxis and severe hemolysis. - There is a potential for fetal harm. - There is interference with pulse oximetry and assessment of the bispectral index.	• The safety profile of ProvayBlue up to 2 mg/kg is largely acceptable. • The safety of cumulative doses more than 2 mg/kg is unknown. • The approach to dosing for patients with organ impairment is unclear. • There are cases of potentially serious or fatal events reported for other methylene blue class products that may not have been reported for ProvayBlue due to the limited exposure to date.
Risk Management	• Safe use of ProvayBlue in practice will depend on the healthcare provider understanding the limitations of the therapeutic effect and the potential serious risks which require vigilance.	• To minimize risks, labeling should include clear dosing instructions, a boxed warning for serotonin syndrome, and warnings and precautions for other serious risks.

Assessment of Efficacy:

There was no prospective study of ProvayBlue for treatment of methemoglobinemia. There were no data on the effect of ProvayBlue on clinical benefit parameters in patients being treated for methemoglobinemia. The efficacy of ProvayBlue was assessed on the basis of a methemoglobin decrease of at least 50% within 1 hour after intravenous administration of 1 – 2 mg/kg after treatment. This endpoint was considered a surrogate reasonably likely to predict clinical benefit.

ProvayBlue was shown to be bioequivalent to Methylene Blue USP 1%. The efficacy endpoint was assessed in 3 subjects with evaluable data in Protocol PVP-2013001, a multicenter retrospective chart review of patients treated with ProvayBlue, in addition to 3 cases of treatment of methemoglobinemia using Methylene Blue USP 1% by literature search. These 6 cases form the Efficacy Population.

The Efficacy Population included 3 males and 3 females of median age 54 years (range, 6 days to 69 years). The median methemoglobin level at baseline was 37% (range, 11% to 47%). All 6 (100%; 95% CI 61% - 100%) patients had a decrease in methemoglobin by at least 50% within 1 hour after treatment.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

An additional 41 cases of treatment of methemoglobinemia with a methylene blue class product were identified in the published literature. These cases form the Literature Population. This population included 24 males and 17 females of median age 33 years (range, 9 days to 80 years). The median methemoglobin level at baseline was 40% (range, 10% to 98%). Of these 41 patients, 37 (90%; 95% CI 77-96%) were reported to have a methemoglobin decrease of at least 50% within 1 hour after intravenous administration of the methylene blue class product.

In a combined analysis of all 47 patients in the Efficacy Population and the Literature Population, there was no difference in response rate by dose, across age groups and by gender. The subgroups with the lowest response rates were those with a baseline methemoglobin > 60%, and when the etiologic agent was a toxic chemical (i.e. aniline, metaflumizone, nitrobenzene and phenazopyridine). The subgroups with the lowest relative reduction in methemoglobin were those with a baseline methemoglobin > 60%, and when the etiologic agent was dapsone or a toxic chemical.

A review of the literature revealed multiple reports of lack of efficacy in patients with glucose-6-phosphate dehydrogenase deficiency and when the intoxicant was aniline, benzocaine, dapsone, nitroethane or phenazopyridine. The incidence of lack of efficacy has not been determined, and the risk factors are unknown.

Assessment of Safety:

There were 82 healthy volunteers treated with at least 1 dose of ProvayBlue. Safety information was also submitted for 47 healthy volunteers treated with Methylene Blue USP 1% and 48 who received placebo. There were also 39 patients treated with ProvayBlue, but the safety data for the patient population was collected retrospectively and was considered incomplete, so the healthy volunteer population was used as the main basis for the assessment of safety. A thorough QT study was also conducted in the healthy volunteers. Additional safety information was sought in the published literature.

The 82 healthy volunteers had a median age of 36 years (range, 19-55 years); 54% were male, and 68% were white. All of these subjects had received a single dose of ProvayBlue 2 mg/kg in a bioequivalence study or in the thorough QT study. Safety follow-up was through 7 days after administration of the study drug. The results in this population showed:

- There were no deaths.
- One subject developed syncope concurrent with sinus pauses on the Holter monitor at 20 minutes after the start of study drug infusion. The subject recovered without intervention.
- There were no early withdrawals due to an adverse event.
- The most common ($\geq 10\%$) TEAE were pain in extremity, chromaturia, dysgeusia, feeling hot, dizziness, hyperhidrosis, nausea, skin discoloration, and headache. Nearly all of the TEAE reported were also considered related. In the SOC Nervous system disorders, the most common ($\geq 5\%$) TEAE were dysgeusia, dizziness, headache and paresthesia.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

- The most common ($\geq 2\%$) moderate-to-severe TEAE were pain in extremity, headache, feeling hot, dizziness, syncope, back pain, hyperhidrosis, and nausea.
- Subgroup analyses by age, gender, race/ethnicity, weight and BMI showed no safety signal.
- The most common treatment-emergent key laboratory abnormalities were neutrophils increased (12%), bilirubin increased (7%), sodium increased (6%), platelets decreased (5%), hemoglobin decreased (2%), creatinine increased (2%), ALT increased (1%), AST increased (1%) and potassium increased (1%). The abnormalities were all no more than grade 1.
- There were no cardiac conduction effects noted in the through QT study or in an outlier analysis of ECG data for a ProvayBlue dose of 2 mg/kg.

The bioequivalence study suggested that ProvayBlue and Methylene Blue USP 1% were bioequivalent. In pooled analyses of all 129 healthy volunteers treated with various doses of ProvayBlue or Methylene Blue USP 1%:

- Twenty-eight (22%) subjects developed dizziness, postural dizziness, somnolence, presyncope or syncope lasting up to 1 - 9 days.
- There was a trend for a dose-toxicity relationship for the adverse events pain in extremity, chromaturia, dysgeusia, feeling hot, dizziness, hyperhidrosis and headache.
- There was a trend for a C_{max}-toxicity relationship for pain in extremity, chromaturia, skin discoloration, dizziness, dysgeusia, hyperhidrosis and headache.
- The dose of 1 mg/kg was considered safe. There was insufficient safety information to support cumulative dosing past 2 mg/kg or for dosing in patients with renal or hepatic impairment.

The literature review of the safety of methylene blue class products revealed the following:

- There were no safety issues identified specific to treatment of methemoglobinemia in the pediatric or geriatric population.
- Additional potential adverse reactions of methylene blue class products included hemolytic anemia, hyperbilirubinemia, tachycardia, hypertension, elevated liver enzymes, fecal discoloration, necrotic ulcer at sites of subcutaneous administration, paradoxical methemoglobinemia, and phototoxicity.
- Serious and potentially fatal adverse reactions included serotonin syndrome, anaphylaxis and severe hemolysis.
- Cardiac, pulmonary, hepatic and neurological toxicity was seen in patients treated with doses of 3.5 mg/kg or more.
- There was an association between administration of methylene blue class products to pregnant women in the second trimester and neonatal intestinal atresia or death, and when

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

given near term, there was an association with multiple manifestations of methylene blue toxicity in the newborn.

- False readings were reported for oxygen saturation by pulse oximetry and for the bispectral index shortly after infusion.

There were no additional safety concerns attributed to ProvayBlue in the postmarketing period in Europe.

Overall Benefit-Risk Assessment:

Acquired methemoglobinemia can be serious or life-threatening. The reduced oxygenation of tissues resulting from severe methemoglobinemia can lead to organ dysfunction and death. There is currently no FDA-approved therapy for treatment of acquired methemoglobinemia.

In the small case series of patients being treated for methemoglobinemia, ProvayBlue (or a bioequivalent formulation) at 1 - 2 mg/kg reduced the methemoglobin by at least 50% within 1 hour after treatment in all 6 patients. The lower 95% confidence limit of 61% suggests that the majority of patients treated with ProvayBlue should experience such a response. The 90% response rate to other methylene blue class products in the literature series is supportive. These data taken together comprise a substantial basis for accelerated approval for this serious condition for which there is no available therapy.

The purpose of treatment of methemoglobinemia is to relieve the organ dysfunction caused by the tissue hypoxia. The effect of ProvayBlue on quantitative measures of such organ dysfunction, such as heart rate, respiratory rate, or neurological status, were not assessed in the efficacy population. There was also no assessment on the durability of the laboratory response to treatment. Hence, additional evidence will be required in order to confirm clinical benefit.

The safety review revealed moderate to severe adverse events in the healthy volunteers at doses as low as 2 mg/kg. Over 20% of the subjects experienced a neurological event that might impair physical or mental functioning. Additional serious and potentially fatal adverse reactions to methylene blue class products were identified in the literature. The risks can be moderated in part by use of the lowest effective dose of ProvayBlue and with vigilance that will allow for intervention as needed should a serious adverse reaction occur. These can be accomplished by appropriate warnings, contraindications and instructions for dosing in the Prescribing Information. With such a mitigation strategy in place, the potential benefit from treatment with ProvayBlue should outweigh the risks for patients with acquired methemoglobinemia.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

1.3 Recommendations for Labeling

The following key recommendations for the ProvayBlue Prescribing Information are based on this review:

- Include a Boxed Warning for the risk of serotonin syndrome with concomitant use of serotonergic drugs.
- Specify in Section 2 that ProvayBlue should not be administered subcutaneously, limit the dosage to up to 2 doses of 1 mg/kg at least 1 hour apart, and recommend monitoring through treatment and recovery.
- Include in Section 4 contra-indications for those with a known hypersensitivity to methylene blue and for those with glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency.
- Include in Section 5 additional Warnings and Precautions for anaphylaxis, potential lack of effectiveness, hemolytic anemia, interference with pulse oximetry and assessment of the bispectral index, and potential effects on the ability to drive or operate heavy machinery.
- Include in Section 6 a listing of the reported class-specific adverse reactions.
- Describe in Section 8 the potential risks to the fetus from use of ProvayBlue during pregnancy.
- Provide in Section 17 advice for counseling patients treated with ProvayBlue regarding serotonin syndrome, risks to the fetus or breast-feeding infant, potential neurological or visual disturbance that might affect physical functioning, and the risk of phototoxicity.

1.4 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.5 Recommendations for Postmarket Requirements and Commitments

PMR 1:

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.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name:	Methylene blue
Proposed Trade Name:	ProvayBlue Injection
Dosage Forms:	Injection, solution (50 mg/10 mL single-dose ampule)
Therapeutic Class:	Antidote
Chemical Class:	Phenothiazine
Pharmacologic Class:	Oxidation-reduction agent
Mechanism of Action:	Methylene blue is a prodrug. NADPH methemoglobin reductase reduces methylene blue to leukomethylene blue, which then reduces the ferric iron of methemoglobin to the ferrous state of normal hemoglobin nonenzymatically.
Proposed Indication:	For the treatment of acquired methemoglobinemia (b) (4)
Proposed Dose-Schedule:	(b) (4)

2.2 Currently Available Treatments for Proposed Indication

There are no therapies approved for treatment of acquired methemoglobinemia in the US.

2.3 Availability of Proposed Active Ingredient in the United States

Methylene blue injection 1% has been marketed in the US as an unapproved drug for treatment of methemoglobinemia by Akorn, Inc under NDC code 17478-504, by General Injectables & Vaccines, Inc., under NDC codes 52584-310 and 52584-504, and by American Reagent, Inc., under NDC codes 0517-0301, 0517-0372 and 0517-0373. In addition, the Ceretec

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

(exametazime) kit, marketed by Medi-Physics Inc., as a diagnostic radiopharmaceutical, contains 1 mL vials of Methylene Blue Injection 1%.

Oral medications that include methylene blue as an active ingredient are the homeopathic drugs CS Lung, and Guna-Kidney. Marketed but unapproved drugs for oral use that include methylene blue are Azuphen, Hyoley, Hyphen, Indiomine, Phosphasal, UR N-C, Uramit, Urelle, Uribel, Urimar-T, Urin D/S, Uro-L, Uro-MP, Urogesic Blue, Urolet, Urophen, Ustell, Uta and Utira-C.

2.4 Important Issues with Consideration to Related Drugs

Methylene blue in various formulations has been in clinical use for over 100 years, but in the absence of a controlled clinical trial, there is no comprehensive assessment of its safety when used for treatment of methemoglobinemia.

Methylene blue is a potent monoamine oxidase inhibitor (MAOI) inhibitor with substantial potential for adverse drug interactions. Numerous cases of serotonin syndrome in patients who received methylene blue while on serotonergic medications have been reported to the FDA Adverse Event Reporting System (AERS) database, and in 2011 FDA issued a safety communication warning that serious CNS reactions may occur when methylene blue in any formulation is administered to patients taking serotonergic drugs (FDA Drug Safety Communication, 2011a, 2011b).

Labels of current marketed but unapproved methylene blue injection formulations include contraindications for use during pregnancy due to potential teratogenicity based on publications of adverse effects in neonates after use during pregnancy. Other warnings and precautions in such labeling include the risk of paradoxical methemoglobin formation with rapid infusion of high doses of methylene blue, and the risk of hemolysis induced by methylene blue in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

NDA 204630 for ProvayBlue Injection 0.5% was initially submitted 8/13/2012 under 505(b)(2) for the indication “treatment of acquired methemoglobinemia.” The key events in the US presubmission regulatory activities include:

01/30/2012	Type B Pre-NDA meeting held under IND 113942
08/13/2012	Original submission of NDA 204630
10/11/2012	Issuance of Refuse-To-File (RTF) Letter
12/18/2012	Type A Refuse-To-File meeting
05/24/2013	Type B Pre-IND meeting held under IND 118156
06/28/2013	Orphan designation for treatment of acquired methemoglobinemia.
09/13/2013	Resubmission after Refusal to File
10/10/2014	Issuance of a Complete Response Letter

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

FDA provided the following key advice and comments to the sponsor regarding the clinical aspects for the preparation of this submission:

- The publications cited are not adequate and well-controlled trials of methylene blue [*Pre-NDA, RTF Letter, Type A*]
- The analysis of reports to the American Association of Poison Control Centers (AAPCC) does not comply with the requirements of an adequate and controlled trial [*Type A*]
- If published data are used as the primary support of the NDA, establish that use of the data is scientifically appropriate [*Pre-NDA, RTF Letter, Type A, Pre-IND*]
- A single-arm clinical trial of ProvayBlue, or a prospectively-defined retrospective study may be acceptable to support submission of an NDA if the study is designed adequately [*Type A*]
- Identify quantifiable primary and secondary endpoints that denote clinical benefit. FDA recommended a 50% reduction in methemoglobin in 1 hour as the primary endpoint and clinical signs of distress such as tachycardia, tachypnea or altered mental status as secondary endpoints [*RTF Letter, Type A, Pre-IND*]
- Categorize and quantify adverse events [*RTF Letter, Type A, Pre-IND*]
- Address QT/QTc prolongation risks of ProvayBlue [*Pre-NDA, RTF Letter, Type A, Pre-IND*]
- The draft case report forms are not sufficiently detailed to allow for collection of all information required to support the assessment of safety and efficacy [*Pre-IND*]
- The datasets submitted should comply with study data standards [*Pre-NDA, Pre-IND*]

Methylthioninium chloride (Proveblue) 5 mg/ml solution for injection was approved by EMA 6/5/2011 for acute symptomatic treatment of medicinal and chemical products-induced methemoglobinemia. The approval was based solely on published case reports and case series of use of methylene blue

2.6 Other Relevant Background Information

Numerous oxidizing drugs, chemicals and toxins are known to cause methemoglobinemia. Cyanosis is apparent when the methemoglobin concentration exceeds 1.5 gm/dL (about 10%). Additional signs and symptoms of reduced oxygenation and organ damage occur as the level of methemoglobin increases (Table 2) (Wright, Lewander, et al. 1999). The absolute level of methemoglobin that causes clinical signs and symptoms other than cyanosis varies by individual, being as low as 10% in some cases (Guay 2009). Methemoglobinemia can be fatal if very high levels persist.

Table 2: Signs And Symptoms By Methemoglobin Concentration

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Adapted from Wright, Lewander, et al. 1999.

The effect of the offending agent on methemoglobin induction is generally reversible once the offending agent is eliminated. The rate of conversion of methemoglobin to hemoglobin by homeostatic processes was estimated as 15% per hour (Finch, 1947). The course of reversion can be protracted, however, if methemoglobinemia was induced by drugs such as dapsone which have a prolonged enterohepatic circulation that extends exposure. In such cases, exchange transfusions can reduce the methemoglobin level quickly, but other ancillary means, such as gastric lavage, activated charcoal or dialysis, may be needed to remove the toxic agent.

The current standard of care for treatment of methemoglobinemia is to administer methylene blue at 1 - 2 mg/kg over 5 minutes to patients with symptomatic methemoglobinemia and/or those with a methemoglobin level acutely elevated to more than 25% (Price, 2011; Howland, 2011). However, there are no published reports of adequate and well-controlled studies of any methylene blue preparation that showed a clinical benefit for subjects with any prespecified risk. The choice of clinical benefit endpoint and intended population suitable for assessment in a marketing application are discussed further in Section 6.1.1.

2.7 Compliance with the Pediatric Research Equity Act

Since this product has orphan designation for treatment of acquired methemoglobinemia, this submission is exempt from the requirements of the Pediatric Research Equity Act.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was received 10/9/2015 in eCTD format. The submission had several documents missing, and there were no datasets for the new studies submitted. Following receipt of responses to information requests, the resubmission was found to be technically complete for review.

The assessments of efficacy and safety in this review depend in part on the information submitted in the previous resubmission on 9/13/2013. The data sets for Protocol PVP-2013001 in that submission had numerous issues which the applicant did not correct after multiple requests. In view of the public health need, this reviewer chose to forego any further attempts to obtain corrected data sets from the applicant and proceeded with a detailed audit of the data tables against what was legible in the case report forms, and with correction and reformatting of the data set based on the material submitted. The data sets constructed by this reviewer for Protocol PVP-2013001 were used for the analyses described in Sections 5 and 6 of this review.

3.2 Compliance with Good Clinical Practices

This submission included results from two new protocols, PVP-2014001 and PVP-2014002. The applicant indicated that both protocols were conducted in compliance with Good Clinical Practice. At the time of this submission, there were no outstanding issues from the prior inspections for Protocol PVP-2013001. There were no new clinical trials in the intended patient population submitted in this supplement, so no new clinical site inspections were requested of the Good Clinical Practice Branch of the Office of Scientific Investigations.

3.3 Financial Disclosures

The applicant provided certification on FDA Form 3454 that there were no financial arrangements that met the requirements for disclosure for the investigators in Protocols PVP-2014001 and PVP-2014002.

4 Significant Issues Related to Other Review Disciplines

4.1 Product

At the time of completion of this review, the Chemistry Manufacturing and Controls review was still pending.

4.2 Preclinical Pharmacology/Toxicology

The following is a summary of relevant information taken from the Pharmacology/Toxicology Review and Evaluation by Dr. Brenda J. Gehrke and Dr. C. J. George Change dated 5/28/2014:

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

4.2.1 General Toxicology

The Preclinical Pharmacology/Toxicology reviewer evaluated one in vivo study of ProvayBlue conducted by the applicant and one in vivo study of methylene blue trihydrate conducted by the National Toxicology Program. These were a 1-month repeat-dose study of ProvayBlue 0.25 – 2 mg/kg/day intravenously in dogs and a 3-month repeat-dose study of methylene blue trihydrate 25 - 200 mg/kg orally in rats. The preclinical reviewers noted toxicities in the following organ systems:

- Hematopoietic (anemia, reticulocytosis, methemoglobinemia, Heinz body formation and marrow hyperplasia)
- Spleen (increased weight of spleen, congestion, lymphoid depletion, capsular fibrosis)
- Liver (increased liver weight, increased bilirubin, inflammatory cell foci, brown pigment in the Kupffer cells)
- Kidney (brown pigment in proximal tubular cells)
- Skin (injection site hemorrhage, edema, inflammatory cell infiltrates, fibrosis)

4.3.2 Genotoxicity and Carcinogenicity

ProvayBlue and methylene blue trihydrate were mutagenic in the Ames test. The latter was also genotoxic in chromatid exchange and chromosomal aberration tests, and caused a dose-related increase in pancreatic islet cell hyperplasia and an increase in the incidence of islet cells adenomas or carcinomas in a 2-year carcinogenicity test. ProvayBlue itself was not tested for genotoxicity or carcinogenicity.

4.3.2 Reproductive and Developmental Toxicology

Only methylene blue trihydrate given orally was evaluated in embryo-fetal studies. These studies showed post-implantation loss (primarily resorptions), spontaneous abortions, and decreased fetal body weight. Teratogenic effects included enlarged ventricles and umbilical herniae. The embryo-fetal toxicities were observed at doses that were maternally toxic. There were no fertility studies conducted.

The Preclinical Pharmacology/Toxicology reviewer noted that there was no new preclinical information in the current submission (Pharmacology/Toxicology Review by Dr. Brenda J. Gehrke dated 3/1 2016). Approval was recommended.

4.3 Clinical Pharmacology

4.3.1 Mechanism of Action

Methylene blue is a prodrug for an oxidation reduction agent. NADPH methemoglobin reductase reduces methylene blue to leukomethylene blue which then reduces methemoglobin to hemoglobin nonenzymatically.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

4.3.2 Pharmacokinetics

The following is a summary of relevant information taken from the Clinical Pharmacology Review by Dr. Salaheldin S. Hamed dated 3/18/2016.

The pharmacokinetics (PK) of ProvayBlue was evaluated in a single-dose study of 2 mg/kg intravenous over 5 minutes in healthy volunteers. There was a concentration-dependent partitioning of methylene blue into red blood cells, and the steady state volume of distribution was large at 255-299 L. The AUC of azure B, the major metabolite of methylene blue, was < 20% of the AUC for methylene blue. The half-lives of both methylene blue and azure B were approximately 24 hrs. The relative contributions of renal and hepatic pathways to the elimination of methylene blue in vivo were not characterized. Multiple-dose pharmacokinetic parameters were not evaluated.

[REDACTED] The Clinical Pharmacology Reviewer judged [REDACTED] to be unreliable, and therefore did not agree with the proposed [REDACTED]

(b) (4)

(b) (4)

(b) (4)

In vitro methylene blue was metabolized by recombinant forms of CYP1A2, CYP2C19, CYP2D6, UGT1A4, and UGT1A9, and metabolism by the CYP450 and UGT pathways was confirmed using human liver microsomes. Also, in vitro methylene blue was a potent reversible inhibitor of the CYP450 enzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4. Based on the data from the pharmacokinetics study, it was estimated that following a single 1 mg/kg dose, blood concentrations of methylene blue would be high enough to cause a drug-drug interactions for 2 - 5 days, depending on the CYP450 enzyme. Methylene blue also inhibited P-glycoprotein (P-gp).

A bioequivalence study comparing ProvayBlue to Methylene Blue USP 1% was confounded by a substantial difference in nominal strength between the two agents, but after correcting for the difference in dose, the reviewer concluded that the results were adequate to establish a pharmacokinetics bridge between ProvayBlue and Methylene Blue USP 1%.

The Clinical Pharmacology Reviewer recommended approval with postmarketing requirements for studies to assess the effect of renal impairment on ProvayBlue pharmacokinetics, to assess the effect of hepatic impairment on ProvayBlue pharmacokinetics, and to assess the effect of ProvayBlue on the pharmacokinetics of CYP450 enzyme substrates.

4.4 Interdisciplinary Review Team (IRT)

The effect of ProvayBlue on cardiac conduction was assessed in a randomized, open-label, single-dose, cross-over thorough QT study in healthy volunteers (PVP-2014002). The IRT concluded that no significant QTc prolongation effect was detected for a single 2 mg/kg intravenous dose of ProvayBlue. They did note that patients treated with multiple hourly doses of ProvayBlue might have blood concentrations of methylene blue well above those achieved in

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

this thorough QT study, and the study results would largely be applicable only to those patients who received no more than 2 mg/kg.

4.5 Pharmacovigilance

The final assessment from the Division of Pharmacovigilance was not available at the time of completion of this review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3 describes the clinical studies as listed by the applicant in Module 5.2.

Table 3: Clinical Trials/Studies

Trials / Status	Design	Population	Primary Endpoint
PVP-2013001	Retrospective chart review · ProvayBlue (dose unspecified)	Patients who had been treated with ProvayBlue for methemoglobinemia · 12 subjects identified	At least 50% reduction of methemoglobin at one hour after infusion
PVP-2013002	Compassionate use program · ProvayBlue 1-2 mg/kg iv hourly up to 7 mg/kg	Adults and children >3 mos old with methemoglobinemia or other diagnosis · 27 subjects enrolled	Safety
PVP-2014001	randomized, double blind, intravenous, single-dose bioequivalence study · ProvayBlue 2 mg/kg · Methylene blue USP 1% 2 mg/kg	Healthy volunteers · 70 subjects enrolled and randomized 1:1	PK equivalence
PVP-2014002	randomized, single-dose, 3-period crossover thorough QT study · ProvayBlue 2 mg/kg iv · Moxifloxacin po · Placebo iv	Healthy volunteers · 48 subjects enrolled	QTcF effects
1MBL12002 (A98923)	Intravenous single-dose PK and safety study · Methylene blue USP 1% 1 mg/kg	Healthy volunteers · 12 subjects enrolled	Safety, tolerability and PK
PVP-2013003	Survey of EU poison centers for database elements	EU poison centers	Not applicable
AAPCC	Statistical analysis of the National Poison Data System · Methylene blue (agent and dose unspecified)	Poisoning reports collected by the AAPCC · 1628 records identified	Not applicable

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

5.2 Review Strategy

The key materials used for the review of efficacy and safety include:

- NDA 204630
- Relevant published literature
- Relevant information in the public domain (including postmarket safety data)

This review is based on the new information and analyses in this submission. Relevant results from the review of the protocols in the prior resubmission are described in Section 5.3.

Statistical analyses by the clinical reviewer were performed using JMP 11.0 (SAS Institute, Inc., Cary, NC), Stata/IC v12.1 (StataCorp, College Station, TX), and MedDRA Adverse Events Diagnostic (MAED) v1.2 (Clinical Trials & Surveys Corporation, Owings Mills, MD). When sample size was small, confidence intervals were calculated by Wilson score.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol PVP-2013001

The Collection Of Retrospective Clinical Data On The Use Of Proveblue® Injection, 0.5%, Methylene Blue, For Treatment Of Acquired Methemoglobinemia

Protocol PVP-2013001 was a retrospective chart review. To ascertain cases, “Provepharm is to contact as many hospitals as possible in an effort to identify patients who have been treated with ProvayBlue Injection, 0.5% for acquired methemoglobinemia” (Protocol PVP-2013001 Section 1). Selected subjects were those who presented with acquired methemoglobinemia precipitated by any etiology and requiring ProvayBlue® Injection, 0.5% under an emergency setting in Europe, during the period 2010 - 2012. Cases were identified from a) a compassionate use protocol in France, b) direct inquiry to hospitals in France and the United Kingdom, and c) direct inquiry to Poison Prevention Center in Taiwan.

The primary efficacy endpoint was defined as a methemoglobin decrease of at least 50% at one hour after IV administration of ProvayBlue® Injection, 0.5%. Other objectives listed included:

- Determine ProvayBlue® Injection, 0.5% initial dosing range.
- Determine re-dosing decision parameters and values.
- Determine effects of ProvayBlue® Injection, 0.5% on QT/QTc alteration of the ECG.
- Determine effects of ProvayBlue® Injection, 0.5% in patients with concomitant kidney disease.
- Determine pediatric dosing

The five categories of data to be collected included Patient Information, Toxic Agent, Clinical Presentation, Treatment and Safety, including all laboratory test results, vital sign changes, ECG changes and incidence of observed and reported signs and symptoms that are available. No statistical analyses were planned. For the assessment of efficacy, the protocol indicated that “all

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

blood levels of MetHb at and post-treatment will be plotted” (Protocol PVP-2013001 Section 6.2) There were no sample size calculations.

The review of the prior submission (Received 9/13/2014) reported the following:

The applicant identified 12 patients treated with ProvayBlue. Demographics of the patients are shown in Table 4. Race and ethnicity were not provided by the applicant.

Table 4: PVP-2013001 - Patient Characteristics

Parameter	All Subjects (n = 12)
Median Age	27 years
(range)	(6 days – 54 years)
Gender	
Male	7 (58%) ^a
Female	5 (42%)
Cause of Methemoglobinemia	
Amyl nitrate	5 (42%)
4-Nitroanilin	1 (8%)
Sodium Nitrite	1 (8%)
Dapsone	1 (8%)
Mesalazine	1 (8%)
Metaclopramide	1 (8%)
Green bean powder	1 (8%)
Cactus leaves	1 (8%)
Reason for Treatment	
Tachycardia, tachypnea	5 (42%)
Tachycardia	3 (25%)
Coma, tachycardia, tachypnea	2 (17%)
Renal failure, tachypnea	1 (8%)
Diaphoresis	1 (8%)
Median Methemoglobin	44%
(range)	(11-75%)

Source: FDA analysis

^a Number (percentage of patients with data available)

The baseline methemoglobin for nine patients was at least 30%, a level consistent with signs and symptoms that would warrant intervention. In all, 83% of the patients were tachycardic, 67% had tachypnea, and 17% were comatose. The applicant reported that four patients had respiratory depression, but this could not be confirmed from the data submitted. The concomitant treatments reported included oxygen for 8 (73%), ascorbic acid for 1 (9%), activated charcoal for 1 (9%), and gastric lavage for 1 (9%).

The patients in Protocol PVP-2013001 were treated between January, 2011 and November, 2012. Seventeen doses of ProvayBlue were administered. Patient 010 received two injections starting 5 minutes apart, and these were considered as one dose for the purposes of this analysis. One subject had 4 doses, 1 had 3 doses, and the others received a single dose of ProvayBlue. It was noted that drug was diluted to 100 mL in 5% dextrose for Patient 009, and it is presumed

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

that the remainder of the doses were administered directly without dilution. The recorded duration of administration varied from 5 to 30 minutes.

The applicant reported that the initial dose was 1 mg/kg for 7 patients, 1.5 mg/kg for 1 patient, and 2 mg/kg for 4 patients. One patient had no recorded weight, so a weight-based dose could not be confirmed. The applicant reported that the cumulative dose was 1 mg/kg for 7 patients, 1.5 mg/kg for 1 patient, 2 mg/kg for 2 patients, 7 mg/kg for 1 patient, and 13 mg/kg for 1 patient. For the 11 evaluable patients, FDA calculated the cumulative dose to be 1-1.2 mg/kg for 6 patients, 1.5 – 2.0 mg/kg for 3 patients, 6.4 mg/kg for 1 patient and 12.8 mg/kg for 1 patient. The highest single dose administered was 9.8 mg/kg (Patient 003) as calculated by FDA.

Follow-up was limited to hospitalization. The median duration of hospitalization was 2.5 days (range 2 hours to 15 days). All patients recovered and were discharged or transferred to an alternative unit for nonmedical care.

The applicant provided no analysis of the primary endpoint. The applicant stated that “all the patients were reported to have had a satisfactory medical outcome so it can be assumed that the metHb level at discharge had decreased to clinically acceptable levels” (Protocol PVP-2013001 Clinical Study Report 4/30/2014 p.23).

Of the 12 patients in the study, 4 had no methemoglobin measured after treatment, 1 had a measurement only after the second dose of ProvayBlue, and 1 had a result after the first dose, but the time of sampling was not indicated. Results after the first dose of ProvayBlue for the other 6 patients as calculated by FDA are shown in Table 5. The applicant provided no formal assessment of vital signs concurrent with treatment of the patients in the study cohort.

Table 5: PVP-2013001 - Methemoglobin Levels After Dose 1 of ProvayBlue

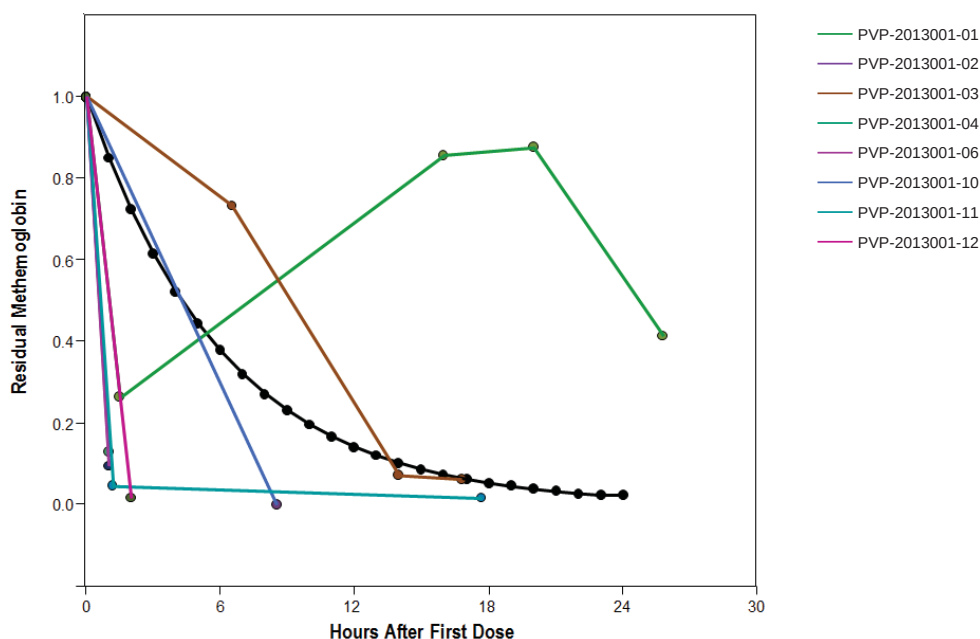
Patient	<u>Methemoglobin (%)</u>		% Reduction	Time After Dose (hr)
	Baseline	After Dose 1		
PVP-2013001-10	47.0	0	100.0	8.5
PVP-2013001-11	44.4	2.1	95.3	0.5
PVP-2013001-01	43.7	11.5	73.7	1.5
PVP-2013001-12	43.5	0.7	98.4	2.0
PVP-2013001-06	29.6	2.8	90.5	1.0
PVP-2013001-04	10.7	1.4	86.9	1.0

Source: FDA analysis

FDA used the additional measurements of methemoglobin available in Protocol PVP-2013001 to assess the durability of response to ProvayBlue. Figure 1 shows the residual proportion of methemoglobin by time after first dose of ProvayBlue. The black line represents the residual expected with homeostatic reduction of methemoglobin (15% per hour). Patients 01 (green line) and 03 (brown line) did not have rapid and durable responses.

Figure 1: PVP-2013001- Residual Methemoglobin After Treatment with ProvayBlue

The black curve represent the expected elimination with homeostatic mechanisms alone.



Source: FDA analysis

Patient 01(green line) had methemoglobinemia due to dapsone with a baseline methemoglobin level of 43.7%. Ninety minutes after the first dose of ProvayBlue, the methemoglobin was reduced to 11.5% (74% reduction), but it rose again at 16 hours to 37.4%. The patient received 3 additional doses of ProvayBlue (total 6.3 mg/kg in 4 doses over 1 day) at which time the methemoglobin fell to 18.1%. No further methylene blue was given, and the methemoglobin finally was below 1% after 3 additional days of observation.

Patient 03 (brown line) had methemoglobinemia due to 4-nitroaniline toxicity with a baseline methemoglobin level of 75%. At 6.5 hours after the first dose of ProvayBlue (2.5 hours after the second dose), the methemoglobin was reduced to only 55% (27% reduction). The patient received 2 additional doses of ProvayBlue (total 12.8 mg/kg in 3 doses over 12 hours), and the methemoglobin fell to 5.5%. No further methylene blue was given, and the methemoglobin was finally below 1% after 2 additional days of observation.

There were no deaths reported. Serious adverse events included one case each of hemolytic anemia, methemoglobinemia, Klebsiella pneumoniae urinary infection, gastric lesions, suicidal thoughts, suicidal attempts, bilirubinemia and polycythemia. The applicant considered none of the serious adverse events to be related to ProvayBlue. The applicant reported 15 adverse events

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

in five patients treated with ProvayBlue (Table 6). There were no events considered by the applicant to be related to ProvayBlue.

Table 6: Adverse Events in Protocol PVP-2013001

System Organ Class	Adverse event	Related	Unlikely	Not related	Not assessible
Blood and Lymphatic system disorders	Methemoglobinemia		N1		
	Hemolytic anemia				N1
	Polycythemia				N4
Skin and subcutaneous tissue disorder	Skin blisters		N1		
Psychiatric disorders	Sleep disorders		N1		
	Suicidal thoughts		N3		
	Suicidal attempts		N3		
Metabolism and nutrition disorders	Hypokalaemia				N1
Infections and infestations	Urinary infection			N2	
Gastrointestinal disorders	Gastric lesions		N3		
Investigations	Increased CPK		N3		
Investigations	Increased LDH		N3		
Investigations	Increased total bilirubin		N3		
Hepatobiliary disorders	Bilirubinemia		N4		
Hypersensitivity	Stuffy nose			N10	

From Protocol PVP-2013001 Clinical Study Report 4/30/2014 Table 17. N = Case number

FDA was not able to confirm the safety profile, since the tabulated summary provided in the clinical study report did not match the case report forms, and there were no dates in the adverse event data file. There were also no dates or times in the data files for vital signs or laboratory tests, so no analysis of these safety parameters could be performed.

5.3.2 Protocol PVP-2013002

Compassionate Use Cases For Named Patients In France

Protocol PVP-2013002 was a compassionate use study of ProvayBlue conducted in France. The indication was for treatment of medicinal and chemical products-induced methemoglobinemia in adults and children over 3 months of age. The ProvayBlue dose described was 1 - 2 mg/kg given intravenously over a period of 5 to 10 minutes with a repeat dose one hour after the first dose, if needed, and a maximum recommended cumulative dose of 7 mg/kg. The protocol required reporting of serious adverse effects, whether expected or unexpected, and unexpected adverse effects of any severity that were related to the treatment.

There were 16 adults and 11 children (total 27 patients) treated on Protocol PVP-2013002 from November, 2010 to October, 2011. One patient was treated for hereditary methemoglobinemia, and the remainder were presumed to have ifosfamide-induced encephalopathy. Nineteen patients received one dose of ProvayBlue, and eight received 2 - 5 doses (Protocol PVP-2013002 Study

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

Report Table 4). The maximum known initial dose of ProvayBlue administered was 2 mg/kg, but no information on dose was available for 23 of the patients (Protocol PVP-2013002 Study Report Table 2). No adverse events were reported by the applicant. There were no case report forms submitted to verify the lack of adverse events.

5.3.3 Protocol PVP-2014001

A Single-Dose, Parallel, Bioequivalence Study of Methylene Blue Intravenous Injection in Healthy Adult Volunteers

Protocol PVP-2014001 was a randomized, parallel-group, open-label, single-dose bioequivalence study in healthy volunteers. Subjects were randomized 1:1 to receive a single injection of 2 mg/kg ProvayBlue iv or 2 mg/kg Methylene Blue USP 1% iv. The primary objective was to assess the bioequivalence for methylene blue. The target accrual (including replacements for potential dropouts) was 70 subjects. The sample size had at least 80% power to have the 90% CI of geometric mean ratio (GMR) of analytes within the 80%-125% acceptance criteria, assuming a true ratio of 95%-105% and an intersubject CV of 27% based on the methylene blue AUCs as reported in Protocol 1MBL12002. There were no major protocol amendments that would affect the analysis of safety. The study assessments are shown in Table 7 below. Follow-up was through 7 days after administration of study drug.

Table 7: PVP-2014001 - Schedule of Assessments

Study Procedures ^a	S ^b	Study Days and Time Points for Treatment A or B																											FU ^c
		C-1 ^d	1																2		3		4						
			0 ^e	0.042	0.083	0.167	0.25	0.5	0.75	1	2	3	4	6	8	12	16 ^f	24	36	48	54	60	72						
Days →	Hours →	Minutes ^g →	0	2.5	5	10	15	30	45																				
Administrative Procedures																													
Informed Consent	X																												
Inclusion/Exclusion Criteria	X	X																											
Medical History	X																												
Safety Evaluations																													
Physical Examination ^h	X	X																										X ⁱ	
Height	X																												
Weight	X	X																											
Single 12-Lead ECG (Safety)	X	X						X		X			X				X											X ⁱ	
Triplicate 12-Lead ECG for extraction			X ^j			X	X	X		X								X										X ⁱ	
Vital Signs (HR & BP)	X		X ^k					X	X	X	X	X	X															X ⁱ	
Vital Signs (RR & T)	X																												
Hematology, Serum Chemistry, and UA ^l	X	X																X ^m									X ⁱ		
MethHb Measurements (sentinel group only)			X ⁿ							X							X		X										
Pulse Co-oximetry			X ⁿ										X			X	X	X	X										
G6PD Deficiency Screen	X																												
Serum Pregnancy Test (♀ only)	X	X																										X ⁱ	
Serum FSH (postmenopausal ♀ only)	X																												
Urine Alcohol and Drug Screen	X	X																											
Urine Cotinine Screen	X																												
HIV/Hepatitis Screen	X																												
Infusion Site Reaction Assessment			X ^o												X		X												
AE Monitoring	X									X																		X	
ConMeds Monitoring	X									X																			
Methylene Blue Administration				X																									
Blood for Methylene Blue and Azure B PK ^q			X ^o	X	X ^o	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Source: Protocol PVP-2014001 Section 6 Study Events Flow Chart

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

Enrollment commenced on 3/8/2015, and subject activities concluded on 5/26/2015. Seventy subjects were randomized (35 on each arm), and all completed the study. There were 196 deviations reported for 59 subjects, but all were considered minor, and none affected the analyses of safety. The demographics and safety results are discussed in Section 7. Table 8 shows the results of the analyses of the PK parameters for bioequivalence of ProvayBlue and Methylene Blue USP 1% based on methylene blue and azure B whole blood concentrations.

Table 8: PVP-2014001 - PK Equivalence Analyses for ProvayBlue vs Comparator

	Methylene Blue Geometric Mean Ratio ^{a,b}	Azure B Geometric Mean Ratio ^a
C _{max}	114.8% (96.5-136.7)	54.3% (48.7-60.4)
AUC _{0-t}	101.9% (95.3-109.0)	94.8% (86.4-104.1)
AUC _{inf}	104.3% (96.5-112.7)	98.7% (90.3-107.9)

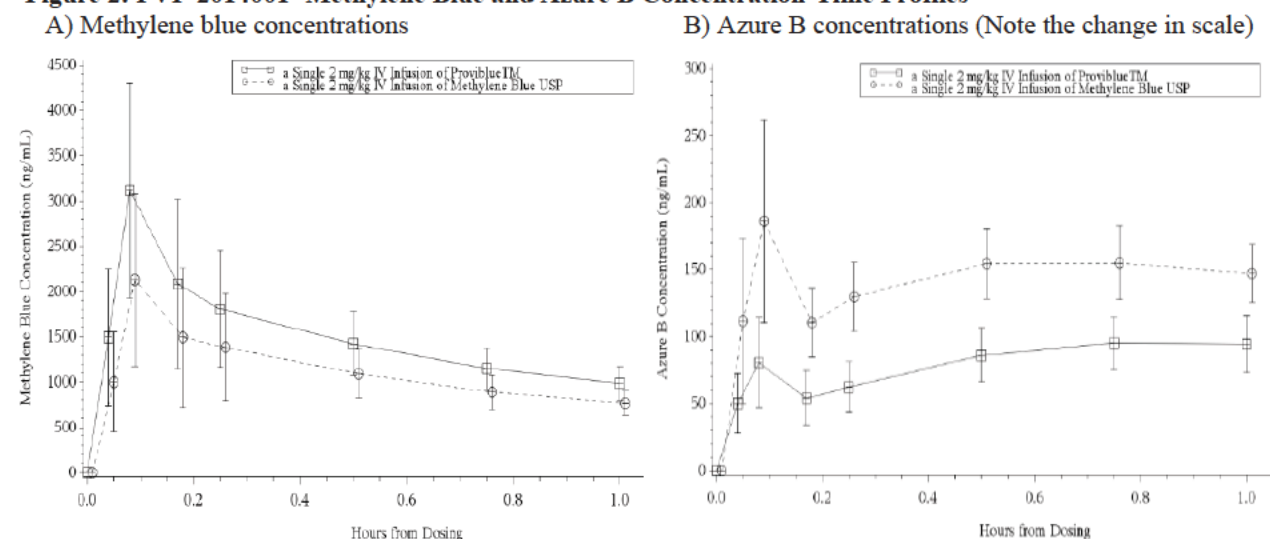
Source Study PVP-2014001 Clinical Study Report Tables 11-3 and 11-7

^a100*(ProvayBlue result/Methylene Blue USP 1% result) (90% CI)

^bDose (mg) normalized

Since the actual strengths of the test and reference products differed by more than 5%, the applicant normalized the methylene blue parameters for actual dose (mg) prior to testing for PK equivalence. Since the upper bound of the 90% confidence interval for methylene blue C_{max} exceeded 120%, the applicant concluded that ProvayBlue and Methylene Blue USP 1% were not bioequivalent (Protocol PVP-2014001 Clinical Study Report Section 11.4.7). Figure 2, the concentration profiles for the analytes in whole blood over the first hour after injection, shows the extent of the difference in methylene blue whole blood C_{max} at 0.1 hours (Figure 2 (A)).

Figure 2: PVP-2014001- Methylene Blue and Azure B Concentration-Time Profiles



Source: Study PVP-2014001 Clinical Study Report Figures 11-1 and 11-2

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

5.3.4 Protocol PVP-2014002

A Single Center, Randomized, Placebo And Positive-Controlled, Cross-Over Thorough QT Study To Assess The Effect Of A Single Intravenous Dose Of Methylthioninium Chloride Proveblue On QTc Interval In Healthy Subjects

Protocol PVP-2014002 was a randomized, open-label, single-dose, cross-over thorough QTc study in healthy volunteers. The Holter-ECG analysts were blinded to the study drug. Subjects were randomized to 1 of 6 sequence groups to receive a single injection of ProvayBlue 2 mg/kg iv, moxifloxacin 400 mg orally, and placebo (sodium chloride) iv with a washout period of 7 days between each treatment. The primary objective was to evaluate the effect of a single dose of ProvayBlue on the change in time-matched QTcF interval. The target accrual (including replacements for potential dropouts) was 48 subjects. The sample size had 90% power to exclude a QTc effect >10 msec if the true effect was up to 3 msec as based on the published effect size for placebo). Safety and PK were also assessed. There were no major protocol amendments after the initiation of the study that would affect the analysis of safety. The study assessments are shown in Table 9 below. Follow-up was through 7 days after the last administration of study drug.

Table 9: PVP-2014002 - Schedule of Assessments

	Treatment Periods 1, 2, and 3 ¹					
	Outpatient	Inpatient Confinement			Outpatient	Outpatient
	Days -28 to -2	Day -1, Day 7, Day 14	Day 1, Day 8, Day 15	Day 2, Day 9, Day 16	Days 3 to 6, Days 10 to 13	Day 22±1
	Screening	Admission or Readmission	Dosing and Observation	Observation and Discharge		Follow-up (after last Treatment Period)
Administrative Procedures						
Informed consent ²	X					
Inclusion/Exclusion criteria ³	X	X				
Demographics, medical history ⁴	X	X				
Concomitant medications ⁵	X	X	X	X		X
Randomization ⁶		X				
Clinic Procedures/Assessments						
Physical examination (PE) ⁷	X	X		X		X
Weight, height and body mass index ⁸	X	X				
12-lead safety electrocardiogram (ECG) ⁹	X		X	X		X
24-hour, 12-lead Holter ECG period ¹⁰			X	X		
Holter ECG extraction times ¹¹			X	X		
Vital signs ¹²	X		X	X		X
IMP administration ¹³			X			
Standard meals ¹⁴			X	X		
Adverse events ¹⁵	X	X	X	X		X
Laboratory Procedures/Assessments						
Clinical laboratory safety tests ¹⁶	X	X		X		X
Follicle stimulating hormone	X					X
Pregnancy tests (all female subjects)	X (serum)	X (urine)				X (urine)
Urine drug screen, alcohol and cotinine testing ¹⁷	X	X				X
HIV/hepatitis screen	X					
Pharmacokinetic Evaluations						
Blood for methylthioninium chloride Proveblue and moxifloxacin ¹⁸			X	X		
Other Procedures						
Confinement and discharge ¹⁹		X	X	X		

Source: Protocol PVP-2014002 Table 8-2

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

Enrollment commenced 5/6/2015, and subject activities concluded on 6/29/2015. Forty-eight subjects were randomized. One subject withdrew after the first treatment period, and the other 47 subjects completed the study. There were 32 protocol deviations reported for 19 subjects, but all were considered minor and none affected the analyses of safety. The demographics and safety results are discussed in Section 7.

5.3.5 Protocol 1MBL12002 (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

Protocol 1MBL12002 was a single-center, open-label, single-dose study of methylene blue in healthy volunteers. The test article, Methylene Blue Injection, USP 1%, was administered as a dose of 1 mg/kg intravenously over 5 minutes. The primary objective was to assess safety, tolerability and PK. The target accrual was 12 subjects; there was no statistical basis for the sample size. There were no amendments following the start of the study. The schedule of study assessments is shown in Table 10 below. Follow-up was through at least 72 hours after administration of study drug.

Table 10: 1MBL12002 - Schedule of Assessments

Study Phase	Screening	Study Days					End of Study or Early Termination ^a
Activity	Within 28 days of dosing	Check-in Day -1 ^b	Day 1	Day 2	Day 3	Day 4	
Informed Consent	X						
Medical History and Demographic Data	X						
Physical Exam ^c	X	X					X
ECG (12-lead) ^d	X		X	X			X
Vital Signs ^e	X	X	X				X
Hematology	X						X
Urinalysis	X						X
Serum Chemistry	X						X
HIV/Hepatitis B & C Screen	X						
Urine Drug/Alcohol Screen	X	X					
G6PD Deficiency Screen	X						
FSH (postmenopausal females only)	X						
Serum Pregnancy Test (for females only)	X	X					X
Record of Concomitant Medication	X	X	X	X	X	X	X
Check-in Procedures		X					
Confinement in Study Unit		X	X	X	X	X	
Drug Dosing			X				
PK Blood Sampling ^f			X	X	X	X	
AEs Monitoring		X	X	X	X	X	X

Source: Protocol 1MBL12002 Section 5 Study Events Flow Chart

Enrollment commenced 10/10/2012, and subject activities were concluded as of 10/13/2012. Twelve subjects were enrolled, and all completed the study. The demographics of the population and the safety results are discussed in Section 7.

6 Review of Efficacy

6.1 Treatment of Acquired Methemoglobinemia

The proposed indication is treatment of acquired methemoglobinemia

6.1.1 Methods

The review strategy has been described in Section 5.2. The analysis of efficacy was based on Protocol PVP-2013001. Details of the protocol design were described in Section 5.3.1.

Efficacy was assessed on the basis of a methemoglobin decrease of at least 50% at 1 hour after IV administration of ProvayBlue or Methylene Blue USP 1%. This was the primary endpoint of Protocol PVP-2013001. Methemoglobin can be estimated by oximetry of an arterial blood sample, measured directly by co-oximetry, or measured noninvasively by pulse co-oximetry. The applicant did not include the method of measurement in the case report forms, so it will not be possible to estimate the potential error of the measurement of the primary endpoint.

Review Comment: It has been established that methemoglobin levels >70% have a high mortality, and that there are few serious symptoms when the methemoglobin is <20%. For patients with life-threatening complications from high levels of methemoglobin, a 50% reduction within 1 hour after a dose would be estimated to reduce the methemoglobin from 70% to 17% after 2 successive doses (2 hours), which would be reasonably likely to rapidly reduce the complications of methemoglobinemia. Moreover, a 50% reduction of methemoglobin in 1 hour could not be achieved by normal homeostatic mechanisms, so the result could be attributed to investigational agent even in a study without concurrent controls. Concomitant resolution of established signs of serious methemoglobinemia, such as tachypnea, tachycardia or coma, within 2 hours would provide an objective measure of a clinical benefit.

The literature was also searched for cases that included sufficient detail to assess efficacy. There were 44 cases of treatment of methemoglobinemia that included a baseline measurement and a follow-up measurement within 1.25 hours (see Appendix 9.2). Since the conclusion of the Clinical Pharmacology reviewer for Protocol PVP-2014001 was that ProvayBlue was sufficiently bioequivalent to Methylene Blue USP 1% (see Section 4.3), the literature cases were further reviewed to identify those which used Methylene Blue USP 1% specifically. None of the references provided the source of the methylene blue used. Twenty-eight of the publications were from US healthcare providers. A query was sent to the corresponding author and/or Director of Pharmacy for 24 of the published reports in which contact information could be identified in order to determine if they could confirm that Methylene Blue USP 1% was used.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

FDA received 16 responses (67% response rate), of which 12 could not confirm, 1 indicated that 1% methylene blue was used but did not confirm that the product was USP, and 3 confirmed that Methylene Blue USP 1% was in use at the institution in the timeframe of the treatment described in the case report. Only these last 3 cases were considered in the analysis of efficacy.

6.1.2 Demographics

The Efficacy Population consisted of the 3 patients treated with ProvayBlue in Protocol PVP-2013001 and the 3 patients in the published cases of methemoglobinemia treated with Methylene Blue USP 1% for whom adequate data were available to assess efficacy. Table 11 shows the demographic characteristics of the Efficacy Population. Race/ethnicity was not recorded for 5 of the 6 patients.

Table 11: Efficacy Population Demographics

Patient	Age	Gender	Cause of Methemoglobinemia	Initial Dose ^a
PVP-2013001-04	6 days	Female	Metoclopramide	1 mg/kg
PVP-2013001-06	40 years	Male	Nitrite	1 mg/kg
PVP-2013001-11	1.8 years	Male	Sodium nitrite	2 mg/kg
Annabi 2009	69 years	Female	Benzocaine	2 mg/kg
Birchem 2005	69 years	Female	Benzocaine	2 mg/kg
Grauer 1996	68 years	Male	Benzocaine	1 mg/kg

Source: FDA analysis

^aInitial dose of ProvayBlue or Methylene Blue USP 1%

6.1.3 Treatment and Disposition

The initial doses of ProvayBlue or Methylene Blue USP 1% administered are listed in Table 11 above. The reported durations of the infusions ranged from “bolus” to 30 minutes. All of the patients were reported to have recovered from the methemoglobinemia.

6.1.4 Primary Efficacy Endpoint

The applicant provided no analysis of the primary endpoint in Protocol PVP-2013001. The applicant stated that “all the patients were reported to have had a satisfactory medical outcome so it can be assumed that the metHb level at discharge had decreased to clinically acceptable levels” (Protocol PVP-2013001 Clinical Study Report 4/30/2014 p.23).

Table 12 shows the results after the first dose of ProvayBlue or Methylene Blue USP 1% for the 6 patients in the Efficacy Population. All 6 patients (100%; 95% CI 61-100%) had > 50% reduction in methemoglobin within 1 hour of treatment.

Table 12: Methemoglobin Levels After Dose 1 of ProvayBlue or Methylene Blue USP 1%

Patient	<u>Methemoglobin (%)</u>		Relative Reduction	Time After Dose (hr)
	Baseline	After Dose 1		
PVP-2013001-04	10.7	1.4	87%	1.0
PVP-2013001-06	29.6	2.8	91%	1.0
PVP-2013001-11	44.4	2.1	95%	0.5
Annabi 2009	33.0	4.0	88%	1.0
Birchem 2005	41.1	18.4	55%	1.0
Grauer 1996	47.2	12.3	74%	0.3

Source: FDA analysis

Review Comment: With results in 6 patients, the lower bound of the 95% confidence interval is now above 50%, supporting the likelihood that the majority of patients with methemoglobinemia might be expected to have a rapid decrease in methemoglobin levels after treatment with ProvayBlue.

On review of the literature, an additional 41 cases of treatment of methemoglobin with a methylene blue class product intravenously included a follow-up measurement within 1 (+/- 0.25) hours (see Appendix 9.2). These cases form the Literature Population. This population included 24 males and 17 females of median age 33 years (range, 9 days to 80 years). The median methemoglobin level at baseline was 40% (range, 10% to 98%). Of these cases, 37 (90%; 95% CI 77-96%) had a methemoglobin decrease of at least 50% by 1 hour after IV administration of the methylene blue class product. The four nonresponders had a baseline methemoglobin >60%. All of the patients were reported to have recovered from the methemoglobinemia, and 2 died subsequently (one on day 2 and one on day 33) from presumably unrelated causes (Attof, Magnin, et al. 2006; Douglas and Fairbanks 1977).

Review Comment: The response rates from this analyses of the Literature Population should be interpreted with caution, since there may have been bias against reporting failures or in obtaining measurements of methemoglobin at one hour when the clinical results were obvious. Overall, however, they are consistent with the results in the Efficacy Population.

6.1.5 Subpopulations

The samples size in the efficacy population was too small for a meaningful analysis by subgroup. All 47 cases were pooled for the subgroup analysis (Pooled Population). The pool of 47 cases included pediatric patients in the following age groups: 3 neonates (less than 1 month), 4 infants (1 month up to less than 2 years), 4 children (2 years up to less than 12 years), and 3 adolescents (12 years to less than 17 years). In addition, there were 8 patients age $\geq$ 65 years. Table 13 shows the response rates by age, gender, baseline methemoglobin and etiology of the

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

methemoglobinemia. Responses were seen across all subgroups. The subgroups with the lowest response rates were those with a baseline methemoglobin > 60%, and when the etiologic agent was a toxic chemical (i.e. aniline, metaflumizone, nitrobenzene and phenazopyridine).

Table 13: Pooled Population – Subgroup Analysis of Response

	Responses ^a	Response Rate (95% CI)
<u>Age</u>		
< 2 years	7/7	100% (65% - 100%)
2 to < 17 years	6/7	86% (49% - 97%)
17 to < 65 years	21/23	91% (73% - 98%)
≥ 65 years	8/9	89% (57% - 98%)
Missing	1/1	100% (21% - 100%)
<u>Gender</u>		
Female	20/20	100% (84% - 100%)
Male	23/27	85% (68% - 94%)
<u>Baseline Methemoglobin</u>		
< 30%	16/16	100% (81% - 100%)
30% to 60%	20/20	100% (84% - 100%)
> 60%	7/11	64% (35% - 85%)
<u>Etiologic Agent</u>		
Nitrate/nitrite	10/10	100% (72% - 100%)
Other	5/5	100% (57% - 100%)
Dapsone	2/2	100% (34% - 100%)
Local anesthetic	20/21	95% (77% - 99%)
Toxic chemicals	6/9	67% (35% - 88%)

Source: FDA analysis

^aNumber of responders per total number in the subgroup. Response is defined as methemoglobin decrease of at least 50% within 1 hour after administration of the methylene blue class product.

The applicant identified a total of 24 published case reports with 29 patients ≥ 65 year old with methemoglobinemia treated a methylene blue class product at varying doses (Module 2.7.3 Summary of Clinical Efficacy Table 14). The tabular summary revealed no age-related pattern of failure in the elderly population.

The applicant identified a total of 40 published reports of children > 3 months old and 12 published reports of children < 3 months old with methemoglobinemia treated a methylene blue class product at varying doses (Module 2.7.3 Summary of Clinical Efficacy Tables 15 and 16). The tabular summary revealed no age-related pattern of failure in the pediatric population.

6.1.6 Analysis of Supporting Efficacy Endpoints

In presubmission meetings, FDA had encouraged the applicant to assess changes in respiratory rate, heart rate and neurological status after dosing as key secondary measures of efficacy (see Section 2.5 above). The applicant provided no formal assessment of vital signs. Although not a stated efficacy endpoint in Protocol PVP-2013001, FDA attempted a post hoc analysis of these

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

measures, but since there were no dates or times in the vital sign data file, the analysis could not be performed. Similarly, there were no vital signs reported for the cases from the literature.

FDA did assess relative percent reduction in methemoglobin as a supporting efficacy endpoint. The percent reduction was defined as $((\text{baseline methemoglobin} - \text{posttreatment methemoglobin}) / \text{baseline methemoglobin}) \times 100$. For the 6 patients in the efficacy population, the median reduction in methemoglobin was 87% (range, 55% - 95%). For the 41 cases in the literature series, the median reduction in methemoglobin was 83% (0% - 98%). Table 14 shows the reduction in methemoglobin by age, gender, baseline methemoglobin and etiology of the methemoglobinemia. The subgroups with the lowest relative reduction in methemoglobin were those with a baseline methemoglobin > 60%, and when the etiologic agent was dapsone or a toxic chemical (i.e. aniline, metaflumizone, nitrobenzene and phenazopyridine).

Table 14: Pooled Population – Subgroup Analysis of Percentage Methemoglobin Reduction

	n	Median Percent Methemoglobin Reduction (range)
<u>Age</u>		
< 2 years	7	92% (86% - 98%)
2 to < 17 years	7	89% (26% - 96%)
17 to < 65 years	23	72% (0% - 93%)
≥ 65 years	9	82% (26% - 93%)
Missing	1	69%
<u>Gender</u>		
Female	20	84% (51% - 98%)
Male	27	85% (0% - 97%)
<u>Baseline Methemoglobin</u>		
< 30%	16	88% (59% - 98%)
30% to 60%	20	87% (55% - 95%)
> 60%	11	51% (0% - 97%)
<u>Etiologic Agent</u>		
Nitrate/nitrite	10	90% (69% - 97%)
Other	5	87% (70% - 98%)
Local anesthetic	21	85% (26% - 94%)
Dapsone	2	65% (59% - 71%)
Toxic chemicals	9	62% (0% - 90%)

Source: FDA analysis

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant provided no analysis of efficacy by initial dose. The samples size in the efficacy population was too small for a meaningful analysis by dose. FDA evaluated the Pooled Population for a dose-response. Table 15 shows the response rates and percent methemoglobin reduction within 1 hour of the first dose of the methylene blue class product by dose. There were no substantial differences in response rate across the dose groups.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

Table 15: Pooled Population – Efficacy Outcomes by First Dose

Methylene Blue Product ^a Dose Group	Responses ^b	Response Rate (95% CI)	n	Median Percent Methemoglobin Reduction (range)
1 mg/kg	15/17	88% (66% - 97%)	17	87% (24% - 98%)
2 mg/kg	12/13	92% (67% - 99%)	13	73% (26% - 97%)
Other or unknown	16/17	94% (73% - 99%)	17	86% (0% - 93%)

Source: FDA analysis

^aIncludes ProvayBlue, Methylene Blue USP 1%, and other methylene blue class products

^bNumber of responders per total number in the subgroup. Response is defined as methemoglobin decrease of at least 50% within 1 hour after administration of the methylene blue class product.

(b) (4)

Review Comment: The results shown in Table 15 suggest that there is no added benefit of using 2 mg/kg over 1 mg/kg as the initial dose of ProvayBlue. However, there are no adequate data to establish the optimal duration of dosing when there is a lack of efficacy initially. This is discussed further in Section 6.1.8. The limitation of dosing based on safety considerations is discussed in Section 7.4.2.

The applicant observed that newborns and infants less than 3 months old were reported to have lower levels of NADH-methemoglobin reductase than adults (Gruener 1976)

(b) (4)

(b) (4)

(b) (4)

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

(b) (4)

In the 12 published reports of treatment of methemoglobinemia using a methylene blue class product in children < 3 months old provided by the applicant (Module 2.7.3 Summary of Clinical Efficacy Table 16), use of less than 1 mg/kg was cited in only 1 other publication (Guay 2009), but that report did not specify the age group for which the lower dose range was used. In 7 of the cases a dose of 1 mg/kg was used, in 2 cases 2 mg/kg was used, and no dose was specified in the other cases.

Review Comment:

(b) (4)

(b) (4)

6.1.8 Discussion of Lack of Efficacy

For the purposes of this review, lack of efficacy is defined as a failure to achieve a tolerable methemoglobin level with use of no more than two doses. As shown in Figure 1 in Section 5.3.1, there were two patients in Protocol PVP-2013001 who did not experience an initial and/or sustained response to treatment with ProvayBlue. Patient 01 (dapsone toxicity) had an initial reduction of methemoglobin from 44% to 12% at 1.5 hours after the first dose of ProvayBlue and then experienced a rebound to a methemoglobin of 37% at 16 hours. Patient 03 (aniline toxicity) had a reduction in methemoglobin from 75% to 55% after two doses of ProvayBlue over 6 hours.

The applicant identified 6 case reports of lack of efficacy (Module 1.11.4 Safety Update Report Table 12). Upon evaluation of these and the case reports and case series submitted to support efficacy (Module 2.7.3 Summary of Clinical Efficacy Tables 13-16), FDA noted a pattern for lack of efficacy in specific circumstances. Table 17 lists the publications describing the circumstances in which there were multiple reports for an individual agent regarding lack of an

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

initial response, a delay in complete resolution, or a risk of rebound following a response to intravenous treatment with a methylene blue class product.

Table 17: Examples of Lack of Efficacy of Methylene Blue Class Products

Category	References
<u>Genetic</u>	
Glucose-6-phosphate dehydrogenase deficiency	Foltz 2006; Golden 1998; Karadsheh2001; Mullick 2007; Rosen, 1971; Yang 2004
<u>Intoxication</u>	
Aniline	Bellik 2001; Ferrer-Gomez 2008; Kearney 1984; Mullick 2007; Pizon 2009;
Benzocaine	Muchmore 1979; Rodriguez 1994; Wurdeman 2000; Voelker 2002
Dapsone	Berlin 1985; Bucaretschi 2000; Canning 2011; Ferguson 1997; Hansen 1994; Lambert 1982; MacDonald 1997; Matisoff 2006; Moodambail 2005; Prasad 2002; Thunga 2008; Wieringa 2014
Nitroethane	Osterhoudt 1995; Shepherd 1998
Phenazopyridine	Christensen 1996; Jeffery 1982; Sharon 1986; Truman 1994

Source: FDA analysis

For the intoxicants listed in Table17, the potential reasons for the lack of efficacy cited in the cases included very high levels of methemoglobin, long half-life of the intoxicant in the body, and continued absorption of the intoxicant from the gastrointestinal tract or the mucosa (in the case of local application). This is not to suggest that ProvayBlue would be ineffective in all cases for treatment of methemoglobinemia from these intoxicants, since the majority of such patients treated with a methylene blue class product survived the event (Barclay, Ziemba, et al. 2011; Song, Li, et al. 2014). However, the incidence of lack of efficacy after chemical intoxication has not been quantitated, and the risk factors for lack of efficacy are unknown.

A false conclusion of lack of efficacy might also results from paradoxical methemoglobinemia induced by an overdose of methylene blue (Section 7.8.8).

Review Comment: Although the effect of ProvayBlue on methemoglobin levels is expected to be prompt, the potential for lack of efficacy merits a warning in the Prescribing Information, especially about the risk of rebound in patients treated for methemoglobinemia due to dapsone.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Protocols PVP-2013001, PVP-2013002, PVP-2014001, PVP-2014002 and 1MBL12002 were used for the analysis of safety. The protocol designs were described in Section 5.3. Since detailed safety data were available only for the studies in healthy volunteers (PVP-2014001, PVP-2014002 and 1MBL12002), these formed the main basis for the quantitative safety analyses in Sections 7.2 - 7.7. The safety information from Protocols PVP-2013001 and PVP-2013002, available published literature, and safety data from studies of other methylene blue class products are reported as such herein.

7.1.2 Categorization of Adverse Events

Adverse events for Protocols PVP-2014001, PVP-2014002 and 1MBL12002 were reported down to the verbatim term. The adverse events were coded using MedDRA versions 17.1, 18.0 and 15.1, respectively. TEAE were defined as AE that began after the start of infusion of the first dose of study drug. The applicant did not prespecify any adverse events of special interest.

7.1.3 Pooling of Data

In order to increase the sensitivity for low incidence adverse reactions, the data for the ProvayBlue cohorts from Protocols PVP-2014001 and PVP-2014002 were pooled where indicated in Section 7.4 and 7.5. Additionally, the safety data for both ProvayBlue and Mehtylene Blue USP 1% were pooled for the analysis of safety by maximal methylene blue concentration measured in Section 7.4.2.

7.2 Adequacy of Safety Assessments

7.2.1 Safety Population

Safety data were evaluated for 39 patients and 82 healthy volunteers who received at least one dose of ProvayBlue. The patient population was reviewed in the previous supplement, and the results are discussed in Section 7.7. The 82 healthy volunteers treated with ProvayBlue had a median age of 36 years (range, 19-55 years); 54% were male, and 68% were white. The demographic characteristics of all healthy volunteers are shown by study in Table 18.

Clinical Review
NDA 204630
ProvayBlue (methylene blue)

Table 18: Healthy Volunteers – Demographics

	<u>PVP-2014001</u>		<u>PVP-2014002</u>	<u>1MBL12002</u>
	PB 2 mg/kg (n=35)	MB 2 mg/kg (n=35)	Cross-over (n=48)	MB 1 mg/kg (n=12)
Median Age (Range)	32 years (20 – 40 years)	32 years (20 - 40 years)	43 years (19 - 55 years)	34 years (25 - 60 years)
Median Weight (Range)	70 kg (56 – 81 kg)	65 kg (55 - 81 kg)	75 kg (54 - 99 kg)	77 kg (58 - 94 kg)
Median BMI (Range)	25 kg/m ² (20 - 31 kg/m ²)	24 kg/m ² (18 - 31 kg/m ²)	24 kg/m ² (20 - 29 kg/m ²)	26 kg/m ² (20 - 29 kg/m ²)
Gender				
Male	20 57%	15 43%	24 50%	7 58%
Female	15 43%	20 57%	24 50%	5 42%
Race/Ethnicity				
White	11 31%	7 20%	46 96%	5 42%
Hispanic	21 60%	26 74%	0 0%	2 17%
Black	3 9%	2 6%	0 0%	5 42%
Other	0 0%	0 0%	2 4%	0 0%
Study Drug				
PB 2 mg/kg	35 100%	0	47 98%	0
MB 2 mg/kg	0	35 100%	0	0
MB 1 mg/kg	0	0	0	12 100%
Saline Control	0	0	48 100%	0

Source: FDA analysis

Abbreviations: MB, Methylene Blue USP 1%; PB ProvayBlue 0.5%

Review Comment: The healthy volunteer population provides no experience for ProvayBlue in children or the elderly.

7.2.2 Explorations for Dose Toxicity Relationship

Table 18 above shows the numbers of subjects treated with ProvayBlue or a comparator in the healthy volunteer studies. Of note for Protocol PVP-2014001, the applicant indicated that the lot

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

of Methylene Blue USP 1% used in the study contained only 82% of the labeled amount the methylene blue (Response to Information Request received 2/29/2016). The mean actual amount of methylene blue administered (corrected for the assayed concentration) was 2.00 (SD 0.002) mg/kg in the ProvayBlue arm and 1.64 (SD 0.006) mg/kg in the Methylene Blue USP 1% arm.

Review Comment: Only a single dose level of ProvayBlue was tested, so it was not possible to perform a detailed assessment of dose-toxicity for this drug specifically. However, since a lower dose of Methylene Blue USP 1% was studied in this population, comparison based on dose across the class can be performed as described in Section 7.4.2.

7.2.3 Special Animal and/or In Vitro Testing

The results of the preclinical studies relevant to safety were summarized in Section 4.2. There was no new nonclinical information about ProvayBlue in this resubmission that warranted special clinical testing.

7.2.4 Routine Clinical Testing

The schedule of safety evaluations for each protocol was described in Section 5.3. The frequency of monitoring was considered adequate in the context of the study designs for the healthy volunteer studies. The implications of the short follow-up for safety testing (as little as 4 days) are discussed further in Section 7.4.3.

7.2.5 Metabolic, Clearance, and Interaction Workup

The results of the studies of human pharmacokinetics and pharmacodynamics relevant to safety were summarized in Section 4.3. The limited eligibility criteria in the healthy volunteer studies precluded meaningful analyses by degree of organ dysfunction or concomitant medications.

7.2.6 Adverse Events of Special Interest

FDA identified the following as anticipated safety issues for detailed review: serotonin syndrome, interference with in vivo monitoring devices, hemolytic anemia, lack of effectiveness, interference with common laboratory tests, hypersensitivity, and infusion site reactions. Lack of effectiveness is discussed in Section 6.1.8 above.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the healthy volunteer studies.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

7.3.2 Serious Adverse Events

There was one serious adverse event reports. Subject 146 was a 34 year-old man participating in Protocol PVP-2014002. He received the moxifloxacin dose on day 1 and the saline dose on day 8 without problems. On day 15, he received an infusion of ProvayBlue 2 mg/kg starting at 8:45. The reported adverse events included dysgeusia and pain in the extremity at 8:46, nausea at 9:00, syncope at 9:05 and chromaturia at 10:00. Twenty minutes after the start of infusion, the subject reported difficulty breathing, he then lost consciousness for approximately 1 minute and had epileptic-like convulsions for about 10 seconds. The heart rate was erratic, varying from 51 to 72 beats per minute. The subject regained consciousness and had no further symptoms. He received no specific treatment for this event. The ECG recording at the time of the event reportedly showed 4 sinus pauses ranging from 2.9 seconds to 14 seconds. Additional changes in the ECG included a very transient shortening of the PR interval and an increase in QTcF.

Review Comment: I agree that the event of syncope due to sinus arrest was at least possibly related to ProvayBlue. This potential risk should be reflected in the Prescribing Information.

7.3.3 Dropouts and/or Discontinuations

One subject in Protocol PVP-2014002 dropped out after completion of Period 1 (saline placebo) because she “was afraid of the pain that the other subjects had experienced” (Module 2.7.4 Summary of Clinical Safety Section 2.1.6). There were no early withdrawals due to adverse events.

7.3.4 Significant Adverse Events

There were no events of serotonin syndrome, interference with in vivo monitoring devices or hemolytic anemia reported in the healthy volunteer studies.

Hypersensitivity was assessed in the healthy volunteer studies by FDA using SMQN_Hypersensitivity and SMQN_Anaphylactic reaction. There were no anaphylactic reaction terms reported. There were 6 (7%) subjects with 7 hypersensitivity terms reported after receiving with ProvayBlue. The hypersensitivity terms included 4 events of contact dermatitis and 1 event each of erythematous rash, maculopapular rash, and infusion site urticaria. Of the subjects who received Methylene Blue USP 1%, 2 had a contact dermatitis and 1 had a maculopapular rash.

Infusion site reactions were assessed by FDA using HLT_Infusion site reactions. There were 6 (7%) subjects with 8 infusion site reaction terms reported after receiving with ProvayBlue. The infusion site reaction terms included 5 events of infusion site pain, 2 of infusion site discomfort, and 1 of infusion site urticaria. Of the subjects who received Methylene Blue USP 1%, 13 had infusion site pain, 3 infusion site discomfort, 2 infusion site erythema, 2 infusion site pruritus and 1 each of infusion site extravasation, infusion site induration and infusion site swelling.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

The applicant included a specific assessment of infusion site reactions at baseline, hour 6 and hour 12 in Protocol PVP-2014001. The results of these assessments are shown in Table 19.

Table 19: Protocol PVP2014001 – Injection Site Reaction Assessments

Local Reaction	Treatment	Time Point	Number of Subjects (%)
Erythema/Redness	A	Predose	0
		Hour 5.8	0
		Hour 11.8	1 (3%)
	B	Predose	0
		Hour 5.8	2 (6%)
		Hour 11.8	1 (3%)
Induration/Swelling	A	Predose	0
		Hour 5.8	0
		Hour 11.8	1 (3%)
	B	Predose	0
		Hour 5.8	1 (3%)
		Hour 11.8	2 (6%)
Pain	A	Predose	0
		Hour 5.8	0
		Hour 11.8	1 (3%)
	B	Predose	0
		Hour 5.8	2 (6%)
		Hour 11.8	0
Tenderness	A	Predose	0
		Hour 5.8	2 (6%)
		Hour 11.8	3 (9%)
	B	Predose	0
		Hour 5.8	5 (14%)
		Hour 11.8	3 (9%)

Treatment A: A single 2 mg/kg IV infusion of ProvayBlue™

Treatment B: A single 2 mg/kg IV infusion of Methylene Blue USP 1%

Source: Study PVP2014001 Clinical Study Report Table 12-3

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 20 shows the TEAE in decreasing frequency by SOC in the 82 healthy volunteers who received a single dose of ProvayBlue 2 mg/kg. Events in the SOCs Musculoskeletal and

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

connective tissue disorders, Renal and urinary disorders, and Nervous system disorders occurred in > 50% of the subjects. SOC with the most frequent TEAE of moderate-to-severe grade included Musculoskeletal and connective tissue disorders (62%), Nervous system disorders (17%), and General disorders and administration site conditions (9%).

Table 20: TEAE by SOC in Healthy Volunteers Treated with ProvayBlue 2 mg/kg

System Organ Class	Any Severity TEAE (n=82)		Moderate- Severe TEAE (n=82)		Related TEAE (n=82)	
Musculoskeletal and connective tissue disorders	75	91%	51	62%	74	90%
Renal and urinary disorders	61	74%	0		61	74%
Nervous system disorders	43	52%	14	17%	42	51%
General disorders and administration site conditions	32	39%	7	9%	27	33%
Skin and subcutaneous tissue disorders	25	30%	4	5%	21	26%
Gastrointestinal disorders	23	28%	2	2%	21	26%
Vascular disorders	4	5%	1	1%	4	5%
Psychiatric disorders	4	5%	0		4	5%
Metabolism and nutrition disorders	3	4%	0		3	4%
Eye disorders	2	2%	0		0	
Respiratory, thoracic and mediastinal disorders	2	2%	0		2	2%
Cardiac disorders	1	1%	0		1	1%
Immune system disorders	1	1%	0		0	
Injury, poisoning and procedural complications	0		0		0	

Source: FDA analysis

Table 21 shows the TEAE in decreasing frequency by PT in the 82 healthy volunteers who received a single dose of ProvayBlue 2 mg/kg. Only PT that occurred in at least 2 subjects were included. The most common ($\geq 10\%$) TEAE were pain in extremity, chromaturia, dysgeusia, feeling hot, dizziness, hyperhidrosis, nausea, skin discoloration, and headache. Nearly all of the TEAE reported were also considered related. The most common ($\geq 2\%$) moderate-to-severe TEAE were pain in extremity, headache, feeling hot, dizziness, syncope, back pain, hyperhidrosis, and nausea.

Pain in the extremity was the most common TEAE (84%) and the most common moderate-to-severe TEAE (56%). The applicant indicated that the pain was in the extremity used for the infusion but differentiated it from infusion site pain (6%). Other events of musculoskeletal pain were reported in 9%. In the SOC Nervous system disorders, the most common ($\geq 5\%$) TEAE were dysgeusia, dizziness, headache and paresthesia.

Clinical Review
NDA 204630
ProvayBlue (methylene blue)

Table 21: TEAE by PT in Healthy Volunteers Treated with ProvayBlue 2 mg/kg

Preferred Term	Any Severity TEAE (n=82)		Moderate- Severe TEAE (n=82)		Related TEAE (n=82)	
Pain in extremity	69	84%	46	56%	69	84%
Chromaturia	61	74%	0		61	74%
Dysgeusia	16	20%	1	1%	16	20%
Feeling hot	14	17%	5	6%	13	16%
Dizziness	13	16%	4	5%	13	16%
Hyperhidrosis	11	13%	2	2%	11	13%
Nausea	11	13%	2	2%	11	13%
Skin discoloration	11	13%	0		11	13%
Headache	8	10%	6	7%	6	7%
Musculoskeletal pain	7	9%	0		7	9%
Paresthesia oral	7	9%	0		7	9%
Paresthesia	7	9%	0		6	7%
Infusion site pain	5	6%	1	1%	5	6%
Feeling cold	5	6%	0		5	6%
Pallor	4	5%	0		4	5%
Dermatitis contact	4	5%	0		0	
Syncope	3	4%	3	4%	3	4%
Influenza like illness	3	4%	1	1%	3	4%
Pruritus	3	4%	1	1%	1	1%
Anxiety	3	4%	0		3	4%
Decreased appetite	3	4%	0		3	4%
Chest discomfort	3	4%	0		2	2%
Back pain	2	2%	2	2%	1	1%
Cold sweat	2	2%	1	1%	2	2%
Dizziness postural	2	2%	1	1%	2	2%
Muscle spasms	2	2%	1	1%	2	2%
Presyncope	2	2%	1	1%	2	2%
Vomiting	2	2%	1	1%	2	2%
Arthralgia	2	2%	1	1%	1	1%
Chills	2	2%	0		2	2%
Diarrhea	2	2%	0		2	2%
Discomfort	2	2%	0		2	2%
Dyspnea	2	2%	0		2	2%
Erythema	2	2%	0		2	2%
Hypoesthesia oral	2	2%	0		2	2%
Infusion site discomfort	2	2%	0		2	2%
Limb discomfort	2	2%	0		1	1%
Oral discomfort	2	2%	0		1	1%
Catheter site pain	2	2%	0		0	
Ecchymosis	2	2%	0		0	

Source: FDA analysis

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

TEAE reported to occur in only 1 subject each when treated with ProvayBlue and not in the saline control group included: abdominal pain lower, abnormal dreams, asthenia, burning sensation, chest pain, dysphagia, flatulence, hot flush, hypoesthesia, infusion site urticaria, muscle tightness, musculoskeletal discomfort, myalgia, ocular hyperemia, palpitations, rash erythematous, rash maculopapular, rash papular, seasonal allergy, somnolence, vessel puncture site pain and vision blurred.

Table 22 shows the common TEAE by study arm for Studies PVP-2014001, PVP2014002 and 1MBL12002. Only PT that occurred in at least 2 subjects treatment with a methylene blue product were included. In general, the adverse event profile for ProvayBlue is consistent across studies. In addition, by comparison to the saline arm in Protocol PVP-2014002, with the exception of a proportion of the events headache, the adverse events are reported only in the treatment arms.

Table 22: Common TEAE in Healthy Volunteers by Study

Preferred Term	PVP-2014001				PVP-2014002			1MBL12002	
	PB 2 mg/kg (n=35)		MB 2 mg/kg (n=35)		PB 2 mg/kg (n=47)		Saline (n=48)	MB 1 mg/kg (n=12)	
Pain in extremity	25	71%	24	69%	44	94%	0	1	8%
Chromaturia	14	40%	17	49%	47	100%	0	0	
Skin discoloration	10	29%	7	20%	1	2%	0	0	
Musculoskeletal pain	7	20%	4	11%	0		0	0	
Nausea	6	17%	4	11%	5	11%	0	2	17%
Feeling hot	6	17%	3	9%	8	17%	0	1	8%
Hyperhidrosis	6	17%	2	6%	5	11%	0	0	
Infusion site pain	5	14%	8	23%	0		0	5	42%
Paresthesia	5	14%	4	11%	2	4%	0	0	
Dysgeusia	5	14%	1	3%	11	23%	0	0	
Feeling cold	4	11%	4	11%	1	2%	0	0	
Pallor	4	11%	4	11%	0		0	0	
Headache	4	11%	2	6%	4	9%	3	0	
Dermatitis contact	4	11%	2	6%	0		0	0	
Dizziness	3	9%	4	11%	10	21%	0	1	8%
Chest discomfort	3	9%	3	9%	0		0	0	
Pruritus	3	9%	1	3%	0		0	0	
Paresthesia oral	3	9%	0		4	9%	0	0	
Anxiety	3	9%	0		0		0	0	
Discomfort	2	6%	7	20%	0		0	0	
Infusion site discomfort	2	6%	3	9%	0		0	0	
Muscle spasms	2	6%	2	6%	0		0	1	8%
Limb discomfort	2	6%	2	6%	0		0	0	
Ecchymosis	2	6%	1	3%	0		0	0	

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

Table 22: Common TEAE in Healthy Volunteers by Study

Preferred Term	<u>PVP-2014001</u>				<u>PVP-2014002</u>		<u>1MBL12002</u>	
	PB 2 mg/kg (n=35)		MB 2 mg/kg (n=35)		PB 2 mg/kg (n=47)		Saline (n=48)	MB 1 mg/kg (n=12)
Arthralgia	2	6%	0		0		0	0
Back pain	2	6%			0		0	0
Catheter site pain	2	6%			0		0	0
Oral discomfort	2	6%			0		0	0
Presyncope	1	3%	3	9%	1	2%	0	0
Myalgia	1	3%	3	9%	0		0	0
Dyspnea	1	3%	2	6%	1	2%	0	0
Decreased appetite	1	3%			2	4%	0	0
Dizziness postural	0		2	6%	2	4%	0	0
Dry mouth	0		2	6%	0		0	0
Infusion site erythema	0		2	6%	0		0	0
Vessel puncture site bruise	0		2	6%	0		0	0
Influenza like illness	0				3	6%	0	0
Syncope	0				3	6%	0	0
Vomiting	0				2	4%	0	1 8%

Source: FDA analysis

TEAE reported to occur in only 1 subject each per treatment arm and not in the saline control group included: alanine aminotransferase increased, infusion site extravasation, tachycardia, vessel puncture site hematoma, asthenia, rash maculopapular, somnolence, dyspepsia, dysuria, eye pruritus, glossodynia, infusion site induration, infusion site swelling, nasal congestion, oropharyngeal pain, papule, peripheral swelling, rhinorrhea, sneezing, thirst, tongue eruption, infusion site pruritus, abdominal distension, abnormal dreams, burning sensation, chest pain, dysphagia, hot flush, hypoesthesia, infusion site urticaria, muscle tightness, musculoskeletal discomfort, rash erythematous, rash papular, vessel puncture site pain, chills, cold sweat, erythema, hypoesthesia oral, diarrhea, abdominal pain lower, flatulence, ocular hyperemia, palpitations and vision blurred.

The vast majority (87%) of the events listed in Table 22 were considered related to study drug. Additionally, the vast majority (82%) were mild in severity.

Table 23 lists by study arm the events considered moderate or severe in intensity for the participants in the healthy volunteer studies.

Table 23: Moderate-to-Severe TEAE in Healthy Volunteers by Study

Preferred Term	<u>PVP-2014001</u>				<u>PVP-2014002</u>				<u>1MBL12002</u>
	PB 2 mg/kg (n=35)		MB 2 mg/kg (n=35)		PB 2 mg/kg (n=47)		Saline (n=48)		MB 1 mg/kg (n=12)
Pain in extremity	6	17%	6	17%	40	85%	0		0
Headache	3	9%	0		3	6%	2	4%	0
Back pain	2	6%	0		0		0		0
Arthralgia	1	3%	0		0		0		0
Cold sweat	1	3%	0		0		0		0
Hot flush	1	3%	0		0		0		0
Infusion site pain	1	3%	1	3%	0		0		0
Muscle spasms	1	3%	1	3%	0		0		0
Myalgia	1	3%	0		0		0		0
Pruritus	1	3%	0		0		0		0
Feeling hot	0		0		5	11%	0		0
Dizziness	0		0		4	9%	0		0
Syncope	0		0		3	6%	0		0
Hyperhidrosis	0		0		2	4%	0		0
Nausea	0		0		2	4%	0		0
Presyncope	0		1	3%	1	2%	0		0
Dizziness postural	0		0		1	2%	0		0
Dysgeusia	0		0		1	2%	0		0
Influenza like illness	0		0		1	2%	0		0
Vomiting	0		0		1	2%	0		0

Source: FDA analysis

7.4.2 Dose Dependency for Adverse Events

Since there was only one dose level of ProvayBlue tested in healthy volunteers, a dose-toxicity relationship could not be assessed for ProvayBlue specifically. However, since bioequivalence to Methylene Blue USP 1% was concluded, and the actual dose of methylene blue administered was 1.6 mg/kg in Protocol PVP-2014001, the data set was assessed for a dose-toxicity relationship across all subjects who received a methylene blue product. Table 24 shows the TEAE by dose (using the corrected dose for subjects from Protocol PVP-2014001) for events occurring in at least 3 subjects at any dose level. The results suggest a dose-toxicity relationship for pain in extremity, chromaturia, dysgeusia, feeling hot, dizziness, hyperhidrosis and headache, but it cannot be excluded that the results may be driven by differences between studies in coding the adverse events.

Clinical Review
NDA 204630
ProvayBlue (methylene blue)

Table 24: Common TEAE in Healthy Volunteers by Methylene Blue Dose

Preferred Term	2 mg/kg (n = 82)		1.6 mg/kg (n = 35)		1 mg/kg (n = 12)	
Pain in extremity	69	84%	24	69%	1	8%
Chromaturia	61	74%	17	49%	0	
Dysgeusia	16	20%	1	3%	0	
Feeling hot	14	17%	3	9%	1	8%
Dizziness	13	16%	4	11%	1	8%
Skin discoloration	11	13%	7	20%	0	
Nausea	11	13%	4	11%	2	17%
Hyperhidrosis	11	13%	2	6%	0	
Headache	8	10%	2	6%	0	
Musculoskeletal pain	7	9%	4	11%	0	
Paresthesia	7	9%	4	11%	0	
Paresthesia oral	7	9%	0		0	
Infusion site pain	5	6%	8	23%	5	42%
Feeling cold	5	6%	4	11%	0	
Pallor	4	5%	4	11%	0	
Dermatitis contact	4	5%	2	6%	0	
Chest discomfort	3	4%	3	9%	0	
Pruritus	3	4%	1	3%	0	
Anxiety	3	4%	0		0	
Decreased appetite	3	4%	0		0	
Influenza like illness	3	4%	0		0	
Syncope	3	4%	0		0	
Discomfort	2	2%	7	20%	0	
Infusion site discomfort	2	2%	3	9%	0	
Presyncope	2	2%	3	9%	0	
Myalgia	1	1%	3	9%	0	

Source: FDA analysis

Reviewer Comment: *Although the side effect profile at 2 mg/kg is not formidable, the lower dose of 1 mg/kg is clearly more tolerable. Since the 1 mg/kg is seemingly as efficacious as 2 mg/kg, the lower dose is the preferred starting dose for treatment.*

Table 25 shows the TEAE by C_{max} (as reported by the sponsor and independent of the assay used) for events occurring in at least 3 subjects in any cohort. The results suggest a C_{max}-toxicity relationship for pain in extremity, chromaturia, skin discoloration, dizziness, dysgeusia, hyperhidrosis and headache, but it cannot be excluded that the results may be driven by differences between studies in assays.

Clinical Review
NDA 204630
ProvayBlue (methylene blue)

Table 25: Common TEAE in Healthy Volunteers by Methylene Blue Cmax

Preferred Term	> 3000 ng/mL (n = 41)		> 1000 to ≤ 3000 ng/mL (n = 73)		≤ 1000 ng/mL (n = 15)	
Pain in extremity	33	80%	57	78%	4	27%
Chromaturia	30	73%	45	62%	3	20%
Skin discoloration	6	15%	12	16%	0	
Dizziness	6	15%	11	15%	1	7%
Dysgeusia	5	12%	12	16%	0	
Nausea	5	12%	10	14%	2	13%
Hyperhidrosis	5	12%	8	11%	0	
Headache	5	12%	5	7%	0	
Musculoskeletal pain	5	12%	4	5%	2	13%
Feeling hot	4	10%	13	18%	1	7%
Infusion site pain	4	10%	8	11%	6	40%
Paresthesia	3	7%	7	10%	1	7%
Discomfort	3	7%	6	8%	0	
Pallor	3	7%	5	7%	0	
Paresthesia oral	3	7%	4	5%	0	
Dizziness postural	3	7%	1	1%	0	
Feeling cold	2	5%	7	10%	0	
Infusion site discomfort	2	5%	3	4%	0	
Chest discomfort	1	2%	5	7%	0	
Dermatitis contact	1	2%	4	5%	1	
Presyncope	1	2%	4	5%	0	
Dyspnea	1	2%	3	4%	0	
Limb discomfort	0		4	5%	0	
Myalgia	0		4	5%	0	
Pruritus	0		4	5%	0	
Anxiety	0		3	4%	0	
Echymosis	0		3	4%	0	

Source: FDA analysis

Reviewer Comment: *Of note, there are no data to address safety of more than 2 mg/kg cumulatively. Given that the half-life of methylene blue is 24 hours, and as such accumulation to high and toxic levels would be expected when repeat doses are given hourly, safety cannot be extrapolated to cumulative doses greater than 2 mg/kg at this time.*

7.4.3 Time Dependency for Adverse Events

Given the short term administration of study drug in these studies, there is insufficient information about time-dependency for adverse events.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

7.4.4 Literature Review – Common Adverse Events

The sponsor provided a listing from the literature of additional adverse reactions attributed to methylene blue class products given intravenously. Table 26 lists the adverse reactions with primary source documentation cited for adverse reactions not listed above for ProvayBlue administered intravenously.

Table 26: Additional Intravenous Methylene Blue Class Adverse Reactions

System Organ Class	Adverse Reaction	Source Cited
Blood and lymphatic system disorders	Methemoglobinemia	Dawson 1989 Goldstein 1974 Harvey 1983 Kearney 1984 Whitwam 1979
	Hemolytic anemia	Anic 1999 Geffner 1981 Goluboff, 1961 Harvey 1983 Hsu 2009 Kearney 1984 Liao 2002 Prasad 2002 Sills 1994
	Hemolysis	Ferguson 1997 Guay 2009 Maddali 2005 Mullick 2007
	Hyperbilirubinemia	Ferguson 1997 Maddali 2005 Sills 1994
Cardiac disorders	Tachycardia	Blass 1976
Vascular disorders	Hypertension	Matisoff 2006
Investigations	Elevated liver enzymes	Berlin 1985
Gastrointestinal disorders	Fecal discoloration	Blass 1976
Skin and subcutaneous tissue disorders	Necrotic ulcer	Perry 1974
General disorders and administration site conditions	Death	Sills 1994

Source: Excerpted from Module 2.7.4 Summary of Clinical Safety Table 23

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

7.5 Results of Safety Tests

7.5.1 Laboratory Findings

The applicant identified no “clinically significant” laboratory abnormalities in PVP-2014001 and PVP-2014002.

FDA assessed the laboratory test results for PVP-2014001, PVP-2014002 and 1MBL12002. In these studies, laboratory testing was performed largely at 1 day (PVP-2014001) or 4 days (PVP-2014002 and 1MBL12002) after infusion of study drug. For the 82 subjects treated with ProvayBlue, the most common treatment-emergent key laboratory abnormalities were neutrophils increased (12%), bilirubin increased (7%), sodium increased (6%), platelets decreased (5%), hemoglobin decreased (2%), creatinine increased (2%), ALT increased (1%), AST increased (1%) and potassium increased (1%). The abnormalities were all no more than CTCAE grade 1.

Table 27 shows the treatment-emergent key laboratory abnormalities by study. The abnormalities were all no more than CTCAE grade 1. There were no analytes with consistent abnormalities that occurred more than rarely across all methylene blue study arms.

Table 27: Key Laboratory Abnormalities in Healthy Volunteers by Study

Preferred Term	<u>PVP-2014001</u>				<u>PVP-2014002</u>				<u>1MBL12002</u>	
	PB 2 mg/kg (n=35)		MB 2 mg/kg (n=35)		PB 2 mg/kg (n=47)		Saline (n=48)		MB 1 mg/kg (n=12)	
<u>Hematology</u>										
Hemoglobin decreased	1	3%	1	3%	1	2%	0			0
Platelets decreased	2	6%	0		2	4%	1	2%		0
Neutrophils decreased	0		0		0		1	2%		0
Neutrophils increased	0		0		10	21%	0			0
<u>Chemistry</u>										
Bilirubin increased	1	3%	0		5	11%	3	6%		0
Creatinine increased	1	3%	0		1	2%	0			0
Sodium increased	5	14%	2	6%	0		0			0
ALT increased	0		0		1	2%	0		1	8%
AST increased	0		0		1	2%	0		1	8%
Potassium increased	0		0		1	2%	0			0

Source: FDA analysis

7.5.2 Vital Signs

Figure 3 shows serial vital signs after infusion of ProvayBlue 2 mg/kg or placebo in Protocol PVP-2014002. There were no substantial differences in the vital sign profiles by treatment period. It should be noted, however, that the first postinfusion measurement was not until 30

Clinical Review

NDA 204630

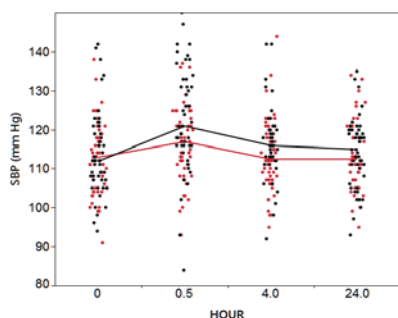
ProvayBlue (methylene blue)

minutes from start of infusion, so abnormalities that might have occurred at the Tmax (median 0.083 hr; Protocol PVP-2014002 Clinical Study Report Table 11-3) would not be detected.

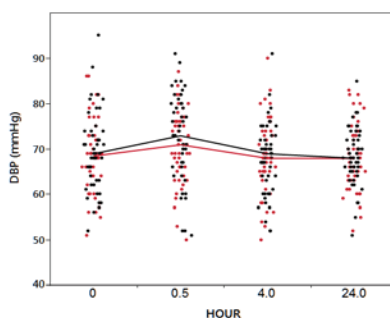
Figure 3: PVP-2014002 - Vital Signs

Vital signs for ProvayBlue 2 mg/kg infusion (red) or placebo infusion (black).

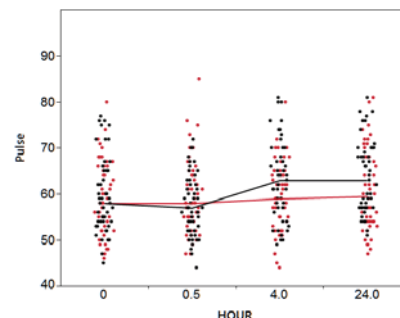
Systolic Blood Pressure



Diastolic Blood Pressure



Pulse



Source: FDA analysis

In the analysis of vital sign outliers, there was a numerically higher number of subjects with heart rate < 50 beats per minute after treatment with ProvayBlue vs Methylene Blue USP 1% (4 vs 0) in Protocol PVP-2014001 and with ProvayBlue vs placebo (8 vs 4) in Protocol PVP-2014002, but in all cases, the subjects had a baseline heart rate ≤ 55 beats per minute. There were no other substantial differences between the treatment groups in vital sign measurements in these two protocols.

7.5.3 Electrocardiograms (ECGs)

The applicant provided an analysis of QT in Protocol 1MBL12002, a single-dose pharmacokinetics study of 1 mg/kg Methylene Blue USP 1% in 12 healthy volunteers. The upper bound of the 2-sided 90% confidence interval for the mean change in QTc from baseline was 22.6 ms observed at 7 minutes postdose. The IRT reviewer was unable to conclude that methylene blue at relevant clinical doses would not cause a significant prolongation of QTc due to study design flaws (IRT Consultation Review dated 6/30/2014). For the thorough QT study, Protocol PVP-2014002, the IRT concluded that ProvayBlue did not induce a significant QTc prolongation effect, but the conclusion was applicable only a single 2 mg/kg intravenous dose (see Section 4.4).

Table 28 shows the outlier analysis for ECG intervals in the 3 studies in healthy volunteers. Difference between studies in the percentage of outliers may reflect differences in the intensity of monitoring. Of note, though, is that there were no substantial differences in the incidence of outliers for any ECG interval when comparing the ProvayBlue treatment period to the placebo treatment period in Protocol PVP-2014002. In addition, the applicant noted that all ECG abnormalities were considered clinically nonsignificant by the investigators (Module 2.7.4 Summary of Clinical Safety Section 4) with the exception of the serious adverse event described in Section 7.3.2.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

Table 28: ECG Outliers in Healthy Volunteers by Study

Preferred Term	<u>PVP-2014001</u>				<u>PVP-2014002</u>				<u>1MBL12002</u>	
	PB 2 mg/kg (n=35)		MB 2 mg/kg (n=35)		PB 2 mg/kg (n=47)		Saline (n=48)		MB 1 mg/kg (n=12)	
PR < 120 msec	3	9%	2	6%	0		0		1	8%
PR > 200 msec	3	9%	1	3%	1	2%	0		1	8%
QRS > 110 msec	4	11%	5	14%	8	17%	7	15%	0	
QTcF increase 31-60 msec	3	9%	7	20%	0		0		2	17%
QTcF increase > 60 msec	0		0		0		0		0	
QTcF > 480 msec	0		0		1	2%	0		0	

Source: FDA analysis

Review Comment: I agree with the IRT that a single dose of ProvayBlue up to 2 mg/kg does not affect cardiac conduction in a clinically meaningful way in the majority of cases.

7.6 Safety in Special Populations

7.6.1 Safety in Pediatric Patients

Protocol PVP-2013001 included 3 children (age 6 days, 1.8 years and 2.2 years). The applicant also reviewed safety data from 40 published reports of children > 3 months old and 12 published reports of children < 3 months old with methemoglobinemia treated a methylene blue class product at varying doses (Module 2.7.4 Summary of Clinical Safety Tables 20 and 21). On the basis of the available data, the applicant identified no additional risks of treatment with ProvayBlue in children (Module 2.7.4 Summary of Clinical Safety Section 5.1).

7.6.2 Safety in Geriatric Patients

There were no patients over the age of 65 years treated with ProvayBlue. The applicant reviewed safety data from 24 published case reports of patients > 65 year old with methemoglobinemia treated a methylene blue class product at varying doses (Module 2.7.4 Summary of Clinical Safety Table 22). On the basis of the available data, the applicant identified no additional risks of treatment with ProvayBlue in children (Module 2.7.4 Summary of Clinical Safety Section 5.1).

7.6.3 Drug-Demographic Interactions

The applicant provided no other analyses of TEAE by demographics. FDA assessed TEAE in the healthy subjects who received ProvayBlue by age, gender, race, weight and BMI. Table 29 lists the TEAE by age group in healthy subjects who received ProvayBlue. Only TEAE with a difference in incidence of at least 10% are shown, and the list is in the order of the difference in incidence between the older and younger age groups.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

Table 29: TEAE by Age in Healthy Volunteers Treated with ProvayBlue 2 mg/kg

Preferred Term	Age ≤ 40 years (n = 57)		Age > 40 years (n = 25)		Risk Difference
Chromaturia	36	63%	25	100%	37%
Pain in extremity	45	79%	24	96%	17%
Influenza like illness	0		3	12%	12%
Musculoskeletal pain	7	12%	0		-12%
Skin discoloration	10	18%	1	4%	-14%
Hyperhidrosis	11	19%	0		-19%

Source: FDA analysis

Table 30 lists the TEAE by gender in healthy subjects who received ProvayBlue. Only TEAE with a difference in incidence of at least 10% are shown, and the list is in the order of the difference in incidence between females and male.

Table 30: TEAE by Gender in Healthy Volunteers Treated with ProvayBlue 2 mg/kg

Preferred Term	Male (n = 44)		Female (n = 38)		Risk Difference
Dysgeusia	5	11%	11	29%	18%
Feeling hot	4	9%	10	26%	17%
Dizziness	4	9%	9	24%	15%
Paresthesia	6	14%	1	3%	-11%

Source: FDA analysis

Table 31 lists the TEAE by race or ethnicity in healthy subjects who received ProvayBlue. The five subjects who were nonwhite and nonHispanic were excluded, since the that group was not large enough for a meaningful comparison. Only TEAE with a difference in incidence of at least 10% are shown, and the list is in the order of the difference in incidence between white and Hispanic subjects.

Table 31: TEAE by Race/Ethnicity in Healthy Volunteers Treated with ProvayBlue 2 mg/kg

Preferred Term	Hispanic (n = 21)		White (n = 56)		Risk Difference
Chromaturia	7	33%	51	91%	58%
Nausea	1	5%	9	16%	11%
Dizziness	2	10%	11	20%	10%
Dermatitis contact	3	14%	1	2%	-13%
Pruritus	3	14%	0		-14%
Feeling cold	4	19%	1	2%	-17%
Musculoskeletal pain	5	24%	2	4%	-20%

Source: FDA analysis

Excludes 5 subjects who were nonwhite and nonHispanic.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

Table 32 lists the TEAE by weight group in healthy subjects who received ProvayBlue. Only TEAE with a difference in incidence of at least 10% are shown, and the list is in the order of the difference in incidence between the higher and lower weight groups.

Table 32: TEAE by Weight in Healthy Volunteers Treated with ProvayBlue 2 mg/kg

Preferred Term	Weight < 80 kg (n = 61)		Weight ≥ 80 kg (n = 21)		Risk Difference
Chromaturia	42	69%	19	90%	22%
Pain in extremity	49	80%	20	95%	15%
Dysgeusia	10	16%	6	29%	12%
Dizziness	8	13%	5	24%	11%
Musculoskeletal pain	7	11%	0		-11%
Skin discoloration	10	16%	1	5%	-12%

Source: FDA analysis

TEAE were assessed by BMI < 25 kg/m² (n=43) vs ≥ 25 kg/m² (n=39). The higher BMI group had a higher incidence of feeling hot (23% vs 12%) and a lower incidence of hyperhidrosis (8% vs 19%). There were no other TEAE with a absolute risk difference > 10% between the BMI groups.

Reviewer Comment: *Although there was a substantial difference in the risk of chromaturia by age, race/ethnicity and weight, there is no unifying biological basis for such trends, so the findings are considered random.*

7.6.4 Safety with Organ Impairment

The applicant identified 1 patient (Patient 02) with renal insufficiency (serum creatinine 1071 micromol/L) treated with ProvayBlue on Protocol PVP-2013001, and they reported no adverse reactions. The applicant concluded, however, that “one patient with renal insufficiency treated with (b) (6) Injection for methemoglobinemia is too few to ascertain a dose for renally impaired patients” (Module 2.7.3 Summary of Clinical Efficacy, page 20).

Reviewer Comment: *I agree with the applicant that there is insufficient information about safety of ProvayBlue in patients with renal or hepatic impairment. This uncertainty will need to be reflected in the prescribing information.*

7.6.5 Drug-Drug Interactions

Given that the healthy volunteers were on few concomitant medications, a meaningful analysis for drug-drug interactions could not be performed.

Reviewer Comment: *The extensive list of potential pharmacokinetic interactions raises serious questions about safety of ProvayBlue when used in critically ill patients receiving multiple*

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

therapeutics. Additionally, there is potential for adverse outcomes due to late interactions due to the prolonged half-life of the drug.

7.7 Additional Safety Evaluations

7.7.1 Human Carcinogenicity

There is insufficient follow-up in the healthy volunteer studies for a meaningful analysis of carcinogenicity risk.

7.7.2 Human Reproduction and Pregnancy Data

There were no studies of ProvayBlue for treatment of methemoglobinemia in pregnant women. The potential for harm to the fetus was determined in epidemiological studies and case reviews. These studies reported that there was an increased risk of neonatal intestinal atresia and fetal death following intra-amniotic injection of a methylene blue class product during the second trimester (reviewed in Cragan 1999).

Intra-amniotic injection of a methylene blue class product hours to days prior to birth was reported to result in hyperbilirubinemia, hemolytic anemia, skin staining, methemoglobinemia, respiratory distress and photosensitivity in the newborn (reviewed in Cragan 1999).

Reviewer Comment: Although there is no evidence that ProvayBlue itself is harmful when given intravenously to pregnant women, the data regarding the effects of other methylene blue class products when administered intra-amniotically should be made clear in the Prescribing Information, and there should also be instructions for evaluation and monitoring of newborns of mothers who received ProvayBlue near term.

7.7.3 Pediatrics and Assessment of Effects on Growth

See Section 7.6.1. There were no additional studies of ProvayBlue in the pediatric population.

7.7.4 Overdose

The highest single dose of ProvayBlue administered in Protocol PVP-2013001 was 9.8 mg/kg. Patient 03 was a 37 year old woman with a methemoglobin level of 75% due to 4-nitroaniline intoxication. Vital signs at baseline included a respiratory rate of 25, heart rate 106 and blood pressure 87/51. On physical examination the patient was cyanotic, and her mental status was depressed (Glasgow 7). The patient was intubated. Treatment consisted of hydroxycobalamin and gastric lavage. ProvayBlue was given (b) (6) 00:00 at 2 mg/kg, 1 mg/kg at 04:00, and 9.8 mg/kg at 12:30 (total reported dose 12.8 mg/kg). Laboratory tests on (b) (6) (time unknown) included CK 319 U/L (normal 30-190) and total bilirubin 31 µmol/L (normal 0-17) The total bilirubin was 51 µmol/L the following day, and the LDH had risen to 509 U/L (normal 240-480).

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

Hemoglobin was not reported. The patient recovered and was discharged. The elevated bilirubin resolved on [REDACTED] (b) (6), but CK and LDH elevations were on-going at last follow-up.

Goluboff and Wheaton (1961) reported 2 infants who received ≥ 15 mg/kg as a single dose and >30 mg/kg cumulatively, one of whom had methemoglobinemia. Both developed bluish discoloration and hemolytic anemia.

Sills and Zinkham (1994) reported an infant treated with 20 mg/kg of a methylene blue class product for butyric aciduria. They reported Heinz body anemia and hyperbilirubinemia.

Nadler, Green, et al. (1934) administered 500 mg (approximately 7 mg/kg) intravenously to 18 subjects. They reported an increase in respiratory rate, a sense of oppression in the chest, difficulty breathing, dull pain over the heart, elevated heart rate, bluish discoloration of the skin and mucous membranes, restlessness, tremors, burning in the mouth, nausea, vomiting, paresthesia. ECG tracing showed T-wave flattening or inversion. There was also nausea, dizziness, headache and mental confusion lasting about 12 hours after the injection.

Whitwam, Taylor, et al (1979) reported that intravenous administration of a methylene blue class product at 5 mg/kg for intraoperative imaging resulted in elevation of the methemoglobin level from 0.6% to 7.1%.

Paciullo, Horner, et al (2010) reviewed a series of studies of methylene blue for treatment of septic shock. They reported a consistent finding of pulmonary vasoconstriction and reduced oxygenation in studies using doses of 3 mg/kg or greater.

Bewick and Pfeleiderer (2014) reported on 98 patients who received a methylene blue class product 3.5 mg/kg intravenously over 1 hour for imaging. The adverse events reported included pain at the infusion site (2), hypotension (2), wheezing (1) and transient bradycardia (1). All adverse events resolved.

7.7.5 Drug Abuse Potential, Withdrawal and Rebound

There is no known abuse potential for ProvayBlue.

7.7.6 Effects on Instrumental Activities of Daily Living

In the healthy volunteer studies, 28 subjects developed events of dizziness, postural dizziness, somnolence, presyncope or syncope after infusion of ProvayBlue or Methylene Blue USP 1%. Table 33 shows the time to onset of the events, duration of the events and interval from the start of infusion to the resolution of the event. One event of dizziness lasted 9 days, and the remainder of the events resolved within 1 day.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

Table 33: Characterization of Key Neurological TEAE in Healthy Volunteer Studies^a

Preferred Term	Subjects	Time (hrs) to Onset	Duration (hrs)	Interval (hrs) to Resolution ^b
Dizziness	18	0.5 (0.0-23.3)	2.1 (0.1-194.5)	3.0 (0.9-217.8)
Syncope	3	1.2 (0.3-4.3)	0.1 (0.1-0.3)	1.3 (0.4-4.6)
Dizziness postural	4	1.3 (0.0-1.4)	2.9 (1.5-4.0)	3.9 (2.7-4.8)
Somnolence	1	1.5 -	2.0 -	3.5 -
Presyncope	5	3.1 (1.7-6.0)	0.3 (0.1-1.4)	3.3 (1.9-6.3)

Source: FDA analysis

^aSubjects from PVP2014001, PVP2014002 or 1MBL12002 treated with ProvayBlue or Methylene Blue USP 1%

^bTime from start of infusion to resolution of the event

Reviewer Comment: *The results in Table 33 along with the reported persistent neurological effects at higher doses (Nadler, Green, et al. 1934) support a causal relationship. Patients treated with ProvayBlue should be counseled regarding the potential neurological effects.*

7.8 Additional Submissions / Safety Issues

7.8.1 Serotonin Syndrome

There were no events of serotonin syndrome in the healthy volunteer studies. See Section 2.4 for a discussion of the risk of serotonin syndrome in patients who received methylene blue and serotonergic drugs concurrently.

Reviewer Comment: *Given the potential for fatal serotonin syndrome, a boxed warning is warranted.*

7.8.2 Hypersensitivity

In the healthy volunteer studies, there were no events in the SMQN Anaphylactic reaction; SMQN Hypersensitivity events included dermatitis contact, infusion site urticaria, rash erythematous and rash maculo-papular (see Section 7.3.4). In the literature, reported hypersensitivity reactions to methylene blue class products included rash, angioedema, urticaria, bronchospasm and anaphylaxis, including anaphylaxis cases with confirmed skin tests (Dewachter, Mouton-Faivre, et al 2005; Jangjoo, Forghani, et al. 2010; Oomah, Dembinski, et al. 2010).

Reviewer Comment: *The potential for anaphylactic reactions warrants a warning in the Prescribing Information.*

7.8.3 Hemolytic Anemia

In Protocol PVP-2013001, Patient 01 was reported to have had hemolytic anemia after treatment with ProvayBlue for methemoglobinemia due to dapsone. No characterization of the hemolytic

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

anemia was provided. There were no cases of hemolytic anemia per se in the healthy volunteer studies. Although there were cases of decreased hemoglobin and increased bilirubin, these were mild and transient.

The applicant identified multiple published cases of hemolytic anemia following treatment of methemoglobinemia with a methylene blue class product (Module 2.7.4 Summary of Clinical Safety Appendix 7). The occurrence was not associated with a specific intoxicant. Hemolysis was reported as early as 1 day after treatment but could also be delayed for several days. Heinz bodies, elevated unconjugated bilirubin, and reduced haptoglobin were also reported.

Muller, Meissner et al. (2012) reported no hemolytic anemia in children with G6PD deficiency who were treated with an oral methylene blue class product for malaria. Safe use of methylene blue in patients with G6PD deficiency and methemoglobinemia has not been established (Liao, Hung, et al. 2002; McDonagh, Bautista, et al. 2013; Mullick, Kumar, et al. 2007).

Reviewer Comment: There is substantial evidence that methylene blue may induce or exacerbate toxic hemolysis when used to treat methemoglobinemia. The potential for delayed onset hemolysis needs to be clear in the Prescribing Information. There is also some controversy in the literature regarding whether use of methylene blue should be contra-indicated in patients with G6PD deficiency and methemoglobinemia. Although Muller et al reported safe use of methylene blue in patients with G6PD deficiency being treated for malaria, the literature is consistent in reporting serious hemolysis in patients with G6PD deficiency and methemoglobinemia treated with a methylene blue class product. The difference in these outcomes may result from the additional insult to the red cell in methemoglobinemia from the intoxicant, making the red cell more sensitive to the toxic effect of methylene blue in patients with G6PD deficiency and methemoglobinemia. I would therefore agree with the applicant's proposal to contra-indicate use of ProvayBlue in patients who are G6PD deficient.

7.8.4 Interference with In Vivo Monitoring Devices

The applicant identified 2 in vivo monitoring devices with which methylene blue class products interfere.

There are numerous reports in the literature of transient low readings of oxygen saturation by pulse oximetry immediately after infusion of 1 - 2 mg/kg of a methylene blue class product intravenously. These events last minutes and are considered artifactual (Kessler, Eide, et al. 1986). Methylene blue absorbs light at the same wavelength used by a pulse oximeter to estimate levels of oxyhemoglobin. The high concentrations of methylene blue in the blood shortly after infusion results in a falsely depressed estimate of oxygen saturation by pulse oximetry.

Administration of a methylene blue class product 1 - 2 mg/kg intravenously was followed by a rapid drop in the bispectral index that lasted 5 - 25 minutes has been reported (Matisoff and Panni 2006; Thiele, Balireddy, et al. 2012). An increase in blood pressure occurred concurrently,

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

and the effect on the bispectral index was recurrent upon rechallenge. The mechanism of the effect on bispectral index has not been determined.

Reviewer Comment: The effect on the oxygen saturation reading appears to be artifactual and as such is truly an interference, but given that the bispectral index changes were accompanied by an increase in blood pressure, this could be a physiological effect rather than an artifact. Until that is confirmed, I agree with the applicant's proposal to include a warning regarding these effects.

7.8.5 Infusion Site Reactions and Extravasation

In the healthy volunteers studies, 7% developed infusion site reactions of various types after administration of ProvayBlue as described in Section 7.3.4. The potential mechanisms of local tissue damage include vasomotor effects, the low pH of the product, and local oxidizing chemical reactions (Khokhar, Aqil, et al. 2015). Bleicher, Kloth, et al. (2009) reported that only 6 of 51 patients with breast cancer who received methylene blue intraparenchymally for lymph node mapping developed inflammatory changes in the skin, but 2 had fat necrosis. Others have reported epidermal erosion or necrotic ulcers requiring skin grafts at sites of methylene blue extravasation or subcutaneous injection for lymph node mapping (Dumbarton, Gorman, et al. 2012; Khokhar, Aqil, et al. 2015; Perry and Meinhard 1974).

Reviewer Comment: The risk of serious infusion site reactions appears to be small, but the seriousness of extravasation cannot be minimized. The administration instructions in the Prescribing Information should clearly indicate the need for patent venous access.

7.8.6 Phototoxicity

Methylene blue is a known photosensitizer (Mellish, Cox et al. 2002). There were no cases of phototoxicity in the healthy volunteer studies. There were 4 published reports of phototoxicity associated with use of a methylene blue class product:

- Kluk, Charles-Holmes, et al. (2012) described 3 adults who developed an erythematous rash in the skin exposed to light during surgery within hours after receiving methylene blue intra-operatively for parathyroid imaging. In one patient, a lesion was also seen on the index finger exposed to the light of the pulse oximeter.
- Lambrecht, Vandeplas, et al. (2012) described a 41 year-old woman who developed an erythematous rash in the skin exposed to a blue-light LED lamp after receiving methylene blue intra-operatively for parathyroid imaging.
- Porat, Gilbert, et al. (1996) described a preterm neonate born to a mother who received intra-amniotic methylene blue prior to birth who developed a bullous eruption and desquamation of about 35% of the body surface area following approximately 16 hours of phototherapy for hyperbilirubinemia.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

- Sills and Zinkham (1994) described 2 term neonates treated with methylene blue postnatally who developed bullae, desquamation and/or a denuding rash after 1-3 days of phototherapy for hyperbilirubinemia. Both neonates died with multiple complications from methylene blue and comorbid conditions.

Reviewer Comment: Given the potential for phototoxic reactions, patients should be counseled to protect themselves from blue light after treatment with ProvayBlue.

7.8.7 Paradoxical Methemoglobinemia

Paradoxical increases in methemoglobin have been reported after administration of high doses of a methylene blue class product (Bilgin, Ozcan, et al. 1998; Whitwam, Taylor, et al. 1979).

Reviewer Comment: There are no reports of clinically significant increases in methemoglobin when methylene blue is given at 1 mg/kg. As such, the risk of paradoxical methemoglobinemia should be minimal if the drug is used according to the instructions for use.

8 Postmarket Experience

The drug substance for ProvayBlue is used in Proveblue 0.5% and as Methylene Blue Intravenous Injection Daiichi Sankyo. Provepharm has marketing authorization for Proveblue 0.5% solution in the EMA as of 5/6/2011, and Daiichi Sankyo has marketing authorization in Japan for Methylene Blue Intravenous Injection Daiichi Sankyo as of 12/26/2014. In the Summary of Clinical Safety, the applicant estimated that approximately (b) (4) ampules of Proveblue 0.5% have been used, and no actions related to safety were taken worldwide from the initial marketing authorization through the data lock date (5/5/2015) (Module 2.7.4 Summary of Clinical Safety Section 6.1).

Table 34 shows a cumulative summary of the adverse reactions from postmarketing data sources reported from the date of marketing authorization through 5/5/2015.

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

Table 34: Cumulative Summary of Postmarket Safety Reports

Preferred Term	Serious		Non-Serious	
	By SOC	By PT	By SOC	By PT
Surgical and Medical Procedures	82		0	
Off-label use		82		
Immune system disorders	5		0	
Anaphylactic reaction		3		
Anaphylactoid reaction		1		
Anaphylaxis		1		
Vascular disorders	5		0	
Circulatory collapse		1		
Shock		1		
Hypotension		3		
Skin and subcutaneous tissue disorders	2		8	
Erythema				3
Rash erythematous		1		
Rash generalized				1
Urticaria				2
Angioedema		1		
Skin irritation				1
Skin discoloration				1
Nervous system disorders	2		2	
Depressed level of consciousness		1		
Hyperreflexia				1
Myoclonus				1
Serotonin syndrome		1		
Cardiac disorders	2		1	
Tachycardia		2		
Transient Bradycardia				1
Injury, poisoning and procedural complications	2		0	
Overdose		2		
General disorders and administration site conditions	1		3	
Extravasation		1		
Pyrexia				1
Pain at infusion site				2
Respiratory, thoracic and mediastinal disorders	1		1	
Respiratory distress		1		
Wheezing				1
Investigations	1		1	
Oxygen saturation decreased				1
Oxygen saturation abnormal		1		
Infections and infestations	1		0	
Pneumonia		1		
Psychiatric disorders	0		2	
Confusional state				1
Agitation				1
Urinary and renal disorders	0		1	
Chromaturia				1

Source: Periodic Safety Update Report dated 7/14/2015

9 Appendices

9.1 Advisory Committee Meeting

There was no advisory committee consulted for this supplement.

9.2 Case Reports of Treatment with Methylene Blue

PubMed was searched using the following criteria: "methylene blue"[All Fields] AND ("methaemoglobinaemia"[All Fields] OR "methemoglobinemia"[MeSH Terms] OR "methemoglobinemia"[All Fields]) AND "humans"[MeSH Terms]. A total of 510 references were retrieved. Of these, there were 44 reports that could be accessed describing treatment of methemoglobinemia with methylene blue with methemoglobin measurements at baseline and within 1 hour (+/- 15 minutes). Table 35 lists the results for these cases in descending order of baseline methemoglobin.

Table 35: Methemoglobin Reduction Using A Methylene Blue Class Product

Reference	Age (yrs)	Gender	Cause	MB Dose (mg/kg)	Baseline MetHgb (%)	Post MetHgb (%)	% Reduction	Time Point (hr)
Sankar 2013	4	Male	Aniline	2.0	98.0	73.0	25.5	1.0
Stambach 1997	-	Female	Nitrite	2.0	83.0	26.0	68.7	1.0
Schimmelman 1978	48	Male	Nitrobenzene	-	75.0	75.0	0.0	0.4
Katz 2004	39	Female	Aniline	2.0	72.4	25.9	64.2	1.0
Wilkerson 2010	19	Female	Nitrite	1.5	72.0	4.9	93.2	1.0
Kearney 1984	32	Male	Aniline	-	70.0	34.0	51.4	1.0
Jaffery 2008	46	Female	Benzocaine	2.0	68.8	33.7	51.0	0.5
Wurdeman 2000	69	Male	Benzocaine	1.0	67.8	50.2	26.0	0.7
Brunato 2003	23	Female	Ammonium nitrate	2.0	66.3	9.0	86.4	1.0
Ferrer Gomez 2008	19	Male	Aniline	1.0	63.0	47.6	24.4	1.0
Freeman 1996	1	Male	Sodium nitrite	2.0	63.0	2.0	96.8	1.0
Modarai 2002	32	Female	Nitrite	-	59.9	4.8	92.0	0.7
Zimmerman 1980	16	Female	Phenazopyridine	2.0	56.9	12.8	77.5	0.5
LeClaire 2005	40	Male	Benzocaine	2.0	51.2	13.9	72.9	1.0
Demirel 1999	54	Male	Aniline	-	50.0	4.9	90.2	1.0
Boylston 2002	73	Female	Benzocaine	-	49.0	9.0	81.6	0.5
Grauer 1996	68	Male	Benzocaine	1.0	47.2	12.3	73.9	0.3
Jacka 2006	45	Female	Benzocaine	0.6	45.0	5.0	88.9	0.3
Ozdogan 2010	0	Male	Prilocaine	1.0	44.0	4.0	90.9	1.0
Messmer 2015	56	Male	Aniline	2.0	42.8	12.3	71.3	0.5
Birchem 2005	69	Female	Benzocaine	2.0	41.1	18.4	55.2	1.0
Hegedus 2005	48	Female	Benzocaine	-	41.0	11.5	72.0	0.3
Hornfeldt 1994	2	Male	Nitroethane	-	40.1	5.7	85.8	1.0
Lin 2007	29	Female	Benzocaine	1.0	39.6	16.8	57.6	1.0
Margulies 2002	16	Male	Benzocaine	2.0	35.0	2.0	94.3	1.0
Tush 1996	0 ^a	Male	Benzocaine	1.0	35.0	2.7	92.3	1.0

Clinical Review

NDA 204630

ProvayBlue (methylene blue)

Table 35: Methemoglobin Reduction Using A Methylene Blue Class Product

Reference	Age (yrs)	Gender	Cause	MB Dose (mg/kg)	Baseline MetHgb (%)	Post MetHgb (%)	% Reduction	Time Point (hr)
Annabi 2009	69	Female	Benzocaine	2.0	33.0	4.0	87.9	1.0
Sin 1996	34	Male	Dapsone	1.0	33.0	9.7	70.6	1.0
Spiller 2014	8	Male	Benzocaine	1.0	32.9	2.3	93.0	1.0
Attof 2006	16	Female	Cerium nitrate	1.5	31.8	3.5	89.0	1.0
Gray 2004	63	Male	Benzocaine	1.0	29.1	3.1	89.3	0.8
White 1991	32	Male	Nitrite	-	28.0	8.0	71.4	1.0
Tsai 2005	3	Male	Sulfadiazine	1.0	27.7	1.0	96.4	1.0
Shepherd 1998	2	Male	Nitroethane	1.0	27.0	8.2	69.6	1.0
Anderson 1988	52	Male	Benzocaine	1.5	26.0	3.9	85.0	1.0
Ellis 1995	76	Female	Benzocaine	1.3	24.0	5.8	75.8	0.5
Spielman 1984	24	Male	Benzocaine	-	23.0	3.8	83.5	0.3
Nguyen 2000	71	Female	Benzocaine	1.0	22.5	2.4	89.3	1.0
Chan 2007	0 ^a	Female	Herbal powder	1.0	20.2	0.5	97.5	1.0
Slaughter 1999	71	Male	Benzocaine	-	19.4	1.8	90.7	0.3
Robicsek 1985	60	Male	Nitroglycerin	-	16.5	1.8	89.1	0.5
Oh 2014	57	Male	Metaflumizone	1.0	15.8	6.0	62.0	1.0
Trillo 1992	60	Female	Dapsone	1.0	10.6	4.4	58.5	0.7
Douglas 1977	80	Female	Benzocaine	-	9.8	0.7	92.9	0.7

Abbreviations: MB, methylene blue; MetHgb, methemoglobin; -, data not provided

^a Neonates 6 (Tush 1996) and 9 (Chan 2007) days old.

9.3 References

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Clinical Review

NDA 204630

ProvayBlue (methylene blue)

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Clinical Review

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ProvayBlue (methylene blue)

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ProvayBlue (methylene blue)

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ProvayBlue (methylene blue)

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ProvayBlue (methylene blue)

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ProvayBlue (methylene blue)

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ProvayBlue (methylene blue)

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/s/

DONNA PRZEPIORKA
03/27/2016

ALBERT B DEISSEROTH
03/28/2016

Secondary Team Leader Review

Date	March 25, 2014
From	Albert Deisseroth, MD, PhD
Subject	Secondary TL Review
NDA Number	204630
Applicant	Provepharm SAS
Date of Submission	October 9, 2015
PDUFA Goal Date	April 9, 2016
Proprietary Name/non-proprietary name	Provayblue/Methylene Blue Injection, 0.5%
Dosage Regimen	1 mg/kg
Applicant's Proposed Indication	Treatment of acquired methemoglobinemia
Intended Population	Methemoglobin level (b) (4) in the presence of clinical symptoms
Recommended:	Approval

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Donna Przepiorka, MD, PhD
Clinical Pharmacology	Hamed Salaheldin, DPharm and Bahru Habtemariam, DPharm
Product Quality	Anamitro Banerjee, PhD, Sithamalli Chandramouli, PhD, Jonathan Swoboda, PhD, Dupeh Palmer, PhD, Rebecca Dombrowski, PhD, and Banu Zolnik, PhD
Non Clinical (Pharmacology/Toxicology)	Brenda Gehrke, PhD and Christopher Sheth, PhD
OMPT	Anthony Orencia, MD
Regulatory Program Manager	Laura Wall

TABLE OF CONTENTS

TABLE OF CONTENTS.....	2
1. EXECUTIVE SUMMARY AND BENEFIT RISK DISCUSSION.....	3
2. BACKGROUND.....	5
3. PHARMACOLOGY TOXICOLOGY.....	5
4. CLINICAL PHARMACOLOGY.....	6
5. PRODUCT QUALITY.....	10
6. EFFICACY.....	10
7. SAFETY.....	14
8. ADVISORY COMMITTEE MEETING.....	18
9. POST MARKETING REQUIREMENTS.....	18
10. OTHER REGULATORY ISSUES: INSPECTIONS OF CLINICAL SITES.....	20
11. LABELING.....	20
12. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT.....	20

1. EXECUTIVE SUMMARY AND BENEFIT RISK DISCUSSION (This section was excerpted from the review of Dr. Donna Przepiorka. Please see her review for details.):

NDA 204630 for Provayblue (Methylene Blue Injection 0.5%) was initially submitted August 13, 2012 under 505(b)(2) for the indication “treatment of acquired methemoglobinemia.” There was no reference listed drug. A Refuse-To-File (RTF) Letter was issued October 11, 2012 citing a lack of data to support the efficacy and safety claims.

On September 13, 2013, a revised application was presented as amended to address the RTF comments, but neither the efficacy nor safety data submitted were considered adequate. On October 13, 2013, a Complete Response Letter was issued due to a lack of substantial evidence that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling (21 CFR 314.125(b)(5)). To address the deficiency, the applicant will need to submit either a prospective trial of Provayblue for treatment of acquired methemoglobinemia, or data to establish that reliance on published outcomes with Methylene blue USP 1% is scientifically valid.

On October 9, 2015, a third application was received from Provepharm SAS which was designed to address all of the issues outlined in the CR.

Background: Methemoglobin is a state in which the iron in the heme molecules is in the oxidized form, which does not bind oxygen well. The result is a net reduction in delivery of oxygen to tissues. Numerous oxidizing drugs, chemicals and toxins are known to cause acquired methemoglobinemia.

If the offending agent is withdrawn, homeostatic mechanisms reduce the oxidized hemoglobin at about 15% per hour, normalizing the level over time. However, when the proportion of hemoglobin that is oxidized is high, the lack of oxygen delivery may be severe enough to cause adverse cardiovascular effects, coma, and death.

Provayblue is a formulation of methylene blue purported to reduce oxidized heme. In presubmission meetings, the Division established with the applicant that efficacy of Provayblue for treatment of acquired methemoglobinemia could be concluded if treatment resulted in a rapid reduction in methemoglobin, and that concurrent rapid improvements in heart rate or respiratory rate and/or resolution of coma would be clinical benefits.

Summary of Efficacy: The data to support efficacy came from Protocol PVP-2013001, a retrospective chart review of patients with acquired methemoglobinemia precipitated by any etiology treated with Provayblue during the period 2010 - 2012. The sponsor identified 12 patients (nine adults and three children) treated with Provayblue. The median methemoglobin was 44% (range, 11-75%) at baseline. The reported initial dose of Provayblue was 1 mg/kg for 7 patients, 1.5 mg/kg for 1 patient, and 2 mg/kg for 4 patients. One subject had 4 doses, 1 had 3 doses, and the others received a single dose of Provayblue.

The primary endpoint of the protocol was the proportion of patients with at least 50% reduction in methemoglobin at one hour after the first dose of Provayblue. Only three patients had a repeat

methemoglobin measured within the required timeframe. The methemoglobin was reduced by at least 50% in all three subjects by one hour. Although the response rate was high (100%), the 95% confidence interval (CI) was wide (44-100%) due to the small sample size, so the point estimate was not considered credible. No data on the effects of treatment with Provayblue on heart rate, respiratory rate or mental status were submitted.

On review of the literature, FDA identified 42 cases of treatment of methemoglobin with methylene blue that included a follow-up measurement within 1 (+/- 0.25) hours. There were no cases that reported use of Provayblue specifically. Of the 42 reported cases, 38 (90%; 95% CI 77-97%) had a methemoglobin decrease of at least 50% by one hour after intravenous administration of methylene blue. However, these reports could not be used to establish the efficacy of Provayblue, since the applicant did not submit sufficient information to bridge its product to any other formulation of methylene blue.

Summary of Safety: Minimal safety data were available from Protocol PVP-2013001. Follow-up was limited to the duration of hospitalization (median 2.5 days; range, 2 hours to 15 days). There were no deaths and no related serious adverse events. There were 15 adverse events reported. None were considered related, and none occurred in more than one patient. The data files for vital signs and laboratory tests were inadequate, and these parameters could not be analyzed.

Additional information was provided from Protocol PVP-2013002 and from postmarketing reports in Europe. Protocol PVP-2013002 was a compassionate use protocol in France that accrued 27 patients (16 adults and 11 children) treated with Provayblue from November, 2010 to October, 2011 for hereditary methemoglobinemia (n=1) or ifosfamide-induced encephalopathy (n=26). There were no adverse events reported for patients treated on Protocol PVP-2013002. The postmarketing review also indicated that no adverse event have been reported with commercial use of Provayblue.

The applicant also submitted the results for Protocol 1MBL12002, a single-center, open-label, single-dose study of Methylene Blue Injection, USP 1% manufactured by American Regent, Inc. The primary objective was to assess pharmacokinetics, safety and tolerability. Twelve subjects were accrued and followed for at least 4 days after treatment. All subjects completed the study. There were no deaths or serious adverse events. The most common adverse events were infusion site pain (42%) and nausea (17%). There was a slight and transient fall in diastolic blood pressure and rise in pulse at 2.83 hours from start of infusion for the group as a whole and one subject had an episode of hypotension. There were no grade 3-4 laboratory abnormalities reported. One subject had an ALT 1.7x ULN and AST 1.1x ULN at the end of study. Four subjects had an abnormal urine leukocyte esterase which the applicant attributed to test interference by methylene blue.

Overall Assessment: The data on use of Provayblue are not sufficient to support a finding of safety and efficacy. Although there are some cases in the literature that might be useful, applicability is limited by the lack of bridging information. A demonstration of bioequivalence of Provayblue and Methylene Blue USP 1% might be sufficient to allow use of the literature to

support a claim of activity of Provayblue in the treatment of methemoglobinemia and would supply the data needed to assess safety.

Benefit-Risk Discussion: The data submitted by the Applicant supports the efficacy of Provayblue which outweighs the acceptable level of toxicity observed.

Recommendation for Regulatory Action: On the basis of the above, this Secondary TL reviewer recommends approval providing that the current issues with the Cenexi manufacturing facility can be resolved by the PDUFA action date.

2. BACKGROUND (This section was excerpted from the review of Dr. Donna Przepiorka. For details, please see her review.):

2.a. Indication: The indication proposed by the Applicant for Provayblue is the treatment of acquired methemoglobinemia.

2.b. Summary of Background: (This section was excerpted from the review of Dr. Donna Przepiorka. For details, please see her review.)

Methemoglobin is a state in which one or more of the iron atoms in the heme molecules is in the oxidized form (ferric), which does not bind oxygen well. The result is a net reduction in delivery of oxygen to tissues. Numerous oxidizing drugs, chemicals and toxins are known to cause acquired methemoglobinemia.

If the offending agent is withdrawn, homeostatic mechanisms reduce the oxidized hemoglobin at about 15% per hour, normalizing the level over time. However, when the proportion of hemoglobin that is oxidized is high, the lack of oxygen delivery may be severe enough to cause adverse cardiovascular effects, coma, and death.

Provayblue is a formulation of methylene blue purported to reduce oxidized heme. In presubmission meetings, the Division established with the Applicant that efficacy of Provayblue for treatment of acquired methemoglobinemia could be concluded if treatment resulted in a rapid reduction in methemoglobin, and that concurrent rapid improvements in heart rate or respiratory rate and/or resolution of coma would be clinical benefits.

3. PHARMACOLOGY TOXICOLOGY (This section was excerpted from the review of Dr. Brenda Gehrke, PhD. For details, please see her review.):

Methylene blue is currently used to treat methemoglobinemia and marketed in the United States as an unapproved product without an approved NDA. Provepharma SAS is developing a methylene blue product for the treatment of acquired methemoglobinemia. NDA 204630 was initially submitted in August 2012.

The Application was determined to be deficient for a substantial review and a Refuse to File letter was issued on October 11, 2012, mainly due to clinical deficiencies. NDA 204630 was resubmitted in September 2013 and the FDA issued a Complete Response letter to the Applicant in October 2014 with clinical, clinical pharmacology, and product quality deficiencies. The primary pharmacology/toxicology review of the NDA was completed and filed on May 28, 2014, and a separate pharmacology/toxicology review for the carcinogenicity studies was completed and filed on March 25, 2014. There were no pharmacology/toxicology concerns with the application and the recommended regulatory action from pharmacology/toxicology was approval.

The current submission, Supporting Document 48 for NDA 204630, is a Class 2 Resubmission. This resubmission contains no new pharmacology/toxicology information. Labeling was completed with this resubmission and changes were made to the pregnancy related sections of the prescribing information in order for the label to be in compliance with the Pregnancy and Lactation Labeling Rule (PLLR). At the time of this CDTL review, the label is still under negotiation, and there are issues to be resolved with the manufacturing facilities.

Regulatory Recommendation: Approval. There are no pharmacology/toxicology issues for NDA 204630 to preclude approval of the drug for the proposed indication.

4. CLINICAL PHARMACOLOGY (This section was excerpted from the review of Dr. Salaheldin S. Hamed, PhD. Please see his review for details.):

Provayblue is an oxidation-reduction agent that reduces the oxidized iron (Fe³⁺) in methemoglobin (metHb) to the reduced form (Fe²⁺) in normal hemoglobin. The applicant is seeking the approval of Provayblue for the treatment of acquired methemoglobinemia.

NDA 204630 was submitted as a 505(b)(2) application; initially, the applicant relied on the published literature to demonstrate safety and efficacy of MB in the treatment of methemoglobin and data from a retrospective study in 12 methemoglobin patients treated with Provayblue. However, there was insufficient relative bioavailability (BA) information to bridge the pharmacokinetics (PK) of Methylene blue 1% USP used in the majority of the reported trials and (b) (4). In addition, the applicant did not provide any clinical pharmacology studies for the proposed product. A Complete Response was issued for lack of information regarding the PK of Provayblue and the ADME properties of MB in general (see Clinical Pharmacology Review by Dr. Joseph Grillo, DARRTS date 09/04/2014).

In the present submission, the applicant provided a relative BA/BE study comparing the PK of Provayblue to Methylene blue 1% USP after a nominal dose of 2 mg/kg, a QT prolongation trial,

(b) (4), and in vitro metabolism and DDI studies.

The applicant conducted a single dose, parallel BE study comparing the PK of MB 1% USP and Provayblue. The concentrations of Methylene blue and Azure B, the major metabolite, were measured in whole blood and plasma. The dose adjusted AUC in whole blood was within the bioequivalence bounds; however, the dose adjusted Provayblue Cmax was higher than that of the USP solution (Table 1).

It was noted during the conduct of the study that the reference formulation was administered at ~ 1.6 mg/kg dose instead of the nominal 2 mg/kg dose. Methylene blue exhibits concentration-dependent partitioning into red blood cells, with higher partitioning at higher concentrations. The concentration-dependent partitioning is likely to be the reason for the observed differences in the dose adjusted Cmax between the two products.

The ADME properties of Methylene blue are not very well characterized in humans. Literature studies report variable PK characteristics of Methylene blue, mainly due to varying sampling times and assay selectivity issues. Recent reports that employ more selective bioanalytical methods suggest 40% of the Methylene blue dose is excreted by renal elimination as parent drug and the balance of the dose undergoes hepatic metabolism.

In vitro metabolism data demonstrate that Methylene blue is metabolized in human hepatocytes (~33% of the initial MB amount). In vitro incubation of Methylene blue with human liver microsomes suggested that UGT enzymes played a more prominent role in metabolism compared to CYP450 enzymes. To characterize the role of individual metabolizing enzymes, MB was incubated with human liver microsomes expressing individual recombinant CYP450 or UGT enzymes in vitro. It was found that CYP1A2, CYP2D6, CYP2C19, UGT 1A9, and UGT 1A4 had the capacity to metabolize Methylene blue. The relative contribution of the individual enzymes or elimination pathways is not thoroughly Reference ID: 3903201 NDA 204630 Page 8 of 24 characterized. However, the multiplicity of the elimination pathways and metabolizing enzymes preclude the need for in vivo DDI studies of Methylene blue as a victim drug.

In vitro studies show that Methylene blue is a potent inhibitor of CYP450 1A2, 2C8, 2C19, 3A4, 2B6, 2D6, 2C9 with R values of 59, 43, 32, 21, 11, 9, and 4, respectively. Even with the acute dosing regimen of Methylene blue, in vivo DDI study of Methylene blue as a perpetrator drug are warranted due to the relatively long elimination half-life (~24 hours).

Based on published safety communications by the FDA, drug interactions of Methylene blue with selective serotonin reuptake inhibitors (SSRI) and other anti-depressants (bupropion, buspirone, venlafaxine, etc.) have been reported to be fatal. The fatality of these interactions has been attributed to the pharmacodynamic interaction of Methylene blue as a monoamine oxidase inhibitor with SSRI. Because it has not been formally investigated, the contribution of pharmacokinetic interactions of MB as an inhibitor of many CYP450 enzymes involved in the metabolism of SSRI and other anti-depressants cannot be ruled out. To mitigate the risk for drug-drug interactions, an in vivo study of Methylene blue as a perpetrator drug is warranted.

The applicant did not submit data regarding dosing in special populations.

(b) (4)

The pediatric dosing will be based on efficacy studies reported in the literature, which is under the purview of the clinical review team.

(b) (4)

In addition, there is no conclusive evidence that renal clearance is the primary route of elimination. Similarly, the contribution of hepatic clearance to the overall elimination of Methylene blue has not been determined. Since higher doses (>2 mg/kg) of Methylene blue have been associated with hemolytic anemia and other severe adverse events, in vivo studies are warranted to support dosing recommendations in patients with hepatic or renal impairment.

Provayblue is an oxidation-reduction agent for the treatment of acquired methemoglobinemia. The proposed dose is 1 mg/kg given as a 5-minute intravenous infusion.

The applicant submitted efficacy data from a retrospective study in patients with acquired methemoglobin (N=12) who were treated with Provayblue doses of 1 or 2 mg/kg in 9 hospitals in France and the UK. The applicant also provided extensive literature reports and case study reports for the use of Methylene blue in the treatment of acquired methemoglobin. Efficacy results are summarized below:

- Retrospective study in 12 subjects (foreign sourced Provayblue): – methemoglobin reduced from $40.7 \pm 18\%$ to less than 3% in 5 patients – methemoglobin eventually resolved in all patients.
- Literature case reports (Dr. Przepiorka Clinical Review, DARRTS date 8/19/2014): – 38 out of 42 cases met primary endpoint (50% reduction of methemoglobin at one hour post infusion) – 1 mg/kg: response rate 86% (60-96%) (n=14) – 2 mg/kg: response rate 91% (62-98%) (n=11)

The limited retrospective and literature data indicate there is no increased efficacy at doses greater than 1 mg/kg. Therefore, the review team is recommending a dose of 1 mg/kg.

In terms of safety, case reports indicate adverse events and fatal toxicities occurred when Methylene blue was given to patients taking anti-depressants, including selective serotonin reuptake inhibitor (SSRI). These anti-depressants are metabolized by CYP450 enzymes.

To establish a PK bridge to the efficacy/safety data reported in the literature, the applicant conducted a single dose parallel bioequivalence (BE) study comparing the PK of Provayblue to the Methylene blue 1% USP product widely used in the clinical studies reported in the literature. The BE study was conducted at a nominal dose of 2 mg/kg dose.

The BE study results indicate that the dose normalized AUC of Methylene blue falls within the acceptance bounds (Table 1) whereas the dose normalized C_{max} 90% CI bounds fall outside the acceptance criteria. The difference in C_{max} between the two products was due to the presence of

reduced amount of active ingredient in the reference product. Thus, from a clinical pharmacology perspective, the study established a PK bridge between Provayblue and Methylene blue 1% USP.

Table 1

Study	Methylene Blue	Geometric Mean Ratio (90% CI)
Whole Blood	AUC _{inf} /Dose	104 (96,113)
Whole Blood	C _{MAX} /Dose	115 (96,137)
Plasma	AUC _{inf} /Dose	103 (96,112)
Plasma	C _{MAX} /Dose	87 (82,96)

ADME information in the submitted literature reports suggests that Methylene blue undergoes hepatic and renal clearance; however, the contribution of renal and hepatic routes in the elimination of Methylene blue has not been determined. As a result, dosing recommendations in patients with renal or hepatic impairment cannot be made. Since higher doses (>2 mg/kg) of Methylene blue have been associated with hemolytic anemia and other severe adverse events, the influence of renal and hepatic impairment needs to be assessed in subjects with varying degrees of renal and hepatic impairment.

In vitro incubation with human hepatocytes resulted in ~33% metabolism of Methylene blue. Further in vitro studies suggested that UGT1A9, UGT1A4, CYP1A2, CYP2D6, and CYP2C19 had the capacity to metabolize Methylene blue.

In vitro studies with CYP450 enzymes indicate that Methylene blue is a potent inhibitor of a number of CYP450 enzymes (CYP1A2, 2C8, 2C19, 3A4, 2B6, 2D6, and 2C9). The R values, which are calculated as the ratio of the C_{max} relative to the K_i in vitro, ranged from 4 to 60, indicating the need for in vivo DDI studies. In addition, the published reports of fatal drug-drug interactions with the anti-depressant drugs further support the need for in vivo drug-drug interaction (DDI) evaluations.

Recommendation of Clinical Pharmacology: This NDA is acceptable from a clinical pharmacology perspective provided that the applicant and the agency come to an agreement regarding the labeling language and the identical any identical clinical studies under the post marketing requirements (PMRs).

Post Marketing Requirements

(b) (4)

5. PRODUCT QUALITY (This section is excerpted from the review of Dr. Anamitro Banerjee. Please see his review for details):

The Cenexi manufacturing site in France was inspected in April, 2015 to ascertain if deficiencies in the past had been resolved. Due to the nature of the deficiencies noted in this inspection, another inspection has been requested to confirm that corrective actions have been implemented such that this site is in an acceptable state of readiness for commercial manufacturing. This inspection, which is about to begin at the time of submission of this CDTL report, will also address program objectives under the Pre-Approval Compliance program (data integrity and conformance to application).

Recommendation: Approval will be contingent upon the upcoming inspection. The recommendation will depend on whether deficiencies noted in the past have been resolved.

6. EFFICACY: (This section is excerpted from the review of Dr. Donna Przepiorka. For details, please see her review).

Efficacy was assessed on the basis of a methemoglobin decrease of at least 50% at 1 hour after IV administration of Provayblue or Methylene Blue USP 1%. This was the primary endpoint of Study PVP-2013001. Methemoglobin can be estimated by oximetry of an arterial blood sample, measured directly by co-oximetry, or measured noninvasively by pulse co-oximetry. The applicant did not include the method of measurement in the case report forms, so it will not be possible to estimate the potential error of the measurement of the primary endpoint.

It has been established that methemoglobin levels >70% have a high mortality, and that there are few serious symptoms when the methemoglobin is <20%. For patients with life-threatening complications from high levels of methemoglobin, a 50% reduction within 1 hour after a dose would be estimated to reduce the methemoglobin from 70% to 17% after 2 successive doses (2 hours), which would be reasonably likely to rapidly reduce the complications of methemoglobinemia. Moreover, a 50% reduction in methemoglobin could not be achieved by normal homeostatic mechanisms, so the result could be attributed to investigational agent even in a study without concurrent controls. Concomitant resolution of established signs of serious methemoglobinemia, such as tachypnea, tachycardia or coma, within 2 hours would provide an objective measure of a clinical benefit.

The literature was also searched for cases that included sufficient detail to assess efficacy. There were 44 cases of treatment of methemoglobinemia that included a baseline measurement and a follow-up measurement within 1.25 hours (see Appendix 9.2Z). Since the conclusion from Study PVP-2014001 was that Provayblue was bioequivalent to Methylene Blue USP 1%, the literature cases were further reviewed to identify those which used Methylene Blue USP 1% specifically. None of the references provided the source of the Methylene blue used. Twenty-eight of the publications were from US healthcare providers. A query was sent to the corresponding author and/or Director of Pharmacy for 24 of the published reports in which contact information could be identified in order to determine if they could confirm that Methylene Blue USP 1% was used. FDA received 16 responses (67% response rate), of which 12 could not confirm, 1 indicated that 1% Methylene blue was used but did not confirm that the product was USP, and 3 confirmed that Methylene Blue USP 1% was in use at the institution in the timeframe of the treatment described in the case report. Only these last 3 cases were considered in the analysis of efficacy.

Demographics: The Efficacy Population consists of the 3 patients treated with Provayblue in Study PVP-2013001 and the 3 patients in the published cases of methemoglobinemia treated with Methylene Blue USP 1% for whom adequate data were available to assess efficacy. Table 2 shows the demographic characteristics of the Efficacy Population. Race/ethnicity was not recorded for 5 of the 6 patients.

Table 2: Efficacy Population Demographics

Patient	Age	Gender	Cause of Methemoglobinemia	Initial Dose ^a
PVP-2013001-04	6 days	Female	Metoclopramide	1 mg/kg
PVP-2013001-06	40 years	Male	Nitrite	1 mg/kg
PVP-2013001-11	1.8 years	Male	Sodium nitrite	2 mg/kg
Annabi 2009	69 years	Female	Benzocaine	2 mg/kg
Birchem 2005	69 years	Female	Benzocaine	2 mg/kg
Grauer 1996	68 years	Male	Benzocaine	1 mg/kg

Source: FDA analysis

^aInitial dose of Provayblue or Methylene Blue USP 1%

Treatment and Disposition: The initial doses of Provayblue or Methylene Blue USP 1% administered are listed in Table 1 above. The reported durations of the infusions ranged from “bolus” to 30 minutes. All of the patients were reported to have recovered from the methemoglobinemia, and 2 died subsequently (one on day 2 and one on day 33) from unrelated causes (Attof 2006; Douglas 1977).

Primary Efficacy Endpoint: The applicant provided no analysis of the primary endpoint in Protocol PVP-2013001. The applicant stated that “all the patients were reported to have had a satisfactory medical outcome so it can be assumed that the methemoglobin level at discharge had decreased to clinically acceptable levels” (Protocol PVP-2013001 Clinical Study Report 4/30/2014 p.23).

Table 3 shows the results after the first dose of Provayblue or Methylene Blue USP 1% for the 6 patients in the Efficacy Population. All 6 patients (100%; 95% CI 61-100%) had >50% reduction in methemoglobin within 1 hour of treatment.

Table3: Methemoglobin Levels After Dose 1 of Provayblue or Methylene Blue USP 1%

Patient	<u>Methemoglobin (%)</u>		Relative Reduction	Time After Dose (hr)
	Baseline	After Dose 1		
PVP-2013001-04	10.7	1.4	87%	1.0
PVP-2013001-06	29.6	2.8	91%	1.0
PVP-2013001-11	44.4	2.1	95%	0.5
Annabi 2009	33.0	4.0	88%	1.0
Birchem 2005	41.1	18.4	55%	1.0
Grauer 1996	47.2	12.3	74%	0.3

Source: FDA analysis

Review Comment: With results in 6 patients, the lower bound of the 95% confidence interval is now above 50%, supporting the likelihood that the majority of patients with methemoglobinemia might be expected to have a rapid decrease in methemoglobin levels after treatment with Provayblue.

On review of the literature, an additional 41 cases of treatment of methemoglobin with a Methylene blue product intravenously included a follow-up measurement within 1 (+/- 0.25) hours (see Appendix 9.2). These cases form the Literature Population. This population included 24 males and 17 females of median age 33 years (range, 9 days to 80 years). The median methemoglobin level at baseline was 40% (range, 10% to 98%). Of these cases, 37 (90%; 95% CI 77-96%) had a methemoglobin decrease of at least 50% by 1 hour after IV administration of the methylene blue product. The four nonresponders had a baseline methemoglobin >60%.

Review Comment: The response rates from this analyses of the Literature Population should be interpreted with caution, since there may have been bias against reporting failures or in obtaining

measurements of methemoglobin at one hour when the clinical results were obvious. Overall, however, they are consistent with the results in the Efficacy Population.

Subpopulations: The samples size in the efficacy population was too small for a meaningful analysis by subgroup. All 47 cases were pooled for the subgroup analysis (Pooled Population). The pool of 47 cases included pediatric patients in the following age groups: 3 neonates (less than 1 month), 4 infants (1 month up to less than 2 years), 4 children (2 years up to less than 12 years), and 3 adolescents (12 years to less than 17 years). In addition, there were 8 patients age $\geq$ 65 years. Table 4 shows the response rates by age, gender, baseline methemoglobin and etiology of the methemoglobinemia. Responses were seen across all subgroups. The subgroups with the lowest response rates were those with a baseline methemoglobin $> 60\%$, and when the etiologic agent was a toxic chemical (i.e. aniline, metaflumizone, nitrobenzene and phenazopyridine).

Table 4: Pooled Population – Subgroup Analysis of Response

	Responses ^a	Response Rate (95% CI)
<u>Age</u>		
< 2 years	7/7	100% (65% - 100%)
2 to < 17 years	6/7	86% (49% - 97%)
17 to < 65 years	21/23	91% (73% - 98%)
$\geq$ 65 years	8/9	89% (57% - 98%)
Missing	1/1	100% (21% - 100%)
<u>Gender</u>		
Female	20/20	100% (84% - 100%)
Male	23/27	85% (68% - 94%)
<u>Baseline Methemoglobin</u>		
< 30%	16/16	100% (81% - 100%)
30% to 60%	20/20	100% (84% - 100%)
> 60%	7/11	64% (35% - 85%)
<u>Etiologic Agent</u>		
Nitrate/nitrite	10/10	100% (72% - 100%)
Other	5/5	100% (57% - 100%)
Dapsone	2/2	100% (34% - 100%)
Local anesthetic	20/21	95% (77% - 99%)
Toxic chemicals	6/9	67% (35% - 88%)

Source: FDA analysis

^aNumber of responders per total number in the subgroup. Response is defined as methemoglobin decrease of at least 50% within 1 hour after administration of the Methylene blue product.

The Applicant identified a total of 24 published case reports with 29 patients $\geq$ 65 year old with methemoglobinemia treated a Methylene blue class product at varying doses. The tabular summary revealed no age-related pattern of failure in the elderly population.

The Applicant identified a total of 40 published reports of children > 3 months old and 12 published reports of children < 3 months old with methemoglobinemia treated a Methylene blue class product at varying doses. The tabular summary revealed no age-related pattern of failure in the pediatric population.

Recommendation of Dr. Przepiorka of DHP: Approval.

7. SAFETY: (This section is excerpted from the review of Dr. Donna Przepiorka. For details, please see her review).

Safety data were evaluated for 39 patients and 82 healthy volunteers who received at least one dose of Provayblue. The 82 healthy volunteers treated with Provayblue had a median age of 36 years (range, 19-55 years); 54% were male, and 68% were white. The demographic characteristics of all healthy volunteers are shown by study in Table 2 (see above).

Deaths: There were no deaths in the healthy volunteer studies.

Serious Adverse Events: There was one serious adverse event reports. Subject 146 was a 34 year-old man participating in Study PVP-2014002. He received the moxifloxacin dose on day 1 and the saline dose on day 8 without problems. On day 15, he received an infusion of Provayblue 2 mg/kg starting at 8:45. The reported adverse events included dysgeusia and pain in the extremity at 8:46, nausea at 9:00, syncope at 9:05 and chromaturia at 10:00. Twenty minutes after the start of infusion, the subject reported difficulty breathing, he then lost consciousness for approximately 1 minute and had epileptic-like convulsions for about 10 seconds. The heart rate was erratic, varying from 51 to 72 beats per minute. The subject regained consciousness and had no further symptoms. He received no specific treatment for this event. The ECG recording at the time of the event reportedly showed 4 sinus pauses ranging from 2.9 seconds to 14 seconds. Additional changes in the ECG included a very transient shortening of the PR interval and an increase in QTcF.

Comment of Primary Reviewer: I agree that the event of syncope due to sinus arrest was at least possibly related to Provayblue. This potential risk should be reflected in the Prescribing Information.

Dropouts and/or Discontinuations: One subject in Study PVP-2014002 dropped out after completion of Period 1 (saline placebo) because she “was afraid of the pain that the other subjects had experienced”. There were no early withdrawals due to adverse events.

Significant Adverse Events:

There were no events of serotonin syndrome, interference with in vivo monitoring devices or hemolytic anemia reported in the healthy volunteer studies.

Hypersensitivity was assessed in the healthy volunteer studies by FDA using SMQN_Hypersensitivity and SMQN_Anaphylactic reaction. There were no anaphylactic reaction terms reported. There were 6 (7%) subjects with 7 hypersensitivity terms reported after receiving with Provayblue. The hypersensitivity terms included 4 events of contact dermatitis and 1 event each of erythematous rash, maculopapular rash, and infusion site urticaria. Of the subjects who received Methylene Blue USP 1%, 2 had a contact dermatitis and 1 had a maculopapular rash. The applicant included a specific assessment of infusion site reactions at baseline, hour 6 and hour 12 in Study PVP-2014001. The results of these assessments are shown in Table 5.

Table 5: Study PVP2014001 – Injection Site Reaction Assessments

Local Reaction	Treatment	Time Point	Number of Subjects (%)
Erythema/Redness	A	Predose	0
		Hour 5.8	0
		Hour 11.8	1 (3%)
	B	Predose	0
		Hour 5.8	2 (6%)
		Hour 11.8	1 (3%)
Induration/Swelling	A	Predose	0
		Hour 5.8	0
		Hour 11.8	1 (3%)
	B	Predose	0
		Hour 5.8	1 (3%)
		Hour 11.8	2 (6%)
Pain	A	Predose	0
		Hour 5.8	0
		Hour 11.8	1 (3%)
	B	Predose	0
		Hour 5.8	2 (6%)
		Hour 11.8	0
Tenderness	A	Predose	0
		Hour 5.8	2 (6%)
		Hour 11.8	3 (9%)
	B	Predose	0
		Hour 5.8	5 (14%)
		Hour 11.8	3 (9%)

Treatment A: A single 2 mg/kg IV infusion of Provayblue

Treatment B: A single 2 mg/kg IV infusion of methylene blue USP

Infusion site reactions were assessed by FDA using infusion site reactions. There were 6 (7%) subjects with 8 infusion site reaction terms reported after receiving with Provayblue. The infusion site reaction terms included 5 events of infusion site pain, 2 of infusion site discomfort, and 1 of infusion site urticaria. Of the subjects who received Methylene Blue USP 1%, 13 had infusion site pain, 3 infusion site discomfort, 2 infusion site erythema, 2 infusion site pruritus and 1 each of infusion site extravasation, infusion site induration and infusion site swelling.

Common Adverse Events:

Table 6 shows the TEAE in decreasing frequency by SOC in the 82 healthy volunteers who received a single dose of Provayblue 2 mg/kg. Events in the SOC Musculoskeletal and connective tissue disorders, renal and urinary disorders, and nervous system disorders occurred in >50% of the subjects. SOC with the most frequent TEAE of moderate-to-severe grade included musculoskeletal and connective tissue disorders (62%), nervous system disorders (17%), and general disorders and administration site conditions (9%).

Table 6: TEAE by SOC in Healthy Volunteers Treated with Provayblue 2 mg/kg

System Organ Class	Any Severity TEAE (n=82)		Moderate-Severe TEAE (n=82)		Related TEAE (n=82)	
Musculoskeletal and connective tissue disorders	75	91%	51	62%	74	90%
Renal and urinary disorders	61	74%	0		61	74%
Nervous system disorders	43	52%	14	17%	42	51%
General disorders and administration site conditions	32	39%	7	9%	27	33%
Skin and subcutaneous tissue disorders	25	30%	4	5%	21	26%
Gastrointestinal disorders	23	28%	2	2%	21	26%
Vascular disorders	4	5%	1	1%	4	5%
Psychiatric disorders	4	5%	0		4	5%
Metabolism and nutrition disorders	3	4%	0		3	4%
Eye disorders	2	2%	0		0	
Respiratory, thoracic and mediastinal disorders	2	2%	0		2	2%
Cardiac disorders	1	1%	0		1	1%
Immune system disorders	1	1%	0		0	
Injury, poisoning and procedural complications	0		0		0	

Source: FDA analysis

Table 7 shows the TEAE in decreasing frequency by PT in the 82 healthy volunteers who received a single dose of Provayblue 2 mg/kg. Only PT that occurred in at least 2 subjects were included. The most common ($\geq 10\%$) TEAE were pain in extremity, chromaturia, dysgeusia, feeling hot, dizziness, hyperhidrosis, nausea, skin discoloration, and headache. Nearly all of the

TEAE reported were also considered related. The most common ($\geq 2\%$) moderate-to-severe TEAE were pain in extremity, headache, feeling hot, dizziness, syncope, back pain, hyperhidrosis, and nausea.

Table 7: TEAE by PT in Healthy Volunteers Treated with Provayblue 2 mg/kg

Preferred Term	Any TEAE (n=82)	Severity Moderate- Severe TEAE (n=82)	Related TEAE (n=82)
Pain in extremity	69	84%	46 56%
Chromaturia	61	74%	0 61 74%
Dysgeusia	16	20%	1 1% 16 20%
Feeling hot	14	17%	5 6% 13 16%
Dizziness	13	16%	4 5% 13 16%
Hyperhidrosis	11	13%	2 2% 11 13%
Nausea	11	13%	2 2% 11 13%
Skin discoloration	11	13%	0 11 13%
Headache	8	10%	6 7% 6 7%
Musculoskeletal pain	7	9%	0 7 9%
Paresthesia oral	7	9%	0 7 9%
Paresthesia	7	9%	0 6 7%
Infusion site pain	5	6%	1 1% 5 6%
Feeling cold	5	6%	0 5 6%
Pallor	4	5%	0 4 5%
Dermatitis contact	4	5%	0 0
Syncope	3	4%	3 4% 3 4%
Influenza like illness	3	4%	1 1% 3 4%
Pruritus	3	4%	1 1% 1 1%
Anxiety	3	4%	0 3 4%
Decreased appetite	3	4%	0 3 4%
Chest discomfort	3	4%	0 2 2%
Back pain	2	2%	2 2% 1 1%
Cold sweat	2	2%	1 1% 2 2%
Dizziness postural	2	2%	1 1% 2 2%
Muscle spasms	2	2%	1 1% 2 2%
Presyncope	2	2%	1 1% 2 2%
Vomiting	2	2%	1 1% 2 2%
Arthralgia	2	2%	1 1% 1 1%
Chills	2	2%	0 2 2%
Diarrhea	2	2%	0 2 2%
Discomfort	2	2%	0 2 2%
Dyspnea	2	2%	0 2 2%
Erythema	2	2%	0 2 2%
Hypoesthesia oral	2	2%	0 2 2%
Infusion site discomfort	2	2%	0 2 2%
Limb discomfort	2	2%	0 1 1%

Table 7: TEAE by PT in Healthy Volunteers Treated with Provayblue 2 mg/kg

Preferred Term	Any TEAE (n=82)	Severity TEAE (n=82)	Moderate-Severe TEAE (n=82)	Related TEAE (n=82)
Oral discomfort	2	2%	0	1 1%
Catheter site pain	2	2%	0	0
Ecchymosis	2	2%	0	0

Source: FDA analysis

Pain in the extremity was the most common TEAE (84%) and the most common moderate-to-severe TEAE (56%). The applicant indicated that the pain was in the extremity used for the infusion but differentiated it from infusion site pain (6%). Other events of musculoskeletal pain were reported in 9%. In the SOC nervous system disorders, the most common ($\geq 5\%$) TEAE were dysgeusia, dizziness, headache and paresthesia.

Recommendation of Dr. Przepiorka: Approval.

8. ADVISORY COMMITTEE MEETING: No Advisory Committee meeting.

9. POST MARKETING REQUIREMENTS (PMRs):

PMR #1: (b) (4)

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. (b) (4)

PMR #2: (b) (4)

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. (b) (4)

(b) (4)

PMR #3:

(b) (4)

Conduct a clinical trial to determine the effect of hepatic impairment on the PK and safety of Methylene blue.

(b) (4)

PMR#4:

(b) (4)

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.

(b) (4)

10. OTHER REGULATORY ISSUES: INSPECTIONS OF CLINICAL SITES. (This section was excerpted in part from the review of Dr. Anthony Orienia. For details, please see his review).

The study data derived from the inspections at some of the clinical sites as well as the Contract Research Organization (CRO) are considered reliable in support of the requested indication. Four clinical sites (Drs. Mehta, Motan, Nagarkar, and Ratnavelu) were selected for audit. The CRO (b) (4) was also inspected.

The preliminary classification for the inspections of Drs. Nagarkar and Ratnavelu, and the CRO is No Action Indicated (NAI). The preliminary classification for the inspections of Drs. Mehta and Motan is Voluntary Action Indicated (VAI).

Observations noted above for the four clinical investigator sites and the CRO are based on communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

11. LABELING: Under negotiation with Applicant.

12. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT: The recommendation of the Secondary TL reviewer is approval providing that the current issues with the Cenexi manufacturing facility can be resolved by the PDUFA action date.

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
03/25/2016

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA #	204630
Supplement #	
Applicant Name	Provepharma SAS
Date of Submission	September 13, 2013
PDUFA Goal Date	July 13, 2014 (received an extension 10/13/14)
Proprietary Name / Established (USAN) Name	(b) (4) Methylene Blue for Injection
Dosage Forms / Strength	50 mg/10 mL ampule
Proposed Indication(s)	for the treatment of acquired methemoglobinemia
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Donna Przepiorka, M.D.,Ph.D./ Albert Deisseroth, M.D., Ph.D.
Statistical Review	N/A
Pharmacology Toxicology Review	Brenda Gehrke, Ph.D./Haleh Saber, Ph.D.
CMC Review/OBP Review	Amit Mitra, Ph.D., Jean Tang, Ph.D./Ali Al-Hakim, Ph.D./Minerva Hughes, Ph.D./Elsbeth Chikhale, Ph.D.
Microbiology Review	Stephen E. Langille/Bryan S. Riley
Clinical Pharmacology Review	Jospeh Grillo, Pharm.D. Julie Bullock, Pharm.D./ Dhananjay D Marathe/Jiang Liu/Qianyu Dang/Norman L. Stockbridge
DDMAC	N/A
OSI	Anthony Orencia, M.D., Janice Pohlman, M.D., Kassa Ayalew, M.D.
CDTL Review	Albert Deisseroth, M.D., Ph.D.
OSE/DMEPA	Michelle Rutledge, Pharm.D./Yelena Maslov, Pharm. D.
OSE/DDRE	
OSE/DSRCS	
Other -MHT	

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMETS=Division of Medication Errors and Technical Support

DSI=Division of Scientific Investigations

DDRE= Division of Drug Risk Evaluation

DSRCS=Division of Surveillance, Research, and Communication Support

CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This 505 b2 submission for NDA 204630 is the second submission for methylene blue for the treatment of acquired methohemoglobinemia. The application was initially submitted in August 2012; however, the application received a refuse-to-file letter due to lack of data to support efficacy and safety claims. The October 10, 2012 letter cited the clinical deficiencies and the clinical pharmacology comments including lack of a assessment of the potential to prolong the QT interval.

The Agency filed the second submission and the original PDUFA goal date was July 13, 2014. Numerous Information requests have been sent to the company. Based on these responses, a decision was made to extend the review clock. The new PDUFA goal is October 13, 2014.

2. Background

Methemoglobinemia is a condition in which the iron in the hemoglobin molecules is in the oxidized form, which does not bind oxygen well. Therefore there is reduction in delivery of oxygen to tissues. The condition can be either congenital or acquired. Numerous oxidizing drugs, chemicals and toxins are known to cause acquired methemoglobinemia. Under certain circumstances where a high percentage of the iron contained in the hemoglobin molecules is oxidized, then the lack of adequate oxygen delivery can result in adverse cardiovascular effects, coma, and death.

3. CMC/Device

The CMC review noted issues with the starting material (b) (4). However due to other identified issues which preclude approval; CMC will include the starting material issue in the CR letter.

From the Office of Biopharmaceutics review:

The Applicant's request for a waiver of the BA/BE study requirement is NOT GRANTED because (1) there is no listed drug to serve as a basis for safety and efficacy and (2) an acceptable bridge to the products used in the literature was not demonstrated. To address this deficiency, the Applicant has agreed to conduct a clinical PK study, which will be evaluated by the Clinical Pharmacology Reviewer. Therefore, the final recommendation on the NDA approvability with respect to the adequacy of the BA/BE data is deferred to the Office of Clinical Pharmacology.

4. Nonclinical Pharmacology/Toxicology

No issues that would preclude approval were identified.

From Dr. Saber's review memo:

Drug-related toxicities in rats and /or dogs in general toxicology studies included the following: anemia as indicated by decreases in erythrocytes, hematocrit, and hemoglobin; methemoglobinemia as indicated by increases in methemoglobin, liver findings (increased weight, inflammatory cell foci, hemosiderin formation indicating hemolysis and hemoglobin degradation, increased bilirubin), enlarged and/or congested spleen and spleen capsule fibrosis, and injection site reactions (necrosis, hemorrhage, mixed inflammatory cell infiltrates and edema, and fibrosis).

Several genetic toxicology studies were conducted by NTP or the Applicant. Methylene blue was genotoxic in three assays (Ames test, in vitro sister chromatid exchange test and an in vitro chromosomal aberration test in CHO cells) and negative for micronucleus induction in animals. Based on these results, methylene blue has the potential to be carcinogenic. For acquired methemoglobinemia, carcinogenicity studies are not required due to the short term administration of the drug. However, as the studies were conducted by NTP and the reports were submitted to the NDA, they have been reviewed by Dr. Gehrke and the results discussed at the Executive Carcinogenicity Assessment Committee. Methylene blue caused pancreatic islet adenomas or carcinomas (combined) in male rats in the 2-year oral carcinogenicity study.

Methylene blue was teratogenic in rats and rabbits when administered during the period of organogenesis. Embryo-fetal toxicities may be due to methemoglobinemia developed in animals and the associated adverse effects (e.g. hypoxia and anemia). The clinical dose of methylene blue will be titrated to doses that will reduce methemoglobin in patients. Therefore, the findings in animals may not be applicable to patients receiving the therapeutic range of methylene blue; pregnancy category C is recommended.

Embryo-fetal toxicities may occur if patients are dosed above the therapeutic range. In an in vitro study, methylene blue reduced the human sperm motility in a concentration dependent manner, suggesting that the drug may reduce fertility in male subjects.

5. Clinical Pharmacology/Biopharmaceutics

From the Office of Clinical Pharmacology review:

The Office of Clinical Pharmacology (OCP) has determined that there is insufficient clinical pharmacology and biopharmaceutics information provided in this NDA to support a recommendation of approval of (b) (4). We recommend a complete response (CR) action until the relative bioequivalence between (b) (4) injection 0.5% (5 mg/mL) solution and methylene blue injection USP 1% (10 mg/mL) solution is established. The applicant should also address the deficiencies below in their resubmission of the application...

The following deficiencies are reproduced from their review:

1.2.1 Conduct a relative BA/BE trial in humans to assess the relative bioequivalence of methylene blue and Azure B concentrations following intravenous administration of (b) (4) injection 0.5% (5 mg/mL) solution or methylene blue injection USP 1% (10 mg/mL) solution. Samples should be analyzed using a validated method (Refer to the Guidance for Industry Bioanalytical Method Validation) and full PK profiling from both methylene blue formulations should be reported for both methylene blue and Azure B.

1.2.2 Identify the pathways by which (b) (4) (and its metabolites) are eliminated and excreted in humans.

1.2.3 (b) (4)

1.2.4 Conduct a clinical trial in humans to determine the potential of (b) (4) to prolong the QT/QTc interval according to the principles of ICH E14.

1.2.5 Evaluate the in vitro partitioning of (b) (4) and its metabolite Azure B into human red blood cells.

1.2.6 Evaluate the in vitro ability of (b) (4) (and its metabolites) to act as substrates of cytochrome P450 enzymes, as well as substrates or inhibitors of conjugating enzymes and transporters. For an updated list of potential metabolic pathways and transporters identified by the Agency please refer to the newly released draft guidance Drug Interaction Studies.

Based on the data submitted, the IRT team concluded:

Large QTc prolongation (> 20 ms) effect of 1 mg/kg methylene blue injection could not be ruled out in this study. The largest upper bound of the 2-sided 90% CI for the mean change from baseline of methylene blue injection (1 mg/kg) was 22.6 ms observed at 7 minutes post-dose...

6. Microbiology

No issues that would preclude approval were identified.

7. Clinical/Statistical-Efficacy

The clinical review team does not recommend approval. Although the applicant provided retrospective data on methylene blue use in patients, the applicant did not provide sufficient information allowing a conclusion regarding the efficacy and safety of their product for the proposed indication.

From Dr. Przepiorka's review:

To address the deficiency, the applicant will need to submit either a prospective trial of (b) (4) for treatment of acquired methemoglobinemia, or data to establish that reliance on published outcomes with methylene blue USP 1% is scientifically valid.

8. Safety

Insufficient data was provided to assess safety of this product.

9. Advisory Committee Meeting

This application did not go to an Advisory Committee meeting because there were multiple deficiencies identified which could not be addressed through the AC process.

10. Pediatrics

This product is not a NME. However the rarity of this condition may make it extremely difficult to conduct trials in pediatric patients.

11. Other Relevant Regulatory Issues

From the OSI review:

The study data collected from these clinical sites that have been inspected appear generally reliable in support of the requested indication.

This product will not be approved this cycle due to deficiencies identified above.

12. Labeling

N/A

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Complete Response letter will include the multiple deficiencies identified by CMC, Biopharmaceutics, Clinical and Clinical Pharmacology

- Risk Benefit Assessment

N/A

- Recommendation for Post marketing Risk Management Activities

N/A

- Recommendation for other Post marketing Study Requirements/Commitments

N/A

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/s/

ANN T FARRELL
10/03/2014

CDTL Review

Date	September 10, 2014
From	Albert Deisseroth, MD, PhD
Subject	CDTL Review
NDA Number	204630
Applicant	Provepharm SAS
Date of Submission	September 13, 2013
PDUFA Goal Date	October 13, 2014
Proprietary Name	(b) (4)
Dosage Regimen	1 mg/kg
Applicant's Proposed Indication	Treatment of acquired methemoglobinemia
Intended Population	Methemoglobin level (b) (4) in the presence of clinical symptoms
Recommended:	Complete Response

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Donna Przepiorka, MD, PhD
Clinical Pharmacology	Joseph Grillo, PharmD and Julie Bullock, PharmD
Biopharmaceutics	Minerva Hughes, PhD and Elsbeth Chikhale, PhD
Product Quality Microbiology	Stephen E. Langille, PhD and Bryan S. Riley, PhD
Non Clinical (Pharmacology/Toxicology)	Brenda Gehrke, PhD and Haleh Saber, PhD
Regulatory Program Manager	Kim Robertson

TABLE OF CONTENTS

TABLE OF CONTENTS.....	2
1. EXECUTIVE SUMMARY AND BENEFIT RISK DISCUSSION.....	3
2. BACKGROUND.....	3
3. CLINICAL PHARMACOLOGY.....	4
4. BIOPHARMACEUTICS.....	5
5. MICROBIOLOGY.....	5
6. PHARMACOLOGY TOXICOLOGY.....	5
7. EFFICACY.....	5
8. SAFETY.....	6
9. ADVISORY COMMITTEE MEETING.....	7
10. OTHER RELEVANT REGULATORY ISSUES.....	7
11. LABELING.....	7
12. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT.....	7

1. EXECUTIVE SUMMARY AND BENEFIT RISK DISCUSSION (This section was excerpted from the review of Dr. Donna Przepiorka):

NDA 204630 for (b) (4) 0.5% was initially submitted 8/13/2012 under 505(b)(2) for the indication “treatment of acquired methemoglobinemia.” There was no reference listed drug. A Refuse-To-File (RTF) Letter was issued 10/11/2012 citing a lack of data to support the efficacy and safety claims.

The present application was presented as amended to address the RTF comments, but neither the efficacy nor safety data submitted were considered adequate. This reviewer recommends that a Complete Response Letter be issued due to a lack of substantial evidence that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling (21 CFR 314.125(b)(5)). To address the deficiency, the applicant will need to submit either a prospective trial of (b) (4) for treatment of acquired methemoglobinemia, or data to establish that reliance on published outcomes with methylene blue USP 1% is scientifically valid.

Recommendation for Regulatory Action: On the basis of the above, this CDTL recommends disapproval (Complete Response).

2. BACKGROUND (This section was excerpted from the review of Dr. Donna Przepiorka):

2.a. Indication: The indication proposed by the Applicant for (b) (4) is the treatment of acquired methemoglobinemia.

2.b. Summary of Background. (This section was excerpted from the review of Dr. Donna Przepiorka):

Methemoglobin is a state in which the iron in the heme molecules is in the oxidized form, which does not bind oxygen well. The result is a net reduction in delivery of oxygen to tissues. Numerous oxidizing drugs, chemicals and toxins are known to cause acquired methemoglobinemia.

If the offending agent is withdrawn, homeostatic mechanisms reduce the oxidized hemoglobin at about 15% per hour, normalizing the level over time. However, when the proportion of hemoglobin that is oxidized is high, the lack of oxygen delivery may be severe enough to cause adverse cardiovascular effects, coma, and death.

(b) (4) is a formulation of methylene blue purported to reduce oxidized heme. In presubmission meetings, the Division established with the applicant that efficacy of (b) (4) for treatment of acquired methemoglobinemia could be concluded if treatment resulted in a rapid reduction in methemoglobin, and that concurrent rapid improvements in heart rate or respiratory rate and/or resolution of coma would be clinical benefits.

3. CLINICAL PHARMACOLOGY (This section was excerpted from the review of Dr. Joseph Grillo):

This application is an NDA for (b) (4) Injection, 0.5% (b) (4) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act). The applicant did not conduct any clinical pharmacology trials using proposed to-be-marketed (b) (4) injection, 0.5% (b) (4). The submission includes literature data to support the safety and effectiveness of (b) (4) injection. The pharmacokinetic (PK) as well as the majority of the safety and efficacy data submitted in this NDA were generated after administration of methylene blue injection USP 1% (MB 1% USP).

The applicant also performed a small (n=12) retrospective clinical trial in patients who were treated for methemoglobinemia with foreign sourced (b) (4) in France and the United Kingdom to support safety and efficacy. The Office of New Drug Quality Assessment (ONDQA) could not grant a biowaiver from determining the relative Bioavailability/Bioequivalence (BA/BE) between MB 1% USP used in the majority of the clinical trials and (b) (4) because there is no listed reference drug to support the waiver. The Agency is also unable to establish BA/BE by linking the submitted published and unpublished MB 1% USP PK literature to (b) (4) because the PK information provided in these papers is highly variable due to a likely combination of assay, formulation, and sampling issues.

In the absence of relative BA/BE between (b) (4) and MB 1% USP, a link to extrapolate from the MB 1% USP based retrospective trials and case reports supporting safety and efficacy cannot be established. In addition, the lack of any dose-concentration-response or ontogeny information for (b) (4) or MB 1% USP does not allow for a formal assessment of the (b) (4) dose. Furthermore, the applicant did not provide mass balance information to adequately describe the metabolic and elimination pathways for either (b) (4) or MB 1% USP. Therefore, this application fails to provide sufficient information to support a recommendation of approval of (b) (4) due to the absence of relative BA/BE between (b) (4) Injection, 0.5% and methylene blue injection USP 1%.

Additional deficiencies include; 1) lack of information regarding the pharmacokinetics of (b) (4) and the ADME of methylene blue (MB) in general, 2) highly variable MB 1% USP pharmacokinetic (PK) information in published and unpublished reports, and 3) the inability to assess the proposed (b) (4) dose in adults, pediatrics, and special populations (e.g., renal impairment).

Recommendation of Clinical Pharmacology: The Office of Clinical Pharmacology (OCP) has determined that there is insufficient clinical pharmacology and biopharmaceutics information provided in this NDA to support a recommendation of approval of (b) (4). We recommend a Complete Response (CR) action until the relative bioequivalence between (b) (4) injection 0.5% (5 mg/mL) solution and methylene blue injection USP 1% (10 mg/mL) solution is established. The applicant should also address the deficiencies below in their resubmission of the application. The acceptability of specific drug information is provided below.

4. BIOPHARMACEUTICS (This section is excerpted from the review of Dr. Minerva Hughes):

The Applicant's request for a waiver of the BA/BE study requirement is NOT GRANTED because (1) there is no listed drug to serve as a basis for safety and efficacy and (2) an acceptable bridge to the products used in the literature was not demonstrated. The Applicant has agreed to conduct a clinical PK study, which will be evaluated by the Clinical Pharmacology Reviewer.

Recommendation of the Biopharmaceutics Reviewer, Office of New Drug Quality Assessment: The final recommendation on the NDA approvability with respect to the adequacy of the BA/BE data is deferred to the Office of Clinical Pharmacology.

5. PRODUCT QUALITY MICROBIOLOGY (This section is excerpted from the review of Dr. Stephen Langille).

The applicant provided a description and validation data for the (b) (4) of (b) (4) Injection 0.5%. No deficiencies were identified based on the information provided.

Recommendation of the Microbiology Reviewer: Approval

6. PHARMACOLOGY TOXICOLOGY (This section is excerpted from the review of Dr. Brenda Gehrke):

The nonclinical studies and literature submitted to this NDA provide sufficient information to support the use of methylene blue for the proposed indication.

Recommendation of Pharmacology Toxicology: Approval.

7. EFFICACY (This section is excerpted from the review of Dr. Donna Przepiorka):

The data to support efficacy came from Protocol PVP-2013001, a retrospective chart review of patients with acquired methemoglobinemia precipitated by any etiology treated with (b) (4) Injection, 0.5% during the period 2010 - 2012. The sponsor identified 12 patients (nine adults and three children) treated with (b) (4). The median methemoglobin was 44% (range, 11-75%) at baseline. The reported initial dose of (b) (4) was 1 mg/kg for 7 patients, 1.5 mg/kg for 1 patient, and 2 mg/kg for 4 patients. One subject had 4 doses, 1 had 3 doses, and the others received a single dose of (b) (4).

The primary endpoint of the protocol was the proportion of patients with at least 50% reduction in methemoglobin at one hour after the first dose of (b) (4). Only three patients had a repeat methemoglobin measured within the required timeframe. The methemoglobin was reduced by at least 50% in all three subjects by one hour. Although the response rate was high (100%), the 95% confidence interval (CI) was wide (44-100%) due to the small sample size, so the point estimate was not considered credible. No data on the effects of treatment with (b) (4) on heart rate, respiratory rate or mental status were submitted.

Recommendation of Dr. Przepiorka of DHP: Complete Response.

8. SAFETY (This section is excerpted from the review of Dr. Donna Przepiorka):

Minimal safety data were available from Protocol PVP-2013001. Follow-up was limited to the duration of hospitalization (median 2.5 days; range, 2 hours to 15 days). There were no deaths and no related serious adverse events. There were 15 adverse events reported. None were considered related, and none occurred in more than one patient. The data files for vital signs and laboratory tests were inadequate, and these parameters could not be analyzed.

Additional information was provided from Protocol PVP-2013002 and from postmarketing reports in Europe. Protocol PVP-2013002 was a compassionate use protocol in France that accrued 27 patients (16 adults and 11 children) treated with (b) (4) from November, 2010 to October, 2011 for hereditary methemoglobinemia (n=1) or ifosfamide-induced encephalopathy (n=26). There were no adverse events reported for patients treated on Protocol PVP-2013002. The postmarketing review also indicated that no adverse event have been reported with commercial use of (b) (4).

The applicant also submitted the results for Protocol 1MBL12002, a single-center, open-label, single-dose study of Methylene Blue Injection, USP 1% manufactured by American Regent, Inc.. The primary objective was to assess pharmacokinetics, safety and tolerability. Twelve subjects were accrued and followed for at least 4 days after treatment. All subjects completed the study. There were no deaths or serious adverse events. The most common adverse events were infusion site pain (42%) and nausea (17%). There was a slight and transient fall in diastolic blood pressure and rise in pulse at 2.83 hours from start of infusion for the group as a whole and one subject had an episode of hypotension. There were no grade 3-4 laboratory abnormalities reported. One subject had an ALT 1.7x ULN and AST 1.1x ULN at the end of study. Four subjects had an abnormal urine leukocyte esterase which the applicant attributed to test interference by methylene blue.

Recommendation of Dr. Przepiorka: Complete Response.

9. ADVISORY COMMITTEE MEETING: No Advisory Committee meeting.

10. OTHER RELEVANT REGULATORY ISSUES: None.

11. LABELING: Not applicable.

12. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT: The recommendation of the CDTL is disapproval (Complete Response).

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/s/

ALBERT B DEISSEROTH
09/10/2014

CLINICAL REVIEW

Application Number	NDA 204630
Application Type	Type 7 Resubmission
Priority or Standard	Standard
Submit Date	9/13/2013
Received Date	9/13/2013
PDUFA Goal Date	10/13/2014
Review Completed	8/13/2014
Office / Division	Office of Hematology and Oncology Products / Division of Hematology Products
Primary Reviewer	Donna Przepiorka, MD, PhD
Team Leader	Albert Deisseroth, MD, PhD
Established Name	Methylene Blue Injection, 0.5%
Trade Name	(b) (4)
Therapeutic Class	Antidote
Applicant	Provepharm SAS
Formulation	Injection, solution (50 mg)
Dosing Regimen	1 mg/kg
Indication	Treatment of acquired methemoglobinemia
Intended Population	Methemoglobin level (b) (4) in the presence of clinical symptoms

Table of Contents

CLINICAL REVIEW	1
TABLE OF CONTENTS	2
TABLE OF TABLES	4
TABLE OF FIGURES	4
TABLE OF ABBREVIATIONS	4
1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	5
1.1 Recommendation on Regulatory Action	5
1.2 Basis of the Recommendation	5
2 INTRODUCTION AND REGULATORY BACKGROUND	7
2.1 Product Information	7
2.2 Currently Available Treatments for Proposed Indication	7
2.3 Availability of Proposed Active Ingredient in the United States	8
2.4 Important Issues with Consideration to Related Drugs	9
2.5 Summary of Presubmission Regulatory Activity Related to Submission	9
2.6 Other Relevant Background Information	10
2.7 Compliance with the Pediatric Research Equity Act	10
3 ETHICS AND GOOD CLINICAL PRACTICES	10
3.1 Submission Quality and Integrity	10
3.2 Compliance with Good Clinical Practices	11
3.3 Financial Disclosures	12
4 SIGNIFICANT ISSUES RELATED TO OTHER REVIEW DISCIPLINES	12
4.1 Product	12
4.2 Preclinical Pharmacology/Toxicology	12
4.3 Clinical Pharmacology	13
4.4 Interdisciplinary Review Team (IRT)	13
4.5 Pharmacovigilance	14
5 SOURCES OF CLINICAL DATA	14
5.1 Tables of Studies/Clinical Trials	14
5.2 Review Strategy	14
5.3 Discussion of Individual Studies/Clinical Trials	15
5.3.1 Protocol PVP-2013001	15
5.3.2 Protocol PVP-2013002	16
5.3.3 Protocol 1MBL12002	16
6 REVIEW OF EFFICACY	16
6.1 Treatment of Acquired Methemoglobinemia	16
6.1.1 Methods	16
6.1.2 Demographics	16

Clinical Review

NDA 204630

(b) (4)
(Methylene Blue Injection 0.5%)

6.1.3	Treatment and Disposition	17
6.1.4	Primary Efficacy Endpoint.....	18
6.1.5	Subpopulations	19
6.1.6	Analysis of the Secondary Efficacy Endpoints	19
6.1.7	Analysis of Clinical Information Relevant to Dosing Recommendations	19
6.1.8	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	19
6.1.9	Additional Efficacy Issues/Analyses.....	20
6.1.10	Literature Review	21
7	REVIEW OF SAFETY	21
7.1	Methods	21
7.1.1	Studies/Clinical Trials Used to Evaluate Safety.....	21
7.1.2	Categorization of Adverse Events	21
7.1.3	Pooling of Data.....	21
7.2	Adequacy of Safety Assessments	21
7.3	Major Safety Results in Protocol PVP-2013001	22
7.4	Supportive Safety Results in Protocol PVP-2013001	22
7.5	Other Safety Explorations	23
7.6	Additional Safety Evaluations	23
7.7	Additional Submissions / Safety Issues.....	23
7.7.1	Safety in Protocol PVP-2013002	23
7.7.2	Safety in the Healthy Volunteer Study.....	24
8	POSTMARKET EXPERIENCE.....	25
9	APPENDICES.....	25
9.1	Advisory Committee Meeting	25
9.2	Case Reports of Treatment with Methylene Blue	25
9.3	References	27

Clinical Review

NDA 204630

(b) (4) (Methylene Blue Injection 0.5%)

Table of Tables

Table 1: Signs And Symptoms By Methemoglobin Concentration.....	8
Table 2: NDA Submission and Amendments	10
Table 3. Clinical Trials	14
Table 4: Characteristics of Patients in Protocol PVP-2013001	17
Table 5: Methemoglobin Levels After Dose 1 of (b) (4)	19
Table 6: Adverse Events in Protocol PVP-2013001	22
Table 7: Adverse Events in Single-Dose Healthy Volunteer Study	24
Table 8: Reduction in Methemoglobin Within One Hour After Treatment with Methylene Blue.	26

Table of Figures

Figure 1: Residual Methemoglobin After Treatment with (b) (4)	20
Figure 2: Vital Signs in Healthy Volunteer Study	24

Table of Abbreviations

AERS	Adverse Event Reporting System
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
CK	creatinine kinase
ECG	electrocardiogram
EMA	European Medicines Agency
G6PD	glucose-6-phosphate dehydrogenase
IRB	institutional review board
IRT	Interdisciplinary Review Team
LDH	lactate dehydrogenase
MAO	monoamine oxidase inhibitor
MB	methylene blue
MetHgb	methemoglobin
NADPH	nicotinamide adenine dinucleotide phosphate
NDC	National Drug Code
PSUR	Periodic Safety Update Report
REMS	risk evaluation and mitigation strategy
RTF	Refuse-To-File
USP	United States Pharmacopoeia

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 204630 for (b) (4) Injection 0.5% was initially submitted 8/13/2012 under 505(b)(2) for the indication “treatment of acquired methemoglobinemia.” There was no reference listed drug. A Refuse-To-File (RTF) Letter was issued 10/11/2012 citing a lack of data to support the efficacy and safety claims.

The present application was presented as amended to address the RTF comments, but neither the efficacy nor safety data submitted were considered adequate. This reviewer recommends that a Complete Response Letter be issued due to a lack of substantial evidence that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling (21 CFR 314.125(b)(5)). To address the deficiency, the applicant will need to submit either a prospective trial of (b) (4) for treatment of acquired methemoglobinemia, or data to establish that reliance on published outcomes with methylene blue USP 1% is scientifically valid.

1.2 Basis of the Recommendation

Background: Methemoglobin is a state in which the iron in the heme molecules is in the oxidized form, which does not bind oxygen well. The result is a net reduction in delivery of oxygen to tissues. Numerous oxidizing drugs, chemicals and toxins are known to cause acquired methemoglobinemia.

If the offending agent is withdrawn, homeostatic mechanisms reduce the oxidized hemoglobin at about 15% per hour, normalizing the level over time. However, when the proportion of hemoglobin that is oxidized is high, the lack of oxygen delivery may be severe enough to cause adverse cardiovascular effects, coma, and death.

(b) (4) Injection 0.5% is a formulation of methylene blue purported to reduce oxidized heme. In presubmission meetings, the Division established with the applicant that efficacy of (b) (4) for treatment of acquired methemoglobinemia could be concluded if treatment resulted in a rapid reduction in methemoglobin, and that concurrent rapid improvements in heart rate or respiratory rate and/or resolution of coma would be clinical benefits.

Summary of Efficacy: The data to support efficacy came from Protocol PVP-2013001, a retrospective chart review of patients with acquired methemoglobinemia precipitated by any etiology treated with (b) (4) Injection 0.5% during the period 2010 - 2012. The sponsor identified 12 patients (nine adults and three children) treated with (b) (4). The median methemoglobin was 44% (range, 11-75%) at baseline. The reported initial dose of (b) (4) was 1 mg/kg for 7 patients, 1.5 mg/kg for 1 patient, and 2 mg/kg for 4 patients. One subject had 4 doses, 1 had 3 doses, and the others received a single dose of (b) (4).

Clinical Review

NDA 204630

(b) (4)® (Methylene Blue Injection 0.5%)

The primary endpoint of the protocol was the proportion of patients with at least 50% reduction in methemoglobin at one hour after the first dose of (b) (4). Only three patients had a repeat methemoglobin measured within the required timeframe. The methemoglobin was reduced by at least 50% in all three subjects by one hour. Although the response rate was high (100%), the 95% confidence interval (CI) was wide (44-100%) due to the small sample size, so the point estimate was not considered credible. No data on the effects of treatment with (b) (4) on heart rate, respiratory rate or mental status were submitted.

On review of the literature, FDA identified 42 cases of treatment of methemoglobin with methylene blue that included a follow-up measurement within 1 (+/- 0.25) hours. There were no cases that reported use of (b) (4) specifically. Of the 42 reported cases, 38 (90%; 95% CI 77-97%) had a methemoglobin decrease of at least 50% by one hour after intravenous administration of methylene blue. However, these reports could not be used to establish the efficacy of (b) (4) since the applicant did not submit sufficient information to bridge its product to any other formulation of methylene blue.

Summary of Safety: Minimal safety data were available from Protocol PVP-2013001. Follow-up was limited to the duration of hospitalization (median 2.5 days; range, 2 hours to 15 days). There were no deaths and no related serious adverse events. There were 15 adverse events reported. None were considered related, and none occurred in more than one patient. The data files for vital signs and laboratory tests were inadequate, and these parameters could not be analyzed.

Additional information was provided from Protocol PVP-2013002 and from postmarketing reports in Europe. Protocol PVP-2013002 was a compassionate use protocol in France that accrued 27 patients (16 adults and 11 children) treated with (b) (4) from November, 2010 to October, 2011 for hereditary methemoglobinemia (n=1) or ifosfamide-induced encephalopathy (n=26). There were no adverse events reported for patients treated on Protocol PVP-2013002. The postmarketing review also indicated that no adverse event have been reported with commercial use of (b) (4).

The applicant also submitted the results for Protocol 1MBL12002, a single-center, open-label, single-dose study of Methylene Blue Injection, USP 1% manufactured by American Regent, Inc. The primary objective was to assess pharmacokinetics, safety and tolerability. Twelve subjects were accrued and followed for at least 4 days after treatment. All subjects completed the study. There were no deaths or serious adverse events. The most common adverse events were infusion site pain (42%) and nausea (17%). There was a slight and transient fall in diastolic blood pressure and rise in pulse at 2.83 hours from start of infusion for the group as a whole and one subject had an episode of hypotension. There were no grade 3-4 laboratory abnormalities reported. One subject had an ALT 1.7x ULN and AST 1.1x ULN at the end of study. Four subjects had an abnormal urine leukocyte esterase which the applicant attributed to test interference by methylene blue.

Overall Assessment: The data on use of (b) (4) are not sufficient to support a finding of safety and efficacy. Although there are some cases in the literature that might be useful, applicability to is limited by the lack of bridging information. A demonstration of bioequivalence of (b) (4)

Clinical Review

NDA 204630

(b) (4) (Methylene Blue Injection 0.5%)

and Methylene Blue USP 1% might be sufficient to allow use of the literature to support a claim of activity of (b) (4) in the treatment of methemoglobinemia and would supply the data needed to assess safety.

2 Introduction and Regulatory Background

2.1 Product Information

Drug Established Name: Methylene Blue Injection, 0.5%

Proposed Trade Name: (b) (4) njection 0.5%

Dosage Forms: Injection, solution (50 mg)

Therapeutic Class: Antidote

Chemical Class: (b) (4)

Mechanism of Action: Methylene blue is a prodrug. NADPH methemoglobin reductase reduces methylene blue to leukomethylene blue which then reduces methemoglobin to hemoglobin nonenzymatically. It is also a reversible inhibitor of monoamine oxidase (MAO)

Proposed Indication: Treatment of acquired methemoglobinemia

Proposed Dose-Schedule: 1 mg/kg 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 may be given one hour after the first dose (b) (4)

2.2 Currently Available Treatments for Proposed Indication

There are no therapies approved for treatment of acquired methemoglobinemia in the US.

Numerous oxidizing drugs, chemicals and toxins are known to cause methemoglobinemia. Cyanosis is apparent when the methemoglobin concentration exceeds 1.5 gm/dL (about 10%). Additional signs and symptoms of reduced oxygenation and organ damage occur as the level of methemoglobin increases (Table 1) (Wright, 1999). The absolute level of methemoglobin that causes clinical signs and symptoms other than cyanosis varies by individual, being as low as 10% in some cases (Guay, 2009). Methemoglobinemia can be fatal if very high levels persist.

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Adapted from Wright, 1999.

The effect of the offending agent on methemoglobin induction is generally reversible once the offending agent is eliminated. The rate of conversion of methemoglobin to hemoglobin by homeostatic processes was estimated as 15% per hour (Finch, 1947). The course of reversion can be protracted, however, if methemoglobinemia was induced by drugs such as dapsone which have a prolonged enterohepatic circulation that extends exposure. In such cases, exchange transfusions can reduce the methemoglobin level quickly, but ancillary means, such as gastric lavage, activated charcoal or dialysis, may be needed to remove the toxic agent.

The current standard of care for treatment of methemoglobinemia is to administer methylene blue at 1-2 mg/kg over 5 minutes to patients with symptomatic methemoglobinemia and/or those with a methemoglobin level acutely elevated to more than 25% (Price, 2011; Howland, 2011). However, there are no published reports of adequate and well-controlled studies of any methylene blue preparation that showed a clinical benefit for subjects with any prespecified risk. The choice of clinical benefit endpoint and intended population suitable for assessment in a marketing application are discussed further in Section 6.1.5.

2.3 Availability of Proposed Active Ingredient in the United States

Methylene blue injection 1% is currently marketed as an unapproved drug for treatment of methemoglobinemia in the US by Akorn, Inc and General Injectables & Vaccines, Inc., in 1 mL and 10 mL single-dose vials under NDC codes 17478-504-10 and 17478-504-01, and by American Reagent, Inc. and General Injectables & Vaccines, Inc., in 1 mL and 10 mL single-dose vials and ampules under NDC codes 0517-0301-10, 0517-0310-10, 0517-0372-71 and 0517-0373-70. In addition, the Ceretec (exametazime) kit, marketed by Medi-Physics Inc., as a diagnostic radiopharmaceutical, contains 1 mL vials of Methylene Blue Injection 1%.

Oral medications that include methylene blue are the over-the-counter drugs Guna-Kidney and Diurex Water Pills. Marketed but unapproved drugs for oral use that include methylene blue are

Clinical Review

NDA 204630

(b) (4)

(Methylene Blue Injection 0.5%)

Phosphasal, Hyphen, UR N-C, Urelle, Uribel, Urimar-T, URIN D/S, Urogesic Blue, Ustell, Uta and Utira-C.

2.4 Important Issues with Consideration to Related Drugs

Methylene blue in various formulations has been in clinical use for over 100 years, but in the absence of a controlled clinical trial, there is no comprehensive assessment of its safety when used for treatment of methemoglobinemia.

Methylene blue is a potent monoamine oxidase inhibitor (MAOI) inhibitor with substantial potential for adverse drug interactions. Numerous cases of serotonin syndrome in patients who received methylene blue while on serotonergic medications have been reported to the FDA Adverse Event Reporting System (AERS) database, and in 2011 FDA issued a safety communication warning that serious CNS reactions may occur when methylene blue in any formulation is administered to patients taking serotonergic drugs (FDA Drug Safety Communication, 2011a, 2011b).

Labels of current marketed but unapproved methylene blue injection formulations include contraindications for use during pregnancy due to potential teratogenicity based on publications of adverse effects in neonates after use during pregnancy. Other warnings and precautions in such labeling include the risk of paradoxical methemoglobin formation with rapid infusion of high doses of methylene blue, and the risk of hemolysis induced by methylene blue in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The key events in the US presubmission regulatory activities for this submission include:

01/30/2012	Type B Pre-NDA meeting held under IND 113942
08/13/2012	Original submission of NDA 204630
10/11/2012	Issuance of Refuse-To-File (RTF) Letter
12/18/2012	Type A Refuse-To-File meeting
05/24/2013	Type B Pre-IND meeting held under IND 118156
06/28/2013	Orphan designation for treatment of acquired methemoglobinemia.

FDA provided the following key advice and comments to the sponsor regarding the clinical aspects for the preparation of this submission:

- The publications cited are not adequate and well-controlled trials of methylene blue [*Pre-NDA, RTF Letter, Type A*]
- The analysis of reports to the American Association of Poison Control Centers does not comply with the requirements of an adequate and controlled trial [*Type A*]
- If published data are used as the primary support of the NDA, establish that use of the data is scientifically appropriate [*Pre-NDA, RTF Letter, Type A, Pre-IND*]
- A single-arm clinical trial (b) (4), or a prospectively-defined retrospective study may be acceptable to support submission of an NDA if the study is designed adequately [*Type A*]
- Identify quantifiable primary and secondary endpoints that denote clinical benefit. FDA recommended a 50% reduction in methemoglobin in 1 hour as the primary endpoint and

Clinical Review

NDA 204630

(b) (4)

(Methylene Blue Injection 0.5%)

clinical signs of distress such as tachycardia, tachypnea or altered mental status as secondary endpoints [RTF Letter, Type A, Pre-IND]

- Categorize and quantify adverse events [RTF Letter, Type A, Pre-IND]
- Address QT/QTc prolongation risks of (b) (4) [Pre-NDA, RTF Letter, Type A, Pre-IND]
- The draft case report forms are not sufficiently detailed to allow for collection of all information required to support the assessment of safety and efficacy [Pre-IND]
- The datasets submitted should comply with study data standards [Pre-NDA, Pre-IND]

2.6 Other Relevant Background Information

Methylthioninium chloride (Proveblue) 5 mg/ml solution for injection was approved by EMA 6/5/2011 for acute symptomatic treatment of medicinal and chemical products-induced methemoglobinemia. The approval was based solely on published case reports and case series of use of methylene blue.

2.7 Compliance with the Pediatric Research Equity Act

Since methylene blue injection 0.5% has orphan designation for treatment of acquired methemoglobinemia, this submission is exempt from the requirements of the Pediatric Research Equity Act.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This application was submitted under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. It was a resubmission of NDA 204630 and included a response to the issues identified in the previous Refuse-To-File Letter. The application was received 9/13/2013 as an electronic submission in eCTD format. The submission had several documents missing, and there were no datasets for the pivotal study. Following receipt of a response to an information request, the application was found to technically include all required elements for review, and it was filed on 11/13/2013. Additional amendments used for this review are listed in Table 2.

Table 2: NDA Submission and Amendments

SDN	Received	Category	Subcategory
9	09/13/2013	Resubmission	After Refusal to File
10	10/28/2013	Labeling	SPL Draft
11	10/31/2013	PNR	Request for Review
12	11/05/2013	Clinical	Clinical Information
14	11/12/2013	Clinical	Clinical Information
15	11/13/2013	Clinical	Clinical Information
17	11/25/2013	Clinical	Clinical Information
18	12/11/2013	Labeling	Revised Label
21	2/18/2014	Clinical	Clinical Information
27	4/30/2014	Clinical	Clinical Information

Clinical Review

30
(b) (4) (Methylene Blue Injection 0.5%)

ial review, it was noted that there was extensive missing data, and the case report forms were not legible due to a heavy watermark. Additional information requests were made, and a telecon was held with the applicant to explain the seriousness of the missing data as well as the need for proper tabulation of data to allow for review. The applicant submitted a revised clinical study report, revised case report forms and a revised data set on 4/30/2014, and this submission was considered a major amendment. The revised case report forms had the same heavy watermark. Issues identified for the data set included the following:

- The units of measurement were not standardized.
- The table of laboratory tests had multiple results in a single row.
- The table of vital signs had no dates or times.
- The table of vital signs include some imaging results and some laboratory tests.
- There were missing dates and times in the tables of laboratory tests and adverse events.
- The table of adverse events did not match the data in the case report forms.
- The define file was not revised to match the new data set.

In view of the public health need, this reviewer chose to forego any further attempts to obtain corrected data sets from the applicant and proceeded with a detailed audit of the data tables against what was legible in the case report forms, and with correction and reformatting of the data set based on the material submitted.

3.2 Compliance with Good Clinical Practices

Compliance was assessed for one prospective study in healthy volunteers (1MBL120020) and one prospectively-defined retrospective chart review (PVP-2013001). The Clinical Study Report for 1MBL120020 indicated that the protocol was conducted according to Good Clinical Practice (Protocol 1MBL120020 Clinical Study Report Section 5.2). The clinical site was audited by the applicant only for compliance with regulations and standard operating procedures. Nine protocol deviations were reported. All were administrative or minor deviations in timing of events and did not affect the assessment of safety of the investigational agent. IRB oversight was provided by (b) (4). (Protocol 1MBL120020 Clinical Study Report Section 5.1), and informed consent was obtained from each study participant (Protocol 1MBL120020 Clinical Study Report Section 5.3).

The original clinical study report for PVP-2013001 indicated the study was conducted in accordance with the Declaration of Helsinki (Protocol PVP-2013001 Clinical Study Report 7/31/2013 Section 5.2), but this statement was later withdrawn (Response to Information Request in SDN 12). Additional standard operating procedures describing audits of the study centers were submitted to demonstrate that adequate controls were in place. Audit reports indicated that data for the clinical sites in France were 100% accurate, but there was missing data for the patients treated in Taiwan, and this could not be corrected within the requested timeframe due to lack of IRB approval. The applicant subsequently provided documentation of exemption for the sites in France from the Committee For The Protection Of Persons Of The Southern Mediterranean I in Marseilles, France, and documentation of approval from Institutional Review Board of Taipei

Clinical Review

(b) (4)
(Methylene Blue Injection 0.5%)

Veterans General Hospital for the sites in Taiwan (Protocol PVP-2013001 Clinical Study Report Revision dated 4/30/2014 Appendix 16.1.3). Informed consent was not obtained from subjects in this retrospective chart review (Protocol PVP-2013001 Clinical Study Report Section 5.3).

The Office of Scientific Investigations conducted inspections at three clinical sites for Protocol PVP-2013001 in France and the applicant's study records. The three clinical sites were among those with the highest accrual. No significant issues regarding data integrity were identified, although it is noted that the inspection occurred prior to the applicant's submission of the revised clinical study report and updated data set that contained new information.

3.3 Financial Disclosures

The applicant indicated that none of the clinical investigators was a full-time or part-time employee of Provepharm. (b) (6) were paid €300 each (b) (6). The applicant provided certification on FDA Form 3454 that there were no other financial arrangements that met the requirements for disclosure.

4 Significant Issues Related to Other Review Disciplines

4.1 Product

At the time of completion of this review, the Chemistry Manufacturing and Controls reviewer indicated that there was an outstanding deficiency with regard to (b) (4). The Clinical Microbiology reviewer found no deficiencies and recommended approval.

4.2 Preclinical Pharmacology/Toxicology

4.2.1 General Toxicology

The Preclinical Pharmacology/Toxicology reviewer evaluated one in vivo study of (b) (4) conducted by the applicant and one in vivo study of methylene blue trihydrate conducted by the National Toxicology Program. These were a 1-month repeat-dose study of (b) (4) 0.25 – 2 mg/kg/day intravenously in dogs and a 3-month repeat-dose study of methylene blue trihydrate 25-200 mg/kg orally in rats. The preclinical reviewers noted toxicities in the following organ systems:

- Hematopoietic (anemia, reticulocytosis, methemoglobinemia, Heinz body formation and marrow hyperplasia)
- Spleen (increased weight of spleen, congestion, lymphoid depletion, capsular fibrosis)
- Liver (increased liver weight, increased bilirubin, inflammatory cell foci, brown pigment in the Kupffer cells)
- Kidney (brown pigment in proximal tubular cells)
- Skin (injection site hemorrhage, edema, inflammatory cell infiltrates, fibrosis)

Clinical Review

NDA 204630

(b) (4) Methylene Blue Injection 0.5%)

4.3.2 Genotoxicity and Carcinogenicity

(b) (4) and methylene blue trihydrate were mutagenic in the Ames test. The latter was also genotoxic in chromatid exchange and chromosomal aberration tests, and caused a dose-related increase in pancreatic islet cell hyperplasia and an increase in the incidence of islet cells adenomas or carcinomas in a 2-year carcinogenicity test. (b) (4) itself was not tested for genotoxicity or carcinogenicity.

4.3.2 Reproductive and Developmental Toxicology

Only methylene blue trihydrate given orally was evaluated in embryo-fetal studies. These studies showed post-implantation loss (primarily resorptions), spontaneous abortions, and decreased fetal body weight. Teratogenic effects included enlarged ventricles and umbilical herniae. The embryo-fetal toxicities were observed at doses that were maternally toxic. There were no fertility studies conducted.

The Preclinical Pharmacology/Toxicology reviewer recommended approval with Pregnancy Category C for labeling.

4.3 Clinical Pharmacology

4.3.1 Mechanism of Action

Methylene blue is a prodrug for an oxidation reduction agent. NADPH methemoglobin reductase reduces methylene blue to leucomethylene blue which then reduces methemoglobin to hemoglobin nonenzymatically.

4.3.2 Pharmacokinetics

The applicant did not submit a study of the pharmacokinetics of (b) (4). The submission did include a study report of pharmacokinetics of methylene blue USP 1% as well as published literature, but there was no bioequivalence study to link those data to (b) (4). A request from the applicant for a biowaiver was denied in the course of this review. The lack of information about the pharmacokinetics of (b) (4) was considered a deficiency.

4.4 Interdisciplinary Review Team (IRT)

The IRT review included a substudy of the ECG data from Protocol 1MBL12002, a single-dose pharmacokinetics study of 1 mg/kg methylene blue USP 1% in twelve healthy volunteers. The upper bound of the 2-sided 90% confidence interval (CI) for the mean change in QTc from baseline was 22.6 ms observed at 7 minutes postdose. The IRT reviewer was unable to conclude that methylene blue at relevant clinical doses would not cause a significant prolongation of QTc and recommended that a thorough QT study be performed.

Clinical Review

(b) (4)
(Methylene Blue Injection 0.5%)

4.5 Pharmacovigilance

The applicant's Risk Management Plan was reviewed. The DRISK reviewer indicated that no REMS is needed.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3 describes the clinical studies as listed by the applicant in Module 5.2.

Table 3. Clinical Trials

Trials / Status	Design	Population	Primary Endpoint
PVP-2013001	Retrospective chart review (b) (4) (dose unspecified)	Patients who had been treated with (b) (4) or methemoglobinemia ·12 subjects identified	At least 50% reduction of methemoglobin at one hour after infusion
PVP-2013002	Compassionate use program (b) (4) 1-2 mg/kg hourly up to 7 mg/kg	Adults and children >3 mos old with methemoglobinemia or other diagnosis ·27 subjects enrolled	Safety
1MBL12002	Single-dose PK and safety ·Methylene blue injection, 1% USP 1 mg/kg IV	Healthy volunteers ·12 subjects enrolled	Safety, tolerability and PK
PVP-2013003	Survey of EU poison centers for database elements	EU poison centers	Not applicable
AAPCC	Statistical analysis of the National Poison Data System ·Methylene blue (agent and dose unspecified)	Poisoning reports collected by the AAPCC ·1628 records identified	Not applicable

5.2 Review Strategy

The key materials used for the review of efficacy and safety include:

- NDA 204630
- Relevant published literature
- Relevant information in the public domain

For the primary analysis of efficacy, only Protocol PVP-2013001 was used, since this was the only study with data that could be verified by inspection. The published literature provided by

Clinical Review

NDA 204630

(b) (4)

(Methylene Blue Injection 0.5%)

nt was also reviewed for efficacy, but contributory information was limited, since the subject agent was not identified in the reports. Issues regarding the efficacy endpoints are discussed in Section 6.1.1.

Protocols 1MBL12002, PVP-2013001, and PVP-2013002 were used for the analysis of safety. Since the study populations, treatment plans and methods of monitoring differed between studies, the data were not pooled.

Study PVP-2013003 contained no clinical outcomes data, and the AAPCC Study Report included no prespecified protocol. As such, these studies were considered unreviewable and were not included in the analyses of efficacy or safety.

Statistical analyses by the clinical reviewer were performed using JMP 10.0 (SAS Institute, Inc., Cary, NC). Unless stated otherwise, all p-values are unadjusted and should be interpreted with caution.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol PVP-2013001

Protocol PVP-2013001 was a retrospective chart review. To ascertain cases, “Provepharm is to contact as many hospitals as possible in an effort to identify patients who have been treated with (b) (4) Injection, 0.5% for acquired methemoglobinemia” (Protocol PVP-2013001 Section 1). Selected subjects were those who presented with acquired methemoglobinemia precipitated by any etiology and requiring (b) (4) Injection, 0.5% under an emergency setting in Europe, during the period 2010 - 2012. Cases were identified from a) a compassionate use protocol in France, b) direct inquiry to hospitals in France and the United Kingdom, and c) direct inquiry to Poison Prevention Center in Taiwan.

The primary efficacy endpoint was defined as a methemoglobin decrease of at least 50% at one hour after IV administration of (b) (4) Injection, 0.5%. Other objectives listed included:

- Determine (b) (4) Injection, 0.5% initial dosing range.
- Determine re-dosing decision parameters and values.
- Determine effects of (b) (4) Injection, 0.5% on QT/QTc alteration of the ECG.
- Determine effects of (b) (4) Injection, 0.5% in patients with concomitant kidney disease.
- Determine pediatric dosing

The five categories of data to be collected included Patient Information, Toxic Agent, Clinical Presentation, Treatment and Safety, including all laboratory test results, vital sign changes, ECG changes and incidence of observed and reported signs and symptoms that are available. No statistical analyses were planned. For the assessment of efficacy, the protocol indicated that “all

Clinical Review

NDA 204630

(b) (4) (Methylene Blue Injection 0.5%)

blood levels of MetHb at and post-treatment will be plotted” (Protocol PVP-2013001 Section 6.2) There were no sample size calculations.

5.3.2 Protocol PVP-2013002

Protocol PVP-2013002 was a compassionate use study of (b) (4) conducted in France. The indication was for treatment of medicinal and chemical products- induced methemoglobinemia in adults and children over 3 months of age. The (b) (4) dose described was 1 - 2 mg/kg given intravenously over a period of 5 to 10 minutes with a repeat dose one hour after the first dose, if needed, and a maximum recommended cumulative dose of 7 mg/kg. The protocol required reporting of serious adverse effects, whether expected or unexpected, and unexpected adverse effects of any severity.

5.3.3 Protocol 1MBL12002

Protocol 1MBL12002 was a single-center, open-label, single-dose study of methylene blue in healthy volunteers. The primary objective was to assess pharmacokinetics, safety and tolerability. The test article, Methylene Blue Injection, USP 1% manufactured by American Regent, Inc., was administered as a dose of 1 mg/kg intravenously over 5 minutes. Subjects were assessed pretreatment and at the end of study by physical examination, serum chemistry and hematological tests, and urinalysis. Adverse event monitoring was continuous through the entire planned four days of follow-up. Frequent ECGs were performed on study day 1 and at end of study. Twelve subjects were enrolled.

6 Review of Efficacy

6.1 Treatment of Acquired Methemoglobinemia

The proposed indication is treatment of acquired methemoglobinemia

6.1.1 Methods

The review strategy has been described in Section 5.2. The analysis of efficacy was based on Protocol PVP-2013001. Details of the protocol design were described in Section 5.3.1. The main objective of the studies was to determine the proportion of patients with a methemoglobin decrease of at least 50% at one hour after IV administration of (b) (4). The literature was also searched for cases that included sufficient detail to assess this endpoint. All tables and figures are from FDA analyses unless stated otherwise.

6.1.2 Demographics

The applicant identified 12 patients treated with (b) (4). Demographics of the patients are shown in Table 4. Race and ethnicity were not provided by the applicant.

Clinical Review

(b) (4)
(Methylene Blue Injection 0.5%)

Table 4: Characteristics of Patients in Protocol PVP-2013001

Parameter	All Subjects (n = 12)
Median Age (range)	27 years (6 days – 54 years)
Gender Male	7 (58%) ^a
Female	5 (42%)
Cause of Methemoglobinemia	
Amyl nitrate	5 (42%)
4-Nitroanilin	1 (8%)
Sodium Nitrite	1 (8%)
Dapsone	1 (8%)
Mesalazine	1 (8%)
Metaclopramide	1 (8%)
Green bean powder	1 (8%)
Cactus leaves	1 (8%)
Reason for Treatment	
Tachycardia, tachypnea	5 (42%)
Tachycardia	3 (25%)
Coma, tachycardia, tachypnea	2 (17%)
Renal failure, tachypnea	1 (8%)
Diaphoresis	1 (8%)
Median Methemoglobin (range)	44% (11-75%)

^a Number (percentage of patients with data available)

The study cohort included nine adults and three children, including one neonate. The underlying causes of methemoglobinemia were diverse, but nitrate or nitrite intoxication was the most common etiology.

The baseline methemoglobin for nine patients was at least 30%, a level consistent with signs and symptoms that would warrant intervention. In fact, 83% of the patients were tachycardic, 67% had tachypnea, and 17% were comatose. One patient had no recorded signs of serious methemoglobinemia (baseline methemoglobin level 30%), but he did complain of diaphoresis and fatigue. The applicant reported that four patients had respiratory depression, but this could not be confirmed from the data submitted.

The concomitant treatments recorded included oxygen for 8 (73%), ascorbic acid for 1 (9%), activated charcoal for 1 (9%), and gastric lavage for 1 (9%).

6.1.3 Treatment and Disposition

The patients in Protocol PVP-2013001 were treated between January, 2011 and November, 2012. Seventeen doses of (b) (4) were administered. Patient 010 received two injections starting 5 minutes apart, and these were considered as one dose for the purposes of this analysis. One subject had 4 doses, 1 had 3 doses, and the others received a single dose of (b) (4). It was noted that drug was diluted to 100 mL in 5% dextrose for Patient 009, and it is presumed

Clinical Review

NDA 204630

(b) (4)

(Methylene Blue Injection 0.5%)

mainder of the doses were administered directly without dilution. The recorded duration of administration varied from 5 to 30 minutes.

The applicant reported that the initial dose was 1 mg/kg for 7 patients, 1.5 mg/kg for 1 patient, and 2 mg/kg for 4 patients. One patient had no recorded weight, so a weight-based dose could not be calculated by FDA. The median initial dose calculated by FDA for the other 11 patients was 1.15 mg/kg (range, 1.0 to 2.0 mg/kg).

The applicant reported that the cumulative dose was 1 mg/kg for 7 patients, 1.5 mg/kg for 1 patient, 2 mg/kg for 2 patients, 7 mg/kg for 1 patient and 13 mg/kg for 1 patient. For the 11 evaluable patients, FDA calculated the cumulative dose to be 1-1.2 mg/kg for 6 patients, 1.5 – 2.0 mg/kg for 3 patients, 6.4 mg/kg for 1 patient and 12.8 mg/kg for 1 patient. The highest single dose administered was 9.8 mg/kg (Patient 003) as calculated by FDA.

Follow-up was limited to hospitalization. The median duration of hospitalization was 2.5 days (range 2 hours to 15 days). All patients recovered and were discharged or transferred to an alternative unit for nonmedical care.

6.1.4 Primary Efficacy Endpoint

6.1.4.1 Relevance of the Primary Endpoint

The primary endpoint of the protocol was methemoglobin decrease of at least 50% at one hour after IV administration of (b) (4). It is established that methemoglobin levels >70% have a high mortality, and that there are few serious symptoms when the methemoglobin is <20%. For patients with life-threatening complications from high levels of methemoglobin, a 50% reduction at one hour after a dose would be estimated to reduce the methemoglobin from 70% to 17% after two successive doses, which would be reasonably likely to rapidly reduce the complications of methemoglobinemia. Moreover, a 50% reduction in methemoglobin could not be achieved by normal homeostatic mechanisms, so the result could be attributed to investigational agent even in a study without concurrent controls. Concomitant improvement in established signs of serious methemoglobinemia, such as tachypnea, tachycardia or coma, as a secondary endpoint would provide an objective measure of a clinical benefit.

6.1.4.2 Measurement of the Primary Endpoint

Methemoglobin can be estimated by oximetry of an arterial blood sample, measured directly by co-oximetry, or measured noninvasively by pulse co-oximetry. The applicant did not include the method of measurement in the case report forms, so it will not be possible to estimate the potential error of the measurement of the primary endpoint.

6.1.4.3 Analysis of the Primary Endpoint

The applicant provided no analysis of the primary endpoint. The applicant stated that “all the patients were reported to have had a satisfactory medical outcome so it can be assumed that the

Clinical Review

NDA 204630

(b) (4) (Methylene Blue Injection 0.5%)

metHb level at discharge had decreased to clinically acceptable levels” (Protocol PVP-2013001 Clinical Study Report 4/30/2014 p.23).

Of the 12 patients in the study, 4 had no methemoglobin measured after treatment, 1 had a measurement only after the second dose of (b) (4) and 1 had a result after the first dose, but the time of sampling was not indicated. Results after the first dose of (b) (4) for the other 6 patients as calculated by FDA are shown in Table 5. Only 3 patients had a methemoglobin level within 1 hour of administration of (b) (4) (Patients 11, 06 and 04), and all 3 patients (100%; 95% CI 44-100% by Wilson Score) had >50% reduction in methemoglobin at that time.

Table 5: Methemoglobin Levels After Dose 1 of (b) (4)

Patient	<u>Methemoglobin (%)</u>		% Reduction	Time After Dose (hr)
	Baseline	After Dose 1		
PVP-2013001-10	47.0	0	100.0	8.5
PVP-2013001-11	44.4	2.1	95.3	0.5
PVP-2013001-01	43.7	11.5	73.7	1.5
PVP-2013001-12	43.5	0.7	98.4	2.0
PVP-2013001-06	29.6	2.8	90.5	1.0
PVP-2013001-04	10.7	1.4	86.9	1.0

6.1.5 Subpopulations

The samples size was too small for a meaningful analysis by subpopulation.

6.1.6 Analysis of the Secondary Efficacy Endpoints

The sample size was too small to allow analysis of the secondary efficacy endpoints as outlined in the protocol.

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

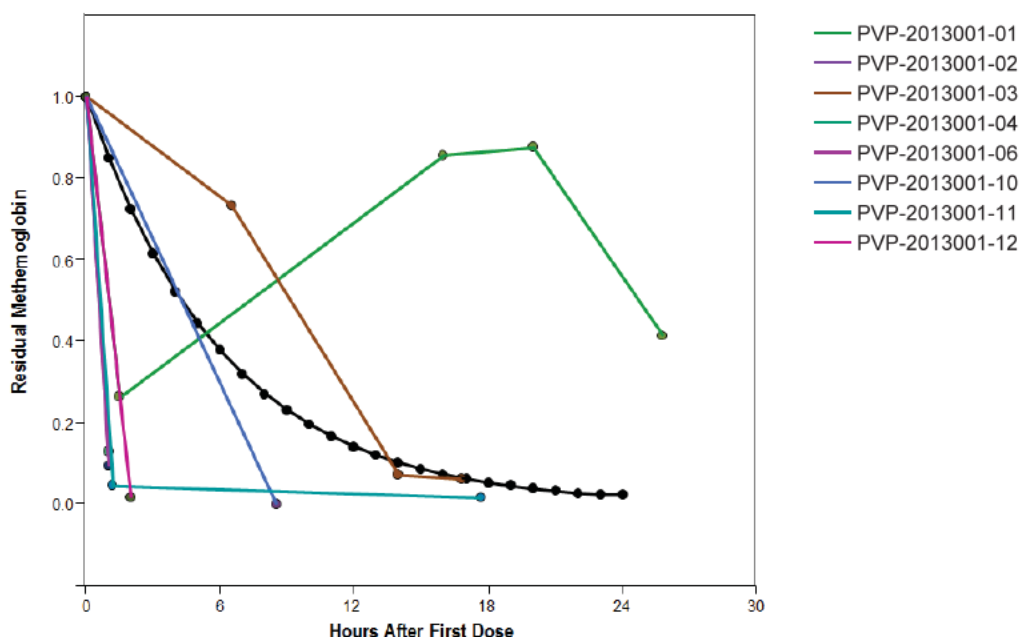
The sample size was too small to assess efficacy by initial dose of (b) (4)

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

FDA used the additional measurements of methemoglobin available to assess the durability of response. Figure 1 shows the residual proportion of methemoglobin by time after first dose of (b) (4). The black line represents the residual expected with homeostatic reduction of methemoglobin (15% per hour). Patients 01 (green line) and 03 (brown line) did not have rapid and durable responses.

Figure 1: Residual Methemoglobin After Treatment with (b) (4)

The black curve represent the expected elimination with homeostatic mechanisms alone.



Patient 01 (green line) had methemoglobinemia due to dapsone with a baseline methemoglobin level of 43.7%. Ninety minutes after the first dose of (b) (4) the methemoglobin was reduced to 11.5%, but it rose again at 16 hours to 37.4%. The patient received 3 additional doses of (b) (4) (total 6.3 mg/kg in 4 doses over 1 day) at which time the methemoglobin fell to 18.1%. No further methylene blue was given, and the methemoglobin finally was below 1% after 3 additional days of observation. Rebound methemoglobinemia is known to occur after treatment of methemoglobinemia due to dapsone intoxication (Berlin, Brodin, et al. 1984).

Patient 03 (brown line) had methemoglobinemia due to 4-nitroaniline toxicity with a baseline methemoglobin level of 75%. One hour after the first dose of (b) (4) the methemoglobin was reduced to only 55%. The patient received 2 additional doses of (b) (4) (total 12.8 mg/kg in 3 doses over 6 hours), and the methemoglobin fell to 5.5%. No further methylene blue was given, and the methemoglobin finally was below 1% after 2 additional days of observation.

6.1.9 Additional Efficacy Issues/Analyses

In presubmission meetings, FDA had encouraged the applicant to assess changes in respiratory rate, heart rate and neurological status at one hour after dosing as key secondary measures of efficacy (see Section 2.5 above). The applicant provided no formal assessment of vital signs. Although not a stated efficacy endpoint in the protocol, FDA attempted a post hoc analysis of these measures, but since there were no dates or times in the vital sign data file, the analysis could not be performed.

Clinical Review

NDA 204630

(b) (4) (Methylene Blue Injection 0.5%)

6.1.10 Literature Review

On review of the literature, 42 cases of treatment of methemoglobin included a follow-up measurement within 1 (+/- 0.25) hours (see Appendix 9.2). Of these cases, 38 (90%; 95% CI 77-97%) had a methemoglobin decrease of at least 50% by one hour after IV administration of methylene blue. The four nonresponders had a baseline methemoglobin >60%. The response rate was 86% (95% CI, 60-96%) for the 14 patients treated with 1 mg/kg methylene blue and 91% (95% CI, 62-98%) for the 11 patients treated with 2 mg/kg methylene blue. Neither the actual brand of methylene blue used nor the clinical signs at one hour after treatment were provided in the case reports. There were no cases that reported use of (b) (4) specifically.

The reported response rates should be interpreted with caution, since there may have been bias against reporting failures or in obtaining measurements of methemoglobin at one hour when the clinical results were obvious.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Protocols PVP-2013001, PVP-2013002 and 1MBL12002 were used for the analysis of safety. Details of the protocol design were described in Section 5.3.1.

7.1.2 Categorization of Adverse Events

Protocols PVP-2013001 indicated that adverse events would be coded according to MedDRA (Protocol PVP-2013001 Section 6.2), but neither the protocol nor the Clinical Study Report identified the MedDRA version. There was no stated plan for adverse event coding for Protocol PVP-2013002. Adverse events for Protocol 1MBL12002 were reported down to the verbatim term. The adverse events for this protocol were coded using MedDRA version 15.1

7.1.3 Pooling of Data

Since the study populations, treatment plans and methods of monitoring differed between studies, the safety data were not pooled.

Note: Due to the limited amount of safety information in this application, subheadings for Sections 7.2 – 7.5 will not be used.

7.2 Adequacy of Safety Assessments

The study population was small but encompassed the usual etiologies of methemoglobinemia and the ranges of ages of patients who would be treated with (b) (4). The demographics of the patients in Protocol PVP-2013001 were described in Section 6.1.2.

Clinical Review

30
(b) (4)

(Methylene Blue Injection 0.5%)

Five patients received the recommended initial (b) (4) dose of 1 mg/kg, six received higher doses, and the dose could not be calculated for one subject. A full description of the treatment by dose and duration was provided in Section 6.1.3.

There was no new nonclinical information about (b) (4) in this application that warranted special clinical testing. There was no routine testing planned in Protocols PVP-2013001 and PVP-2013002. The routine testing and four days of follow-up in Protocol 1MBL12002 was considered adequate. There were no specific studies of metabolism, drug-drug interactions or adverse events of special interest.

7.3 Major Safety Results in Protocol PVP-2013001

There were no deaths reported. Serious adverse events included one case each of hemolytic anemia, methemoglobinemia, Klebsiella pneumoniae urinary infection, gastric lesions, suicidal thoughts, suicidal attempts, bilirubinemia and polycythemia. The applicant considered none of the serious adverse events to be related to (b) (4).

7.4 Supportive Safety Results in Protocol PVP-2013001

The applicant reported 15 adverse events in five patients treated with (b) (4) (Table 6). There were no events considered by the applicant to be related to (b) (4).

Table 6: Adverse Events in Protocol PVP-2013001

System Organ Class	Adverse event	Related	Unlikely	Not related	Not assessable
Blood and Lymphatic system disorders	Methemoglobinemia		N1		
	Hemolytic anemia				N1
	Polycythemia				N4
Skin and subcutaneous tissue disorder	Skin blisters		N1		
Psychiatric disorders	Sleep disorders		N1		
	Suicidal thoughts		N3		
	Suicidal attempts		N3		
Metabolism and nutrition disorders	Hypokalaemia				N1
Infections and infestations	Urinary infection			N2	
Gastrointestinal disorders	Gastric lesions		N3		
Investigations	Increased CPK		N3		
Investigations	Increased LDH		N3		
Investigations	Increased total bilirubin		N3		
Hepatobiliary disorders	Bilirubinemia		N4		
Hypersensitivity	Stuffy nose			N10	

From Protocol PVP-2013001 Clinical Study Report 4/30/2014 Table 17. N = Case number

FDA was not able to confirm the safety profile, since the tabulated summary did not match the case report forms, and there were no dates in the adverse event data file.

Clinical Review

(b) (4)
Methylene Blue Injection 0.5%)

There were also no dates or times in the data files for vital signs or laboratory tests, so no analysis of these parameters could be performed.

7.5 Other Safety Explorations

There was insufficient information to allow an assessment of dose-dependency of adverse events, time dependency of adverse events, drug-demographic interactions or drug-disease interactions. There were no drug-drug interaction studies conducted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There were no cases of cancer reported in the (b) (4) study cohort.

7.6.2 Human Reproduction and Pregnancy Data

There were no pregnancies reported in patients treated with (b) (4).

7.6.3 Pediatrics and Assessment of Effects on Growth

There were no assessments of the effects of (b) (4) in the pediatric population specifically.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The highest single dose of (b) (4) administered in Protocol PVP-2013001 was 9.8 mg/kg. Patient 03 was a 37 year old woman with a methemoglobin level of 75% due to 4-nitroaniline intoxication. Vital signs at baseline included a respiratory rate of 25, heart rate 106 and blood pressure 87/51. On physical examination the patient was cyanotic, and her mental status was depressed (Glasgow 7). The patient was intubated. Treatment consisted of hydroxycobalamin and gastric lavage. (b) (4) was given (b) (6) 00:00 at 2 mg/kg, 1 mg/kg at 04:00, and 9.8 mg/kg at 12:30 (total reported dose 12.8 mg/kg). Laboratory tests on (b) (6) (time unknown) included CK 319 U/L (normal 30-190) and total bilirubin 31 µmol/L (normal 0-17). The total bilirubin was 51 µmol/L the following day, and the LDH had risen to 509 U/L (normal 240-480). Hemoglobin was not reported. The patient recovered and was discharged. The elevated bilirubin resolved on (b) (6), but CK and LDH elevations were on-going at last follow-up.

7.7 Additional Submissions / Safety Issues

7.7.1 Safety in Protocol PVP-2013002

There were 16 adults and 11 children (total 27 patients) treated on Protocol PVP-2013002 from November, 2010 to October, 2011. One patient was treated for hereditary methemoglobinemia, and the remainder were presumed to have ifosfamide-induced encephalopathy. Nineteen patients received one dose of (b) (4), and eight received 2-5 doses. The maximum known dose of

Clinical Review

NDA 204630

(b) (4) (Methylene Blue Injection 0.5%)

(b) (4) administered was 2 mg/kg, but no information on dose was available for 23 of the patients. No adverse events were reported by the applicant. There were no case report forms submitted to verify the lack of adverse events.

7.7.2 Safety in the Healthy Volunteer Study

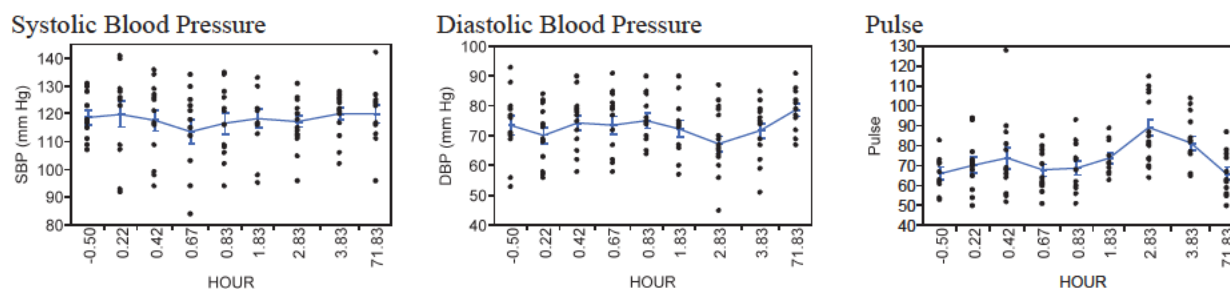
There were 12 subjects enrolled in Protocol 1MBL12002. The median age was 34 years (range, 25-60 years). There were 7 (58%) males and 5 (42%) females. In the group, 5 subjects (42%) were white, 5 (42%) black, and 2 (17%) Hispanic. All received a single dose of methylene blue USP, 1%. All subjects completed the study. There were no deaths or serious adverse events. Adverse events reported are listed in Table 7. The most common adverse events were infusion site pain (42%) and nausea (17%). Infusion site pain lasted 0.25, 0.5, 1.2, 3.4 and 13.5 hrs.

Table 7: Adverse Events in Single-Dose Healthy Volunteer Study

Preferred Term	Healthy Volunteers (n = 12)	
	N	%
Infusion site pain	5	42
Nausea	2	17
Alanine aminotransferase increased	1	8
Diarrhea	1	8
Dizziness	1	8
Dyspepsia	1	8
Feeling hot	1	8
Infusion site extravasation	1	8
Infusion site pruritus	1	8
Muscle spasms	1	8
Pain in extremity	1	8
Tachycardia	1	8
Vessel puncture site hematoma	1	8
Vomiting	1	8

Vital signs over time are shown in Figure 2. There was a slight and transient fall in diastolic blood pressure and rise in pulse at 2.83 hours from start of infusion. In the outlier analysis, one subject had systolic blood pressure of 115 mm Hg at baseline which fell to 84 mm Hg at hour 0.67 and returned to baseline at hour 1.83. This subject also had a rise in pulse from 61 at baseline to 128 at hour 0.42 with return to baseline minutes thereafter.

Figure 2: Vital Signs in Healthy Volunteer Study



Clinical Review

NDA 204630

(b) (4)
(Methylene Blue Injection 0.5%)

There were no grade 3-4 laboratory abnormalities reported. One subject had an ALT 1.7x ULN and AST 1.1x ULN at the end of study, and the elevations were still present on retest two weeks later. The bilirubin was normal at both time points. There was no cause for the elevated transaminases other than the test article. No further follow-up was provided. Four (33%) of the study subjects had an abnormal urine leukocyte esterase at end of study, and no follow-up information was provided for these cases.

8 Postmarket Experience

Provepharm has marketing authorization for Proveblue 0.5% solution in the EMA as of 5/6/2011. In the Summary of Clinical Safety, the applicant estimated that approximately (b) (4) ampoules of Proveblue have been used, and no adverse events were reported (Module 2.7.4 Summary of Clinical Safety Section 6.1).

The Periodic Safety Update Report (PSUR) for the period 11/7/2012 to 5/5/2013 was reviewed. The following (b) (4) information was provided in this PSUR:

- (b) (4) is approved in 30 countries.
- It has been marketed in Denmark, Finland, Sweden, France, Ireland, Norway, Portugal, Austria and Great Britain.
- Cumulatively, (b) (4) ampoules of Proveblue have been sold. (b) (4) the worldwide exposure cannot be determined.
- There are no completed or on-going studies of (b) (4)
- There was one report of accidental exposure to Proveblue, but no clinical effects were provided.
- There have been no serious adverse events reported with use of Proveblue.

9 Appendices

9.1 Advisory Committee Meeting

There was no advisory committee consulted for this application.

9.2 Case Reports of Treatment with Methylene Blue

PubMed was searched using the following criteria: "methylene blue"[MeSH Terms] OR ("methylene"[All Fields] AND "blue"[All Fields]) OR "methylene blue"[All Fields]) AND ("methaemoglobinaemia"[All Fields] OR "methemoglobinemia"[MeSH Terms] OR "methemoglobinemia"[All Fields]) AND "humans"[MeSH Terms]. A total of 461 references were retrieved. Of these, there were 42 reports that could be accessed describing treatment of methemoglobinemia with methylene blue with methemoglobin measurements at baseline and within 1 hour (+/- 15 minutes). Table 8 lists the results for these cases in descending order of baseline methemoglobin. None of the cases identified the brand of methylene blue that was administered.

Clinical Review

NDA 204630

(b) (4)
(Methylene Blue Injection 0.5%)

Table 8: Reduction in Methemoglobin Within One Hour After Treatment with Methylene Blue

Reference	Age (yrs)	Gender	Cause	MB Dose (mg/kg)	Baseline MetHgb (%)	Post MetHgb (%)	% Reduction	Time Point (hr)
Sankar 2013	4	Male	Aniline	2.0	98.0	73.0	25.5	1.0
Stambach 1997	-	Female	Nitrite	2.0	83.0	26.0	68.7	1.0
Schimelman 1978	48	Male	Nitrobenzene	-	75.0	75.0	0.0	0.4
Katz 2004	39	Female	Aniline	2.0	72.4	25.9	64.2	1.0
Wilkerson 2010	19	Female	Nitrite	1.5	72.0	4.9	93.2	1.0
Kearney 1984	32	Male	Aniline	-	70.0	34.0	51.4	1.0
Jaffery 2008	46	Female	Benzocaine	2.0	68.8	33.7	51.0	0.5
Wurdeman 2000	69	Male	Benzocaine	1.0	67.8	50.2	26.0	0.7
Brunato 2003	23	Female	Ammonium nitrate	2.0	66.3	9.0	86.4	1.0
Ferrer Gomez 2008	19	Male	Aniline	1.0	63.0	47.6	24.4	1.0
Freeman 1996	1	Male	Sodium nitrite	2.0	63.0	2.0	96.8	1.0
Modarai 2002	32	Female	Nitrite	-	59.9	4.8	92.0	0.7
Zimmerman 1980	16	Female	Phenazopyridine	2.0	56.9	12.8	77.5	0.5
LeClaire 2005	40	Male	Benzocaine	2.0	51.2	13.9	72.9	1.0
Demirel 1999	54	Male	Aniline	-	50.0	4.9	90.2	1.0
Boylston 2002	73	Female	Benzocaine	-	49.0	9.0	81.6	0.5
Grauer 1996	68	Male	Benzocaine	1.0	47.2	12.3	73.9	0.3
Jacka 2006	45	Female	Benzocaine	0.6	45.0	5.0	88.9	0.3
Ozdogan 2010	0	Male	Prilocaine	1.0	44.0	4.0	90.9	1.0
Birchem 2005	69	Female	Benzocaine	2.0	41.1	18.4	55.2	1.0
Hegedus 2005	48	Female	Benzocaine	-	41.0	11.5	72.0	0.3
Hornfeldt 1994	2	Male	Nitroethane	-	40.1	5.7	85.8	1.0
Lin 2007	29	Female	Benzocaine	1.0	39.6	16.8	57.6	1.0
Margulies 2002	16	Male	Benzocaine	2.0	35.0	2.0	94.3	1.0
Tush 1996	0 ^a	Male	Benzocaine	1.0	35.0	2.7	92.3	1.0
Annabi 2009	69	Female	Benzocaine	2.0	33.0	4.0	87.9	1.0
Sin 1996	34	Male	Dapsone	1.0	33.0	9.7	70.6	1.0
Attof 2006	16	Female	Cerium nitrate	1.5	31.8	3.5	89.0	1.0
Gray 2004	63	Male	Benzocaine	1.0	29.1	3.1	89.3	0.8
White 1991	32	Male	Nitrite	-	28.0	8.0	71.4	1.0
Tsai 2005	3	Male	Sulfadiazine	1.0	27.7	1.0	96.4	1.0
Shepherd 1998	2	Male	Nitroethane	1.0	27.0	8.2	69.6	1.0
Anderson 1988	52	Male	Benzocaine	1.5	26.0	3.9	85.0	1.0
Ellis 1995	76	Female	Benzocaine	1.3	24.0	5.8	75.8	0.5
Spielman 1984	24	Male	Benzocaine	-	23.0	3.8	83.5	0.3
Nguyen 2000	71	Female	Benzocaine	1.0	22.5	2.4	89.3	1.0
Chan 2007	0 ^a	Female	Herbal powder	1.0	20.2	0.5	97.5	1.0
Slaughter 1999	71	Male	Benzocaine	-	19.4	1.8	90.7	0.3
Robicsek 1985	60	Male	Nitroglycerin	-	16.5	1.8	89.1	0.5
Oh 2014	57	Male	Metaflumizone	1.0	15.8	6.0	62.0	1.0
Trillo 1992	60	Female	Dapsone	1.0	10.6	4.4	58.5	0.7
Douglas 1977	80	Female	Benzocaine	-	9.8	0.7	92.9	0.7

Abbreviations: MB, methylene blue; MetHgb, methemoglobin; -, data not provided

^a Neonates 6 (Tush 1996) and 9 (Chan 2007) days old.

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Clinical Review

NDA 204630

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(Methylene Blue Injection 0.5%)

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Clinical Review

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Clinical Review

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