

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use (PROVAYBLUE™) safely and effectively. See full prescribing information for (PROVAYBLUE™).

PROVAYBLUE™ (methylene blue) injection, for intravenous use
Initial U.S. Approval: 2016

-----INDICATIONS AND USAGE-----

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. (1, 14)

-----DOSAGE AND ADMINISTRATION-----

- Administer 1 mg/kg intravenously over 5-30 minutes. (2.1)
- If methemoglobin level remains above 30% or if clinical symptoms persist, give a repeat dose of up to 1 mg/kg one hour after the first dose. (2.1)

-----DOSAGE FORMS AND STRENGTHS-----

50 mg/10 mL (5 mg/mL) single-dose ampule. (3)

-----CONTRAINDICATIONS-----

- PROVAYBLUE™ is contraindicated in the following conditions (4):
- Severe hypersensitivity to methylene blue
 - Patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) due to the risk of hemolytic anemia

-----WARNINGS AND PRECAUTIONS-----

- Hypersensitivity: If severe or life threatening allergic reaction occurs, discontinue PROVAYBLUE™, treat the allergic reaction, and monitor until

signs and symptoms resolve (5.2)

- Lack of Effectiveness: Consider alternative treatments if there is no resolution of methemoglobinemia after 2 doses (2.1, 5.3)
- Hemolytic Anemia: Discontinue PROVAYBLUE™ and transfuse (5.4)
- Interference with In-Vivo Monitoring Devices: Use methods other than pulse oximetry to assess oxygen saturation (5.5)
- Effects on Ability to Drive and Operate Machinery: Advise patients to refrain from these activities until neurologic and visual symptoms have resolved (5.6)

-----ADVERSE REACTIONS-----

The most commonly reported adverse reactions (≥10%) are pain in extremity, chromaturia, dysgeusia, feeling hot, dizziness, hyperhidrosis, nausea, skin discoloration and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact American Regent at 1-800-734-9236 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Only use during pregnancy if the potential benefit justifies the potential risk to the fetus. (8.1)
- Lactation: Discontinue breast-feeding for up to 8 days after treatment. (8.2).
- Renal Insufficiency: Monitor patients longer for toxicity and drug interactions due to delayed clearance. (8.6)
- Hepatic Impairment: Monitor patients longer for toxicity and drug interactions due to delayed clearance. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 4/2016

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FULL PRESCRIBING 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 (5.1, 7.1). [see Warnings and Precautions (5.1) and Drug Interactions (7.1)]

1 INDICATIONS AND USAGE

PROVAYBLUE™ 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 [see Clinical Studies (14.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Dosage and Administration

- Ensure patent venous access prior to administration of PROVAYBLUE™. Do not administer PROVAYBLUE™ subcutaneously.
- Monitor vital signs, electrocardiogram and methemoglobin levels during treatment with PROVAYBLUE™ and through resolution of methemoglobinemia.
- Administer PROVAYBLUE™ 1 mg/kg intravenously over 5-30 minutes.
- If the methemoglobin level remains greater than 30% or if clinical signs and symptoms persist, a repeat dose of PROVAYBLUE™ 1 mg/kg may be given one hour after the first dose.
- If methemoglobinemia does not resolve after 2 doses of PROVAYBLUE™, consider initiating alternative interventions for treatment of methemoglobinemia.

2.2 Preparation and Storage

Each mL of PROVAYBLUE™ contains 5 mg methylene blue

Each 10 mL ampule of PROVAYBLUE™ contains 50 mg methylene blue.

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.

Do not mix with sodium chloride 9 mg/mL (0.9%) solution for injection, 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.

Keep the ampule in the original package to protect from light.

3 DOSAGE FORMS AND STRENGTHS

Injection: 50 mg/10 mL (5 mg/mL) clear dark blue solution in single-dose ampules

4 CONTRAINDICATIONS

PROVAYBLUE™ is contraindicated in the following conditions:

- Severe hypersensitivity reactions to methylene blue or any other thiazine dye [see Warnings and Precautions (5.2)].
- Patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) due to the risk of hemolytic anemia [see Warnings and Precautions (5.3, 5.4)]

5 WARNINGS AND PRECAUTIONS

5.1 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. Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, and hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, and incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Avoid concomitant use of PROVAYBLUE™ with serotonergic drugs.

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 to not to take serotonergic drugs within 72 hours after the last dose of PROVAYBLUE™ [*see Drug Interactions (7), Patient Counseling Information (17)*].

5.2 Hypersensitivity

Anaphylactic reactions to methylene blue class products have been reported. Patients treated with PROVAYBLUE™ should be monitored for anaphylaxis. 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.

5.3 Lack of Effectiveness

Methemoglobinemia may not resolve or may rebound after response to treatment with PROVAYBLUE™ in patients with methemoglobinemia due to aryl amines such as aniline or sulfa drugs such as dapsone. Monitor response to therapy with PROVAYBLUE™ through resolution of methemoglobinemia. If methemoglobinemia does not respond to 2 doses of PROVAYBLUE™ or if methemoglobinemia rebounds after a response, consider additional treatment options [*see Dosage and Administration (2.2)*].

Patients with glucose-6-phosphate dehydrogenase deficiency may not reduce PROVAYBLUE™ to its active form in vivo. PROVAYBLUE™ may not be effective in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

5.4 Hemolytic Anemia

Hemolysis can occur during treatment of methemoglobinemia with PROVAYBLUE™. Laboratory testing may show Heinz bodies, elevated indirect bilirubin and low haptoglobin, but the Coombs test is negative. The onset of anemia may be delayed 1 or more days after treatment with PROVAYBLUE™. The anemia may require red blood cell transfusions. [*see Adverse Reactions (6.1)*]. 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 glucose-6-phosphate dehydrogenase (G6PD) deficiency with PROVAYBLUE™ may result in severe hemolysis and severe anemia. PROVAYBLUE™ is contraindicated for use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency [*see Contraindications (4)*].

5.5 Interference with In Vivo Monitoring Devices

- Inaccurate Pulse Oximeter Readings

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 of PROVAYBLUE™, it is advisable to obtain an arterial blood sample for testing by an alternative method.

- Bispectral index monitor

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.

5.6 Effects on Ability to Drive and Operate Machinery

Treatment with PROVAYBLUE™ may cause confusion, dizziness and disturbances in vision [*see Adverse Reactions (6)*]. 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.

5.7 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.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Serotonin Syndrome with Concomitant Use of Serotonergic Drugs [see Warnings and Precautions (5.1)]
- Anaphylaxis [see Warnings and Precautions (5.2)]
- Lack of Effectiveness [see Warnings and Precautions (5.3)]
- Hemolytic Anemia [see Warnings and Precautions (5.4)]
- Interference with In-Vivo Monitoring Devices [see Warnings and Precautions (5.5)]
- Effects on Ability to Drive and Operate Machinery [see Warnings and Precautions (5.6)]
- Interference with Laboratory Tests [see Warnings and Precautions (5.7)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of PROVAYBLUE™ was determined in 82 healthy adults of median age of 36 years (range, 19-55 years); 54% were male, and 68% were white. Each individual in the safety population received a single dose of PROVAYBLUE™ 2 mg/kg intravenously. There was one serious adverse reaction reported (syncope due to sinus pauses of 3-14 seconds). The most common ($\geq 2\%$) moderate or severe adverse reactions were pain in the extremity (56%), headache (7%), feeling hot (6%), syncope (4%), back pain (2%), hyperhidrosis (2%) and nausea (2%). Table 1 lists the adverse reactions of any severity that occurred in at least 2% of individuals who received PROVAYBLUE™.

Table 1. Adverse Reactions Following Infusion of PROVAYBLUE™ 2 mg/kg

Adverse Reaction	Any Grade TEAE (n=82)		Moderate- Severe TEAE (n=82)	
	n	%	n	%
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%

Table 1. Adverse Reactions Following Infusion of PROVAYBLUE™ 2 mg/kg

Adverse Reaction	Any Grade TEAE (n=82)		Moderate- Severe TEAE (n=82)	
	n	%	n	%
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	

Other adverse reactions reported to occur following administration of methylene blue class products include the following:

Blood and lymphatic system disorders: hemolytic anemia, hemolysis, hyperbilirubinemia, methemoglobinemia

Cardiac disorders: palpitations, tachycardia

Eye disorders: eye pruritus, ocular hyperemia, vision blurred

Gastrointestinal disorders: abdominal pain lower, dry mouth, flatulence, glossodynia, tongue eruption

General disorders and administration site conditions: death, infusion site extravasation, infusion site induration, infusion site pruritus, infusion site swelling, infusion site urticaria, peripheral swelling, thirst

Investigations: elevated liver enzymes

Musculoskeletal and connective tissue disorders: myalgia

Renal and urinary disorders: dysuria

Respiratory, thoracic and mediastinal disorders: nasal congestion, oropharyngeal pain, rhinorrhea, sneezing

Skin and subcutaneous tissue disorders: necrotic ulcer, papule, phototoxicity

Vascular disorders: hypertension

7 DRUG INTERACTIONS

7.1 Serotonergic Drugs

Avoid concomitant use of PROVAYBLUE™ with medicinal products that enhance serotonergic transmission including SSRIs (selective serotonin reuptake inhibitors), MAO inhibitors, bupropion, buspirone, clomipramine, mirtazapine and venlafaxine; because of the potential for serious CNS reactions, including potentially fatal serotonin syndrome. Although the mechanism is not clearly understood, literature reports suggest inhibition of MAO by methylene blue may be involved. In addition, in vitro studies cannot rule out the potential involvement of CYP 2D6 inhibition by methylene blue. 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 [see *Warning and Precautions (5.1)*, *Clinical Pharmacology (12.3)*].

7.2 Agents Metabolized by Cytochrome P450 Enzymes

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

could be more pronounced with narrow therapeutic index drugs that are metabolized by one of these enzymes (e.g, digoxin, warfarin, phenytoin, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus). However, the clinical relevance of these in vitro interactions is unknown.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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. Methylene blue produced adverse developmental outcomes in rats and rabbits when administered orally during organogenesis at doses at least 32 and 16 times, respectively, the clinical dose of 1 mg/kg [see Data]. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/neonatal adverse reactions

Intra-amniotic injection of a methylene blue class product hours to days prior to birth can result hyperbilirubinemia, hemolytic anemia, skin staining, methemoglobinemia, respiratory distress and photosensitivity in the newborn. Following administration of PROVAYBLUE™ to a pregnant woman at term, observe the newborn for these adverse reactions and institute supportive care.

Data

Animal Data

Methylene blue was administered orally to pregnant rats at doses of 50 to 350 mg/kg/day, during the period of organogenesis. Maternal and embryofetal toxicities were observed at all doses of methylene blue, and were most evident at the 200 and 350 mg/kg/day doses. Maternal toxicity consisted of increased spleen weight. Embryo-fetal toxicities included reduced fetal weight, post-implantation loss, edema, and malformations including enlarged lateral ventricles. The dose of 200 mg/kg (1200 mg/m²) in rats is approximately 32 times a clinical dose of 1 mg/kg based on body surface area.

Methylene blue was administered orally to pregnant rabbits at doses of 50, 100, or 150 mg/kg/day, during the period of organogenesis. Maternal death was observed at the methylene blue dose of 100 mg/kg. Embryofetal toxicities included spontaneous abortion at all dose levels and a malformation (umbilical hernia) at the 100 and 150 mg/kg/day doses. The dose of 50 mg/kg (600 mg/m²) in rabbits is approximately 16 times a clinical dose of 1 mg/kg based on body surface area.

8.2 Lactation

Risk Summary

There is no information regarding the presence of methylene blue in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions, including genotoxicity discontinue breast-feeding during and for up to 8 days after treatment with PROVAYBLUE™ [see Clinical Pharmacology (12.3)].

8.4 Pediatric Use

The safety and effectiveness of PROVAYBLUE™ have been established in pediatric patients. Use of PROVAYBLUE™ is supported by two retrospective case series that included 2 pediatric patients treated with PROVAYBLUE™ and 12 treated with another methylene blue class product. The case series 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). The efficacy outcomes were consistent across pediatric and adult patients in both case series [see Clinical Studies (14)].

8.5 Geriatric Use

The retrospective case series included 3 patients age 65 years and over treated with PROVAYBLUE™ (or a bioequivalent formulation) and 5 treated with another methylene blue class product. The efficacy outcomes were consistent across adult and elderly patients in both case series [see Clinical Studies (14)]. This drug is known to be substantially excreted by the kidney, so the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, treatment of methemoglobinemia in these patients should use the lowest number of doses needed to achieve a response [see Dosage and Administration (2)].

8.6 Renal Impairment

Approximately 40% of methylene blue is excreted by the kidneys. Patients with any renal impairment should be monitored for toxicities and potential drug interactions for an extended period of time following treatment with PROVAYBLUE™.

8.7 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™.

10 OVERDOSAGE

Hypotension, wheezing and reduced oxygenation have been reported in patients who received methylene blue class products in single doses of 3 mg/kg or more.

Administration of large intravenous doses (cumulative dose ≥ 7 mg/kg) of a methylene blue class product caused nausea, vomiting, precordial pain, dyspnea, tachypnea, chest tightness, tachycardia, apprehension, tremor, mydriasis, blue staining of the urine, the skin and mucous membranes, abdominal pain, dizziness, paresthesia, headache, confusion, mild methemoglobinemia (up to 7%) and electrocardiogram changes (T-wave flattening or inversion). These effects lasted 2-12 hours following administration.

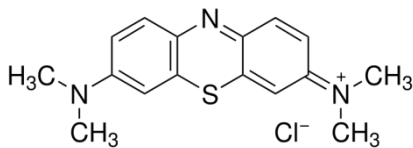
A severe overdosage (single dose of 20 mg/kg or more) of a methylene blue class product caused severe intravascular hemolysis, hyperbilirubinemia and death.

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 as necessary.

11 DESCRIPTION

PROVAYBLUE™ is an oxidation-reduction agent. PROVAYBLUE™ (methylene blue) is a sterile solution intended for intravenous administration. Each PROVAYBLUE™, 10 mL ampule contains 50 mg Proveblue® methylene blue and water for injection q.s. Each mL of solution contains 5 mg methylene blue and water for injection q.s.

Methylene blue is 3,7-bis(dimethylamino)phenothiazin-5-ium, chloride. The molecular formula of methylene blue is $C_{16}H_{18}ClN_3S$ and its molecular weight is 319.86 g/mol. Its structural formula is:



PROVAYBLUE™ is a clear dark blue solution with a pH value between 3.0 and 4.5. The osmolality is between 10 and 15 mOsm/kg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylene blue is a water soluble thiazine dye that promotes a non-enzymatic redox conversion of methHb to hemoglobin. In situ, methylene blue is first converted to leucomethylene blue (LMB) via NADPH reductase. It is the LMB molecule which then reduces the ferric iron of methHb to the ferrous state of normal hemoglobin.

12.2 Pharmacodynamics

Low concentrations of methylene blue speeds up the in vivo conversion of methemoglobin to hemoglobin. Methylene blue has been observed to stain tissues selectively. The exposure-response or –safety relationship for methylene is unknown.

Cardiac Electrophysiology

The results of a thorough QT study demonstrated PROVAYBLUE™ at an intravenous dose of 2 mg/kg as a 5-minute intravenous infusion had no effect on the QT, PR or QRS intervals.

12.3 Pharmacokinetics

The mean (CV%) C_{max} and AUC of methylene blue 2,917 ng/mL (39%) and 13977 ng.hr/mL (21%) following a 2 mg/kg dose administered as a 5-minute intravenous infusion.

Distribution

The mean \pm standard deviation steady state volume of distribution of a 2 mg/kg dose of PROVAYBLUE™ was 255 L \pm 58. The mean plasma protein binding of methylene blue is approximately 94% in vitro. Methylene blue exhibits concentration-dependent partitioning into blood cells in vitro. The blood-to-plasma ratio was 5.1 \pm 2.8 at 5 minutes from the start of a 2 mg/kg dose administered as a 5-minute intravenous infusion and reached a plateau of 0.6 at 4 hours in a clinical study. Methylene Blue is a substrate for the P-glycoprotein (P-gp, ABCB1) transporter, but not for BCRP or OCT2 in vitro.

Elimination

Methylene blue has a half-life of approximately 24 hours.

Metabolism

Methylene blue is metabolized by CYPs 1A2, 2C19 and 2D6 in vitro; however, the predominant in vitro pathway appears to be UGT-mediated conjugation by multiple UGT enzymes, including UGT1A4 and UGT1A9.

Azure B, which is a minor impurity in methylene blue, is also formed in humans as a metabolite of methylene blue, with an overall drug/metabolite AUC ratio of greater than 6:1. Azure B has 8-fold lower potency than methylene blue.

Excretion

Approximately 40% of methylene blue is excreted in to the urine unchanged.

Drug Interaction Studies

The clinical relevance of in vitro inhibition or induction of the metabolizing enzymes and transporter systems described below is unknown, but it cannot be excluded that the systemic exposure of medicinal products being substrates for these enzymes or transporter systems may be affected with concomitant administration with PROVAYBLUE™ Injection.

Cytochrome P450

Methylene blue inhibits CYP isozymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5 in vitro. Possible time-dependent inhibition of CYP2C9, CYP2D6 and CYP3A4/5 (testosterone as substrate) was also observed in vitro. Methylene blue induces CYP1A2, but does not induce CYP2B6 or CYP3A4 in vitro.

Glucuronosyltransferase

Methylene blue inhibits UGT1A9 and UGT1A4 in in vitro, but did not significantly inhibit UGTs 1A1, 1A3, 1A6, 2B7 or 2B15.

Transporter Interactions

Methylene blue is both a substrate for and an inhibitor of P-gp, but is not a substrate for BCRP or OCT2 in vitro. Methylene blue is not a significant inhibitor of BCRP, OAT1, OAT3, OAT1B1 or OAT1B3 in vitro. Methylene blue inhibits OCT2, MATE1 and MATE2-K in vitro. The OCT2/MATE pathway for renal transport is reported to play a significant role in the elimination of several substances, including metformin, cimetidine, acyclovir and creatinine

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year carcinogenicity study, rats were administered oral doses of methylene blue at 5, 25, or 50 mg/kg. Methylene blue caused pancreatic islet adenomas or carcinomas (combined) in male rats. In a two-year year carcinogenicity study, mice were administered oral doses of methylene blue at 2.5, 12.5, or 25 mg/kg. There were no drug-related neoplastic findings in mice.

Methylene blue was genotoxic in gene mutation assays in bacteria (Ames test), and in an in vitro sister chromatid exchange test and an in vitro chromosomal aberration test in Chinese hamster ovary (CHO) cells. Methylene blue was negative for micronucleus induction in bone marrow or peripheral blood collected from mice treated with methylene blue.

Fertility studies with methylene blue have not been conducted. In vitro, methylene blue reduced motility of human sperm in a concentration dependent manner.

14 CLINICAL STUDIES

14.1 Treatment of Acquired 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 PROVAYBLUE™ (or a bioequivalent formulation) in 6 patients identified by retrospective chart review or literature search. The 6 patients 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%) 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 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%) had 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 treated intravenously with PROVAYBLUE™ (or a bioequivalent formulation) or with another methylene blue class product, there was no difference in response rate by dose. The methemoglobin decreased by at least 50% within 1 hour of infusion for 15/17 (88%) of patients treated with 1 mg/kg, 12/13 (92%) treated with 2 mg/kg and 16/17 (94%) treated with a different dose or for those whose dose was not reported.

16 HOW SUPPLIED/STORAGE AND HANDLING

PROVAYBLUE™ is supplied in 10 mL single-dose ampules. Each 10 mL ampule contains 50 mg of methylene blue as a clear dark blue solution. A box contains five ampules placed in a tray.

Box of 5 ampules: NDC 0517-0374-05

Storage:

Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature]

Any unused product or waste material should be disposed of in accordance with local practice.

Do not refrigerate or freeze.

Keep the ampule in the original package to protect from light.

17 PATIENT COUNSELING INFORMATION

Serotonin Syndrome

Advise patients of the possibility of serotonin syndrome, especially with concomitant use of serotonergic agents such as medications to treat depression and migraines. Advise patients to seek immediate medical attention if the following symptoms occur after treatment with PROVAYBLUE™: changes in mental status, autonomic instability, or neuromuscular symptoms with or without gastrointestinal symptoms [see Warnings and Precautions (5.1)].

Pregnancy

Advise pregnant women of the potential risk to the fetus with the use of PROVAYBLUE™ during pregnancy [see Use in Specific populations (8.1)].

Breastfeeding

Advise patients to discontinue breast-feeding for up to 8 days after treatment with PROVAYBLUE™ [see Use in Specific populations (8.2)].

Driving and Using Machines

Advise patients to avoid driving and use of machines during treatment with PROVAYBLUE™. Driving can be affected as a result of a confusional state, dizziness and possible eye disturbances [see Warnings and Precautions (5.6)].

Phototoxicity

Advise patients to take protective measures against exposure to light, because phototoxicity may occur after administration of methylene blue [see Adverse Reactions (6.1)].

Skin and Body Fluid Blue Discoloration

Advise patients that PROVAYBLUE™ may cause a blue discoloration of the skin and body fluids [see Adverse Reactions (6.1)].

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