February 8, 2019

Re: ProvayBlue® (methylene blue) injection USP 0.5%—Methemoglobinemia: Suggested Minimum Stocking Level

Dear Healthcare Professional,

Methemoglobinemia is a condition characterized by increased quantities of hemoglobin in which the iron of heme is oxidized to the ferric (Fe^{3+}) form. Methemoglobin is useless as an oxygen carrier and thus causes a varying degree of cyanosis.[1]

Most cases of methemoglobinemia are acquired, resulting from increased Methemoglobin formation by various exogenous agents. These may include medication overdoses or poisoning but may also occur with medications given at standard doses, particularly in individuals with partial deficiencies of cytochrome b5 reductase.[2]

In children and adults with acute acquired methemoglobinemia, levels of Methemoglobin > 20 percent are associated with clinical symptoms. Mortality rates are high when Methemoglobin levels exceed 40 percent. Accordingly, acute acquired methemoglobinemia should be considered a **medical emergency**.[2]

PROVAYBLUE® (METHYLENE BLUE) IS AN OXIDATION-REDUCTION AGENT INDICATED FOR THE 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.

SEE IMPORTANT SAFETY INFORMATION BELOW INCLUDING BOXED WARNING.

Toxicity in Acute Acquired Methemoglobinemia[2]	
Methemoglobin Level	**Symptoms***
0 to 3 percent	Normal range for adults (mean: 1 percent)
3 to 12 percent	Minimal level associated with clinically detectable cyanosis or skin discoloration
3 to 20 percent	Usually asymptomatic unless pre-existing condition present
20 to 50 percent	Mild to moderate symptoms of hypoxemia†
50 to 70 percent	Severe, life-threatening symptoms of hypoxemia‡
>70 percent	Usually fatal

* Pre-existing conditions such as anemia, heart disease, and lung disease may exacerbate toxicity.
† Symptoms of mild to moderate toxicity include lightheadedness, fatigue, tachycardia, dyspnea, and lethargy.
‡ Symptoms of severe toxicity include respiratory depression, altered sensorium, coma, shock, and seizures.

2 CARTONS (10 AMPULES) OF PROVAYBLUE® IS THE SUGGESTED MINIMUM AMOUNT THAT SHOULD BE STOCKED IN THE PHARMACY TO TREAT ONE PATIENT§3

§Amount of antidote needed to treat one patient weighing 100 kg for a period of 8 hours

PROVAYBLUE® IS THE **ONLY** FDA APPROVED METHYLENE BLUE INJECTION

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A Daiichi Sankyo Group Company

Please refer to the Full Prescribing Information for complete information about the preparation and storage, as well as dosage and administration of ProvayBlue®.

See below for Important Safety Information including BOXED WARNING.
For full prescribing information, visit www.americanregent.com

You are encouraged to report Adverse Drug Events (ADEs) to American Regent:
Email: pv@americanregent.com; Fax: 1-610-650-0170; Phone: 1-800-734-9236

ADEs may also be reported to the FDA at 1-800-FDA-1088 or to www.fda.gov/Medwatch

Drug Information:
1-888-354-4855 (9:00 am - 5:00 pm Eastern Time, Monday - Friday)

For urgent drug information outside of normal business hours, assistance is available at 1-877-845-6371

Please contact American Regent at 1-800-645-1706, if you have any questions about ProvayBlue® (methylene blue) injection USP, 0.5% or the information above.

Sincerely,

Arun Mathew, PharmD, MBA
Post-Doctoral Fellow, Medical Affairs & Pharmaceutical Marketing
American Regent, Inc.

For Intravenous Use. Ensure patent venous access prior to administration of ProvayBlue®.

INDICATIONS AND USAGE

ProvayBlue® (methylene blue) injection USP, 0.5% is indicated for the 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.

IMPORTANT SAFETY INFORMATION

WARNING: SEROTONIN SYNDROME WITH CONCOMITANT USE OF SEROTONERGIC DRUGS

ProvayBlue® may cause serious or fatal serotonergic syndrome when used in combination with serotonergic drugs. Avoid concomitant use of ProvayBlue® with selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors.

DOSAGE AND ADMINISTRATION

Preparation and Storage

ProvayBlue® is hypotonic and may be diluted before use in a solution of 50 mL 5% Dextrose in Water (D5W) in order to avoid local pain, particularly in the pediatric population. Use the diluted solution immediately after preparation.

Avoid diluting with sodium chloride solutions, because it has been demonstrated that chloride reduces the solubility of methylene blue.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

CONTRAINDICATIONS

ProvayBlue® is contraindicated in patients with severe hypersensitivity reactions to methylene blue or any other thiazine dye; and in patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) due to the risk of hemolytic anemia.

WARNINGS AND PRECAUTIONS

Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

The development of serotonin syndrome has been reported with use of methylene blue class products. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors). Some of the reported cases were fatal. Patients treated with ProvayBlue® should be monitored for the emergence of serotonin syndrome. If symptoms of serotonin syndrome occur, discontinue use of ProvayBlue® and initiate supportive treatment. Inform patients of the increased risk of serotonin syndrome and advise them not to take serotonergic drugs within 72 hours after the last dose of ProvayBlue®.

Hypersensitivity

Anaphylactic reactions to methylene blue class products have been reported. If anaphylaxis or other severe hypersensitivity reactions (e.g., angioedema, urticaria, bronchospasm) should occur, discontinue use of ProvayBlue® and initiate supportive treatment. ProvayBlue® is contraindicated in patients who have experienced anaphylaxis or other severe hypersensitivity reactions to a methylene blue class product in the past.

Lack of Effectiveness

Methemoglobinemia due to aryl amines or sulfa drugs may not resolve or may rebound after response to treatment with ProvayBlue®.

If methemoglobinemia does not respond to 2 doses of ProvayBlue® or if methemoglobinemia rebounds after a response, consider additional treatment options.

Patients with G6PD deficiency may not reduce ProvayBlue® to its active form. ProvayBlue® may not be effective in patients with G6PD deficiency.

Hemolytic Anemia

Hemolysis can occur during treatment of methemoglobinemia with ProvayBlue®. The onset of anemia may be delayed one or more days after treatment with ProvayBlue®. The anemia may require red blood cell transfusions. Use the lowest effective number of doses of ProvayBlue® to treat methemoglobinemia. Discontinue ProvayBlue® and consider alternative treatments of methemoglobinemia if severe hemolysis occurs.

Treatment of patients with G6PD deficiency with ProvayBlue® may result in severe hemolysis and severe anemia. ProvayBlue® is contraindicated for use in patients with G6PD deficiency.

Interference with In Vivo Monitoring Devices

The presence of methylene blue in the blood may result in an underestimation of the oxygen saturation reading by pulse oximetry. If a measure of oxygen saturation is required during or shortly after infusion with ProvayBlue®, it is advisable to obtain an arterial blood sample for testing by an alternative method.

A fall in the Bispectral Index (BIS) has been reported following administration of methylene blue class products. If ProvayBlue® is administered during surgery, alternative methods for assessing the depth of anesthesia should be employed.

Effects on Ability to Drive and Operate Machinery

Treatment with ProvayBlue® may cause confusion, dizziness and disturbances in vision. Advise patients to refrain from driving or engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery until such adverse reactions to ProvayBlue® have resolved.

Interference with Laboratory Tests

ProvayBlue® is a blue dye that passes freely into the urine and may interfere with the interpretation of any urine test that relies on a blue indicator, such as the dipstick test for leucocyte esterase.

ADVERSE REACTIONS

The safety of ProvayBlue® was determined in 82 healthy adults 19-55 years of age, with a median age of 36 years. Each individual in the safety population received a single dose of ProvayBlue® 2 mg/kg intravenously.

The most commonly reported adverse reactions ($\geq$10%) are pain in extremity, chromaturia, dysgeusia, feeling hot, dizziness, hyperhidrosis, nausea, skin discoloration and headache. There was one serious adverse reaction reported (syncope due to sinus pauses of 3-14 seconds).

Other adverse reactions reported to occur following administration of methylene blue class products include the following: hemolytic anemia, hemolysis, hyperbilirubinemia, methemoglobinemia; palpitations, tachycardia; eye

pruritus, ocular hyperemia, vision blurred; abdominal pain lower, dry mouth, flatulence, glossodynia, tongue eruption; death, infusion site extravasation, infusion site induration, infusion site pruritus, infusion site swelling, infusion site urticaria, peripheral swelling, thirst; elevated liver enzymes; myalgia; dysuria; nasal congestion, oropharyngeal pain, rhinorrhea, sneezing; necrotic ulcer, papule, phototoxicity; and hypertension.

Table 1. Adverse Reactions Following Infusion of ProvayBlue® 2 mg/kg

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

Catheter site pain	2	2%	0
Ecchymosis	2	2%	0

DRUG INTERACTIONS

Avoid concomitant use of ProvayBlue® with medicinal products that enhance serotonergic transmission including SSRIs, MAO inhibitors, bupropion, buspirone, clomipramine, mirtazapine and venlafaxine because of the potential for serious CNS reactions, including potentially fatal serotonin syndrome. If the intravenous use of ProvayBlue® cannot be avoided in patients treated with serotonergic medicinal products, choose the lowest possible dose and observe closely the patient for CNS effects for up to 4 hours after administration.

Methylene blue inhibits a range of CYP isozymes in vitro, including 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5.

USE IN SPECIFIC POPULATIONS

Pregnancy and Lactation

ProvayBlue® may cause fetal harm when administered to a pregnant woman. Intra-amniotic injection of pregnant women with a methylene blue class product during the second trimester was associated with neonatal intestinal atresia and fetal death. Advise pregnant women of the potential risk to the fetus.

There is no information regarding the presence of methylene blue in human milk. Because of the potential for serious adverse reactions, including genotoxicity discontinue breast-feeding during and for up to 8 days after treatment with ProvayBlue®.

Renal Impairment

Patients with any renal impairment should be monitored for toxicities and potential drug interactions for an extended period of time following treatment with ProvayBlue®.

Hepatic Impairment

Methylene blue is extensively metabolized in the liver. Monitor patients with any hepatic impairment for toxicities and potential drug interactions for an extended period of time following treatment with ProvayBlue®.

OVERDOSAGE

In case of overdose of ProvayBlue®, maintain the patient under observation until signs and symptoms have resolved, monitor for cardiopulmonary, hematologic and neurologic toxicities, and institute supportive measures.

For additional safety information, included BOX WARNING, please see Full Prescribing Information.

You are encouraged to report Adverse Drug Events to American Regent Inc. at 1-800-734-9236 or to the FDA by visiting www.fda.gov/medwatch or calling 1-800-FDA-1088.

References

1. Rehman HU. Methemoglobinemia. West J Med. 2001;175(3):193-6.
2. Prchal, J. T., MD. (2017). Clinical features, diagnosis, and treatment of methemoglobinemia. UpToDate.
3. Dart RC, Goldrank LR, Erstad BL. Expert Consensus Guidelines for Stocking of Antidotes in Hospitals That Provide Emergency Care. Annals of Emergency Medicine. 2017; https://doi.org/10.1016/J.ANNEMERGMED.2017.05.021.