April 4, 2022

Re: ProvayBlue® (methylene blue) Injection, USP – Important Dilution Information

Dear Healthcare Professional,

American Regent, Inc., would like to reinforce the appropriate preparation of ProvayBlue® (methylene blue) Injection, USP using a solution of 50 mL 5% Dextrose Injection.

ProvayBlue® 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.

WARNING: SEROTONIN SYNDROME WITH CONCOMITANT USE OF SEROTONERGIC DRUGS. See below for Important Safety Information, including **BOXED WARNING**.

Reports have documented compounding errors using sodium chloride 9 mg/mL (0.9%) solution for injection with ProvayBlue® that led to precipitation of the drug and potential IV administration despite possibly visible particulates in the solution or IV tubing.[1]

Chloride ions significantly reduce the solubility of methylene blue, therefore ProvayBlue® (methylene blue) Injection, USP is not compatible with 0.9% saline due to risk of precipitation.

Errors may arise because healthcare professionals were familiar with preparation and administration of older versions of the 1% formulations of methylene blue injection with saline.

The following preparation information for ProvayBlue® (methylene blue) Injection, USP is included in the ProvayBlue® package insert: [2]

> ProvayBlue® is hypotonic and may be diluted before use in a solution of 50 mL 5% Dextrose Injection 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. The following are additional key points relating to preparation and dosing from the package insert to help reduce and prevent medication errors:

- ProvayBlue® may be diluted before use in a solution of 50 mL 5% Dextrose Injection
- Use the diluted solution immediately after preparation
- Ensure patent venous access prior to administration of ProvayBlue®
- Do not administer ProvayBlue® subcutaneously
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit

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Please refer to the ProvayBlue® Full Prescribing Information for a complete discussion of the preparation and storage and dosage and administration of ProvayBlue®.

See below for Important Safety Information, including **BOXED WARNING**.

You are encouraged to report adverse drug events (ADEs) to American Regent, Inc.:
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) Email: inquiry@americanregent.com

For drug information outside of normal business hours that cannot wait until the next day, please call: 1-877-845-6371

Medication Errors may be reported to the Institute for Safe Medication Practices National Medication Errors Reporting Form (ISMP MERP), available through the link below:

https://www.ismp.org/report-medication-error

Please contact American Regent, Inc. at 1-888-354-4855 if you have any questions about ProvayBlue® (methylene blue) Injection, USP or the information above.

Sincerely,

Medical Affairs
American Regent, Inc.

See following pages for Important Safety Information, including **BOXED WARNING**.

References:

1. ISMP. Safety Wires - Don't dilute ProvayBlue in normal saline. *Nurse AdviseERR*. 2017;15:1-2.
2. ProvayBlue® (methylene blue) Injection, USP [package insert]. Shirley, NY: American Regent, Inc. 12/2021.

ProvayBlue® (methylene blue) Injection, USP

For Intravenous Use. Ensure patent venous access prior to administration of ProvayBlue®.
Do not administer subcutaneously.

INDICATIONS AND USAGE
ProvayBlue® (methylene blue) injection, USP 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 Injection 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.

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®. 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.

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 which passes freely into the urine and may interfere with the interpretation of any urine test which 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 (≥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, but are not limited to, 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.

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

Methylene blue concentrations increased in subjects with renal impairment (eGFR 15 to 89 mL/min/1.73 m^2). Adjust ProvayBlue® dosage in patients with moderate or severe renal impairment (eGFR 15 to 59 mL/min/1.73 m^2). No dose adjustment is recommended in patients with mild renal impairment.

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, including BOXED 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.