CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204630Orig1s000

SUMMARY REVIEW

APPEARS THIS WAY
ON ORIGINAL

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	204630
Applicant	Provepharm SAS
Date of Submission	October 9, 2015
PDUFA Goal Date	April 9, 2016
Proprietary Name / **Non-Proprietary Name**	ProvayBlue/methylene blue
Dosage Form(s) / Strength(s)	Injection: methylene blue (0.5%) as 50 mg/10 mL (5 mg/mL) single-dose ampule
Applicant Proposed Indication(s)/Population(s)	treatment of adults and children with acquired methemoglobinemia (b) (4)
Action/Recommended Action for NME:	Accelerated Approval
Approved/Recommended Indication/Population(s) (if applicable)	Treatment of pediatric and adult patients with acquired methemoglobinemia. This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification of clinical benefit in subsequent trials.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Donna Przepiorka, M.D., Ph.D./Albert Deisseroth, M.D., Ph.D.
Regulatory Health Project Manager	Laura Wall, BSN, MS
Statistical Review	N/A
Pharmacology Toxicology Review	Brenda Gehrke, Ph.D./C.J. Chang, Ph.D./ Christopher Sheth, Ph.D./Haleh Saber, Ph.D./John Leighton, Ph.D.
OPQ Review	Sithamalli Chandramouli/Sung Kim/ Rebecca Dombrowski/Banu Zolnik/Angelica Dorantes/Rabiya Laiq/Anamitro Banerjee, Ph.D.
Microbiology Review	Stephen E. Langille, Ph.D./Bryan S. Riley, Ph.D. Jonathan Swoboda, PhD/Dupeh Palmer, PhD
Clinical Pharmacology Review	Salaheldin S. Hamed, Ph.D./Bahru Habtemariam, Pharm D./Nam Atiqur Rahman, Ph.D.
OPDP	Rachel Conklin/Kathleen Davis
OSI	Anthony Orencia, M.D./Susan D. Thompson, M.D./ Kassa Ayalew, M.D., M.P.H.
CDTL Review	Albert Deisseroth, M.D., Ph.D.
OSE/DEPI	none
OSE/DMEPA	Michele Rutledge, Pharm.D./Nicole Garrison, PharmD, BCPS/Yelena Maslov, Pharm. D.
OSE/DRISK	none
Other	Moh Jee Ng/Jiang Liu/Anshu Marathe/Qianyu Dang/Michael Li/Christine Garnett LaShawn Griffiths, MSHS-PH, BSN, RN/Barbara Fuller, RN, MSN, CWOCN/Morgan Walker, PharmD, MBA

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader

OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

APPEARS THIS WAY ON ORIGINAL

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Acquired methemoglobinemia is a serious and life-threatening condition that occurs in individuals exposed to oxidizing drugs, chemicals and toxins. The condition does not allow 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. There are no therapeutics approved for treatment of acquired methemoglobinemia. However, methylene blue is a marketed unapproved drug that has been used for many decades to treat patients with acquired methemoglobinemia.

This application was based on retrospective case reports and a review of the literature. Efficacy 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. Provayblue was demonstrated to be bioequivalent to Methylene Blue USP 1%. All 6 (100%; 95% CI 61% - 100%) patients had a decrease in methemoglobin by at least 50% within 1 hour after treatment. An additional 41 cases of treatment of methemoglobinemia with a methylene blue class product were identified in the published literature. 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.

Safety information was based on a healthy volunteer trial data and review of the literature. From the trials, the most common (≥ 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 (≥ 5%) TEAE were dysgeusia, dizziness, headache and paresthesia. The most common (≥2%) moderate-to-severe TEAE were pain in extremity, headache, feeling hot, dizziness, syncope, back pain, hyperhidrosis, and nausea.

From the literature 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. Literature reports also included 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. Literature review noted an association between administration of methylene blue class products to pregnant women in the second trimester and neonatal intestinal atresia or death, and when given near term, there was an association with multiple manifestations of

methylene blue toxicity in the newborn. Also false readings were reported for oxygen saturation by pulse oximetry and for the bispectral index shortly after infusion.

In summary, 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acquired methemoglobinemia is a serious and life-threatening condition that 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	• Methemoglobinemia at high levels may cause symptomatic or fatal multiorgan dysfunction.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	fatal.	
Current Treatment Options	• There are no therapeutics approved for treatment of acquired methemoglobinemia.	• Treatment of acquired methemoglobinemia is an unmet need.
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.
Risk	• In healthy volunteers who received a single dose of 2 mg/kg ProvayBlue, the most common (≥ 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	• 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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.	
Risk Management	Labeling – includes a complete description of the safety observed in the healthy volunteer trial with additional safety information coming from the literature.	To minimize risks, labeling should include clear dosing instructions, a boxed warning for serotonin syndrome, and warnings and precautions for other serious risks.

2. Background

This submission is a response to an October 10, 2014 Complete Response letter issued by the Agency. The Complete Response letter outlined Clinical deficiencies, Clinical Pharmacology deficiencies and Product Quality deficiencies.

On October 9, 2015 Provepharm SAS submitted their response to a Complete Response letter from the Agency. The PDUFA goal date is April 9, 2016.

Methylene Blue is a marketed unapproved drug currently used for treatment of acquired methemoglobinemia.

3. Product Quality

No issues were identified that would preclude approval. The product has a strength of: 0.5% and is available in 10 mL ampules. Each ampule contains 50 mg of methylene blue (5mg/mL).

From the summary quality review:

The applicant has provided 18 month stability data under long term storage conditions. The applicant requested (b) (4) *months shelf life. However, 30 month shelf life was found acceptable at the time as per ICH Q1E guidelines. As the applicant did not provide any additional drug product stability data in this resubmission, a shelf life of 30 months may granted at this time.*

The facilities inspection is acceptable.

I concur with the recommendation for approval.

4. Nonclinical Pharmacology/Toxicology

No issues that would preclude approval were identified. From the 2014 primary review:

General toxicology studies of methylene blue include a 3-month repeat-dose toxicology study conducted by NTP with oral administration of methylene blue trihydrate in rats and a 1-month repeat-dose toxicology study with intravenous administration of the Provepharma's methylene blue in dogs. In the 3-month repeat-dose toxicology study in rats, F344/N rats were administered methylene blue trihydrate (0, 25, 50, 100, or 200 mg/kg; 0, 150, 300, 600, and 1200 mg/m2) by oral gavage at a dose volume of 5 mL/kgonce daily 5 days per week for 14 weeks. In the 1-month repeat-dose toxicology studyin dogs, Beagle dogs were administered Provepharma's methylene blue (0, 0.25, 0.50, or 1.0 mg/kg/day; 0, 5, 10, or 20

mg/m2/day; concentration 5 mg/mL) or a comparator drug of methylene blue injection USP 1% w/v from Martindale (1.0 mg/kg/day; 20 mg/m2) by intravenous infusion into the cephalic or saphenous vein at a flow rate of 0.5 mL/minute once daily for 4 weeks. Despite the difference in the routes of administration, similar toxicities were observed in rats and dogs. Hematological responses in both species included anemia as indicated by decreases in erythrocytes, hematocrit, and hemoglobin and increases in reticulocytes and methemoglobinemia as indicated by increases in methemoglobin and/or Heinz bodies (inclusions within red blood cells composed of denatured hemoglobin). Liver and spleen were organs of toxicity in both rats and dogs. Liver findings included increased liver weight, presence of inflammatory cell foci, and increased bilirubin. Increases in bilirubin may be secondary to hemolysis and degradation of hemoglobin. Increases in absolute and relative spleen weights, enlarged spleen, and congestion in the spleen were observed in both species. Additional microscopic findings in the spleen were hematopoietic cell proliferation, lymphoid depletion of lymphoid follicles, and capsular fibrosis. Additional toxicities observed with intravenous administration of methylene blue in dogs were injection site toxicity (e.g. hemorrhage, edema, inflammatory cell infiltrates, fibrosis) and increased brown pigment in the kidney. Provepharma's methylene blue (5 mg/mL) had a similar toxicological and toxicokinetic profile in dogs as the comparator drug Methylene blue injection USP 1% w/v (Martindale) at a dose of 1 mg/kg/day (20 mg/m2/day) when administered intravenously once daily for 4 weeks.

The genotoxicity of methylene blue has been evaluated in both in vitro and in vivo studies conducted by NTP with methylene blue trihydrate and in an in vitro bacterial reverse mutation assay (Ames test) conducted with Provepharma's methylene blue. Methylene blue trihydrate and Provepharma's methylene blue were mutagenic when tested in in vitro bacterial cell assays. Methylene blue trihydrate was also genotoxic in an in vitro sister chromatid exchange test and an in vitro chromosomal aberration test in Chinese hamster ovary (CHO) cells. Methylene blue trihydrate was negative for micronucleus induction in bone marrow or peripheral blood in male mice treated with single doses up to 150 mg/kg (450 mg/m2) and in peripheral blood samples from male and female mice at the end of a 3-month repeat-dose toxicity study of doses up to 200 mg/kg (600 mg/m2).

Two-year carcinogenicity studies in mice and rats were conducted by NTP with methylene blue trihydrate; the studies were done by oral gavage. Based on the FDA criteria for a positive carcinogenicity response, there are no statistically significant neoplastic findings in the 2-year mouse carcinogenicity study. The FDA concluded that methylene blue caused pancreatic islet adenomas or carcinomas (combined) in male rats in the 2-year carcinogenicity study based on the incidences exceeding the historical control incidence. In addition, there was a dose-related increase in pancreatic islet hyperplasia.

Embryo-fetal development studies in rats and rabbits were conducted by NTP; methylene blue trihydrate was administered by oral gavage. Methylene blue produced maternal toxicity as indicated by increases in maternal spleen weight at doses of ≥50 mg/kg/day (≥300 mg/m2/day) in rats and maternal death at 100 mg/kg/day (1200

mg/m2/day) in rabbits. Post-implantation loss, consisting primarily of resorptions, was increased compared to controls at doses of >200 mg/kg/day (≥1200 mg/m2/day) in rats and ≥50 mg/kg/day (≥600 mg/m2/day) in rabbits. Treatment with methylene blue caused spontaneous abortion at all doses (≥50 mg/kg/day; ≥600 mg/m2/day) in rabbits. Fetal body weight was decreased with treatment of methylene blue compared to controls at doses of ≥200 mg/kg/day (≥1200 mg/m2/day) in rats. Methylene blue produced teratogenicity including enlarged ventricles in rats and a malformation of umbilical hernia at doses of ≥100 mg/kg/day (≥1200 mg/m2/day) in rabbits when administered during organogenesis. The embryo-fetal toxicities including teratogenicity were observed at maternally toxic doses. In addition, healthy animals given methylene blue develop drug-induced methemoglobinemia, causing hypoxia. The clinical dose of methylene blue will be titrated to doses that will reduce methemoglobin and hence hypoxia, and only in an overdose situation would adverse embryo-fetal effects be anticipated. Since the above adverse fetal effects are not expected in patients at the therapeutic range of methylene blue, pregnancy category C is recommended.

Fertility studies with methylene blue have not been conducted. According to published literature (Coddington et al., 1989), in vitro, methylene blue reduced motility of human sperm in a concentration-dependent manner.

I concur with the recommendation for approval.

5. Clinical Pharmacology

No issues that would preclude approval were identified. The clinical pharmacology team relied on literature and a submitted BE study. The following text is from the primary review:

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 identified clinical studies under the post-marketing requirements (PMRs)…

I concur with the Clinical Pharmacology review and the request for PMRs.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

From the primary clinical review:

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.

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.

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.

I agree with Dr. Przepiorka's recommendation that the clinical benefits remains to be confirmed; thus the application will be approved under the Subpart H.

8. Safety

The following text is from the primary review:

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 (≥ 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 (≥ 5%) TEAE were dysgeusia, dizziness, headache and paresthesia.*
- *The most common (≥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 Cmax-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 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.

I concur with the review. Additional safety data will be collected via a post-marketing requirement.

Routine Pharmacovigilance should be adequate for post-approval safety monitoring.

9. Advisory Committee Meeting

This application was not referred for an Advisory Committee meeting as no clinical efficacy or safety issues arose that required an Advisory Committee meeting convened to get outside expertise.

10. Pediatrics

This application contained pediatric data.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigation (OSI) did not find the data unreliable in support of the application.

Financial Disclosure information was provided and reviewed. No issues identified.

12. Labeling

All disciplines made recommendations for labeling.

From the primary clinical review:
Methylene blue is a potent monoamine oxidase inhibitor (MAO) 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).

Dr. Przepiorka's recommendations for labeling from her 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.*

All disciplines participated in labeling.

I agree with the proposed labeling and at the current time do not have any additional suggestions.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

None except for the labeling

- Other Postmarketing Requirements and Commitments (Draft provided below)

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.

PMR2 – Drug-Drug Interaction

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 (b) (4) CYP450 enzyme substrates.

PMR3—Hepatic Impairment
Conduct a clinical trial to determine the effect of hepatic impairment on the PK and safety of methylene blue.

PMR4—Renal Impairment

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.

Refer to action letter for final wording and milestones of the post-marketing requirements.

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

/s/

ANN T FARRELL
04/07/2016