January 10, 2024

To,
Division of Docket management
Food and Drug Administration
Department of Health and Human Services,
5630, Fisher Lane, Room 1061 (HFA -305)
Rockville, MD 20852

SUITABILITY PETITION

Dear Sir/Madam:

The undersigned (petitioner) submits this Suitability Petition pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act ("FDC Act") and in accordance with 21 C.F.R. § 314.93 and 21 C.F.R. §§ 10.20 and 10.30, to request that the Commissioner of the U.S. Food and Drug Administration ("FDA") determine that the drug product Methylene Blue Injection, USP, 5 mg/1 mL, is suitable for submission in an Abbreviated New Drug Application ("ANDA").

I. ACTION REQUESTED

The petitioner requests that FDA declare that Methylene Blue Injection, USP, 5 mg/1 mL is suitable for submission as an ANDA. As designated in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book"), the Reference Listed Drug ("RLD") upon which this petition is based is PROVAYBLUE® (methylene blue) injection USP, for intravenous use, 50 mg/10 mL (5 mg/mL) and 10 mg/2 mL (5 mg/mL), held by PROVEPHARM SAS, which FDA approved under NDA # 204630.

The petitioner, hereby, seeks an additional strength (total drug content) from that of RLD: 5 mg/1 mL (5 mg/mL). It should be noted that the change in strength is only a change in the total drug content and not in concentration (5 mg/mL). The active ingredients, route of administration, dosage form and dosage regimen for use are the same as that of the RLD.

Office of Regulatory Affairs
Zydus Pharmaceuticals (USA) Inc.
(A wholly owned subsidiary of Zydus Lifesciences Limited)
73- B Route 31 North • Pennington, NJ 08534 | Phone: 609-730-1900 | Fax: 609-730-1999

II. STATEMENT OF GROUNDS

FDC Act § 505(j)(2)(A)(iii) provides for the submission of an ANDA for a drug product that differs in strength from that of the Reference Listed Drug provided FDA has first approved a petition permitting the submission of such an application.

PROVAYBLUE (methylene blue) injection USP, is supplied as 50 mg/10 mL or 10 mg/2 mL clear dark blue solution in single-dose ampules or single-dose vials. It is indicated for the treatment of pediatric and adult patients with acquired methemoglobinemia.

Dosing recommendations in the RLD package insert are as follows:

Recommended Dosage for Renal Impairment

- The recommended dosage of PROVAYBLUE in patients with moderate or severe renal impairment (eGFR 15-59 mL/min/1.73 m2) is a single dose of 1 mg/kg.
- If the methemoglobin level remains greater than 30% or if the clinical symptoms persist 1 hour after dosing, consider initiating alternative interventions for the treatment of methemoglobinemia.

The availability of additional strengths would provide additional flexibility in achieving the proper dose. Also being lower strength, it would reduce pharmaceutical wastage by addressing need for smaller dose particularly in pediatric population.

There are no proposed changes in labelling with the exception of the obvious changes in strength. The active ingredient, dosage form and route of administration, as well as the uses, indications, warnings, and directions for use will remain the same as that of the RLD.

A copy of the relevant excerpt on RLD from the current electronic Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations is provided as **Attachment 1**. A copy of the current labelling for PROVAYBLUE® (methylene blue) injection USP, for intravenous use, 50 mg/10 mL (5 mg/mL) and 10 mg/2 mL (5 mg/mL) is provided in **Attachment 2.** The draft Package Insert incorporating the proposed additional strengths is provided in **Attachment 3.**

This petition is seeking a change in strength (total drug content) and proposes new strengths of 5 mg/1 mL (5 mg/mL). Note that the change in strength from RLD is only a change in the total drug content and not in concentration, as detailed in the Table below.

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Table 1 - Comparison of Approved Drug Products to Proposed Drug Product

	RLD: PROVAYBLUE® (methylene blue) injection USP, for intravenous use, held by PROVEPHARM SAS, NDA 204630		**Proposed Drug Product**		
Active Ingredient	Methylene Blue		Methylene Blue		
Strength (Total Drug Content)	50 mg	10 mg	50 mg	10 mg	5 mg
Concentration	5 mg/1 mL	5 mg/1 mL	5 mg/1 mL	5 mg/1 mL	5 mg/1 mL
Fill Volume	10 mL	2 mL	10 mL	2 mL	1 mL
Dosage Form	Solution		Solution		
Route of Administration	Intravenous		Intravenous		
Indications and Usage	PROVAYBLUE® USP is indicated for the treatment of pediatric and adult patients with acquired methemoglobinemia.		Methylene Blue Injection is indicated for the treatment of pediatric and adult patients with acquired methemoglobinemia.		

In view of the aforesaid, the petitioner's request for the Commissioner to find that a change in strength as proposed in the form of a new strengths of 5 mg/1 mL (5 mg/mL) for Methylene Blue Injection should raise no questions of safety and effectiveness, and the Agency is thereby requested to approve the petition.

The Pediatric Research Equity Act ("PREA"), enacted in December 2003, amended the FDC Act by requiring certain applications for a drug submitted under FDC Act § 505 to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is deferred or waived. See FDC Act § 505B(a)(1)(A)(i). Specifically, PREA applies to all applications for a new active ingredient, dosage form, indication, route of administration, or dosing regimen. *See id*. ANDAs submitted under an approved suitability petition for a change in strength are ***not*** subject to PREA requirements. *See FDA, Draft Guidance for Industry, How to Comply with the Pediatric Research Equity Act, 4 (Sep. 2005).* Petitioner asserts that PREA is not applicable to the proposed Methylene Blue Injection, USP, 5 mg/1 mL, drug product because the proposed change concerns only a new strength. As such, PREA should not serve as an impediment to the Agency granting this petition.

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III. ENVIROMENTAL IMPACT

A claim for categorical exclusion of the requirements for an environmental assessment is made pursuant to 21 C.F.R. § 25.31.

IV. ECONOMIC IMPACT

In accordance with 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition. Petitioner hereby commits to promptly provide this information, if requested.

V. CERTIFICATION

The petitioner certifies that, to the best of knowledge and belief of Petitioner, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition.

Sincerely,

Digitally signed by Srinivas Gurram
DN: cn=Srinivas Gurram, o=Zydus Pharmaceuticals USA Inc., ou=Office of Regulatory Affairs, email=gsrinivas@zydususa.com, c=US
Date: 2024.01.10 15:18:47 -05'00'
Adobe Acrobat version: 2017.012.30262

Srinivas Gurram (Srini)
Senior Vice President - Head of RA and CQA lead –Americas
Zydus Pharmaceuticals (USA) Inc.

Attachment:

Attachment 1: Orange Book Pages of RLD, PROVAYBLUE® (methylene blue) injection USP.

Attachment 2: Current labeling for PROVAYBLUE® (methylene blue) injection USP, for intravenous use, 50 mg/10 mL (5 mg/mL) and 10 mg/2 mL (5 mg/mL), held by PROVEPHARM SAS, NDA 204630 (5/2021 version, source: Drugs@FDA).

Attachment 3: Draft Package Insert incorporating the proposed additional strength.

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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Mkt.Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	METHYLENE BLUE	PROVAYBLUE	N204630	SOLUTION	INTRAVENOUS	10MG/2ML (5MG/ML)		RLD	RS	PROVEPHARM SAS
RX	METHYLENE BLUE	PROVAYBLUE	N204630	SOLUTION	INTRAVENOUS	50MG/10ML (5MG/ML)		RLD	RS	PROVEPHARM SAS

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Search Results

Product Details for NDA 204630

Expand all

PROVAYBLUE (METHYLENE BLUE)
10MG/2ML (5MG/ML)
Marketing Status: Prescription

Active Ingredient: METHYLENE BLUE
Proprietary Name: PROVAYBLUE
Dosage Form; Route of Administration: SOLUTION; INTRAVENOUS
Strength: 10MG/2ML (5MG/ML)
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N204630
Product Number: 002
Approval Date: Jul 18, 2019
Applicant Holder Full Name: PROVEPHARM SAS
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=002&Appl_No=204630&Appl_type=N)

PROVAYBLUE (METHYLENE BLUE)
50MG/10ML (5MG/ML)
Marketing Status: Prescription

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Search Results

Product Details for NDA 204630

Expand all

PROVAYBLUE (METHYLENE BLUE)
10MG/2ML (5MG/ML)
Marketing Status: Prescription

PROVAYBLUE (METHYLENE BLUE)
50MG/10ML (5MG/ML)
Marketing Status: Prescription

Active Ingredient: METHYLENE BLUE
Proprietary Name: PROVAYBLUE
Dosage Form; Route of Administration: SOLUTION; INTRAVENOUS
Strength: 50MG/10ML (5MG/ML)
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N204630
Product Number: 001
Approval Date: Apr 8, 2016
Applicant Holder Full Name: PROVEPHARM SAS
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=204630&Appl_type=N)

Top (https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=204630#38824)

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 USP, for intravenous use
Initial U.S. Approval: 2016

WARNING: SEROTONIN SYNDROME WITH CONCOMITANT USE OF SEROTONERGIC DRUGS AND OPIOIDS

See full prescribing information for complete boxed warning.

PROVAYBLUE® may cause serious or fatal serotonergic syndrome when used in combination with serotonergic drugs and opioids. Avoid concomitant use of PROVAYBLUE® with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and opioids. ***(5.1, 7.1)***

----------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)
- Administer a single dose of 1 mg/kg in patients with moderate or severe renal impairment. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
50 mg/10 mL (5 mg/mL) single-dose ampule. (3)
10 mg/2 mL (5 mg/mL) single-dose ampule. (3)
50 mg/10 mL (5 mg/mL) single-dose vial. (3)
10 mg/2 mL (5 mg/mL) single-dose vial. (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).
- Hepatic Impairment: Monitor patients longer for toxicity and drug interactions due to delayed clearance. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: SEROTONIN SYNDROME WITH CONCOMITANT USE OF SEROTONERGIC DRUGS AND OPIOIDS

PROVAYBLUE® may cause serious or fatal serotonergic syndrome when used in combination with serotonergic drugs and opioids. Avoid concomitant use of PROVAYBLUE® with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and opioids. *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*

1 INDICATIONS AND USAGE

PROVAYBLUE® 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 *[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 Recommended Dosage for Renal Impairment

- The recommended dosage of PROVAYBLUE in patients with moderate or severe renal impairment (eGFR 15-59 mL/min/1.73 m^2) is a single dose of 1 mg/kg.
- If the methemoglobin level remains greater than 30% or if the clinical symptoms persist 1 hour after dosing, consider initiating alternative interventions for the treatment of methemoglobinemia.

2.3 Preparation and Storage

Each mL of PROVAYBLUE® contains 5 mg methylene blue.

Each 10 mL ampule and vial of PROVAYBLUE® contains 50 mg methylene blue. Each 2 mL ampule and vial of PROVAYBLUE® contains 10 mg methylene blue.

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.

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

Keep the ampule and the vial in the original package to protect from light**.**

Discard unused portion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 50 mg/10 mL (5 mg/mL) or 10 mg/2 mL (5 mg/mL) clear dark blue solution in single-dose ampules or single-dose vials.

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 and Opioids

The development of serotonin syndrome has been reported with the 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 (MAOIs). Opioids and dextromethorphan may increase the risk of developing serotonin syndrome 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 and opioids.

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 (≥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)	
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%

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

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

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

Clinically significant drug interactions with PROVAYBLUE® are described below:

The concomitant use of PROVAYBLUE® with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. Although the mechanism is not clearly understood, literature reports suggest PROVAYBLUE® is a potent reversible inhibitor of monoamine oxidase. Avoid concomitant use of PROVAYBLUE® with medicinal products that enhance serotonergic transmission including antidepressants like SSRIs (selective serotonin reuptake inhibitors), SNRIs (serotonin and norepinephrine reuptake inhibitors), MAOIs (monoamine oxidase inhibitors), bupropion, buspirone, clomipramine, mirtazapine, linezolid, opioids, and dextromethorphan 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 the patient closely for CNS effects for up to 4 hours after administration *[see Warning and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

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/m^2) 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/m^2) 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

Methylene blue concentrations increased in subjects with renal impairment (eGFR 15 to 89 mL/min/1.73m^2) significantly *[see Clinical Pharmacology (12.3)]*. Adjust PROVAYBLUE® dosage in patients with moderate or severe renal impairment (eGFR 15 to 59 mL/min/1.73 m^2) *[see Dosage and Administration (2.2)]*. No dose adjustment is recommended in patients with mild renal impairment (eGFR 60 – 89 mL/min/1.73 m^2).

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.

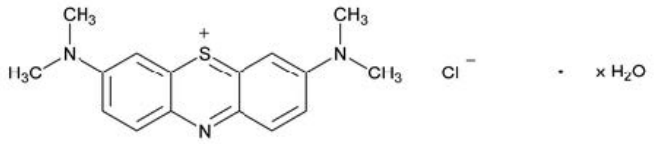
A severe overdosage (single dose of 20 mg/kg or more) of a methylene blue class product caused severe intravascular hemolysis, hyperbilirubinemia and death.

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

Methylene blue is an oxidation-reduction agent.

Its chemical name is 3,7-bis(dimethylamino)phenothiazin-5-ium, chloride hydrate. The molecular formula of methylene blue is $C_{16}H_{18}ClN_3S.xH_2O$ and its molecular weight of 319.86 g/mol for the anhydrous form. The structural formula of methylene blue is:



PROVAYBLUE® (methylene blue) injectionis a sterile solution intended for intravenous administration. Each mL of solution contains 5 mg methylene blue and water for injection. 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. PROVAYBLUE® (methylene blue) injection strength is expressed in terms of trihydrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylene blue is a water soluble thiazine dye that promotes a non-enyzmatic redox conversion of metHb 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 metHb 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%) Cmax 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± standard deviation steady state volume of distribution of a 2 mg/kg dose of PROVAYBLUE® was 255 L ± 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±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 in humans.

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 into the urine unchanged.

Specific Populations

Renal Impairment

After a single 1 mg/kg dose of PROVAYBLUE®, $AUC_{0\text{-}96h}$ increased by 52%, 116%, and 192% in subjects with mild (estimated glomerular filtration rate (eGFR) 60 – 89 mL/min/1.73 m^2), moderate (eGFR 30-59 mL/min/1.73m^2), and severe (eGFR 15-29 mL/min/1.732m^2) renal impairment, respectively. C_{max} increased by 42%, 34%, and 15% in subjects with mild, moderate, and severe renal impairment respectively *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)].* The half-life was unchanged in patients with mild to moderate renal impairment.

The $AUC_{0\text{-}96h}$ of Azure B after a single 1 mg/kg dose increased by 29%, 94%, and 339% in subjects with mild (estimated glomerular filtration rate (eGFR) 60 – 89 mL/min/1.73 m^2), moderate (eGFR 30-59 mL/min/1.73m^2), and severe (eGFR 15-29 mL/min/1.732m^2) renal impairment, respectively. C_{max} increased by 23%, 13%, and 65% in subjects with mild, moderate, and severe renal impairment, respectively *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*

Drug Interactions Studies

Clinical Studies:

The coadministration of 2 mg/kg dose of PROVAYBLUE® with midazolam (a CYP3A4 substrate), caffeine (a CYP1A2 substrate), warfarin (a CYP2C9 substrate), and dextromethorphan (a CYP2D6 substrate) in a cocktail study did not affect the exposure of these substrates compared to their exposure without PROVAYBLUE® administration.

In Vitro Studies:

Cytochrome P450 (CYP450) Enzymes:

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

UDP-Glucuronosyltransferase (UGT):

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

Transporter:

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. Methylene blue inhibits OCT2, MATE1 and MATE2-K.

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 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 and 2 mL single-dose ampules or single-dose vials. Each 10 mL ampule and vial contains 50 mg of methylene blue as a clear dark blue solution. Each 2 mL ampule and vial contains 10 mg of methylene blue as a clear dark blue solution. A box contains five ampules or vials.

Box of 5 ampules of 50 mg/10 mL: NDC 0517-0374-05

Box of 5 ampules of 10 mg/2 mL: NDC 0517-0125-05

Box of 5 vials of 50 mg/10 mL: NDC 0517-0381-05

Box of 5 vials of 10 mg/2 mL: NDC 0517-0371-05

Storage:

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°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 or the vial 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)]*.

Manufactured for:
PROVEPHARM SAS
22 rue Marc Donadille
13013 Marseille, France

Ampules manufacturedby:
CENEXI
52 rue Marcel et Jacques Gaucher
94120 Fontenay sous Bois, France

Vials manufactured by: CENEXI HSC
2 rue Louis Pasteur
14200 Hérouville-Saint-Clair, France

Distributed by:
American Regent, Inc.
Shirley, NY 11967
Questions? : 1-800-734-9236
[controlled part number code]

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use METHYLENE BLUE INJECTION safely and effectively. See full prescribing information for METHYLENE BLUE INJECTION.

METHYLENE BLUE Injection, USP for intravenous use

Initial U.S. Approval: 2016

WARNING: SEROTONIN SYNDROME WITH CONCOMITANT USE OF SEROTONERGIC DRUGS AND OPIOIDS

See full prescribing information for complete boxed warning.

Methylene blue may cause serious or fatal serotonergic syndrome when used in combination with serotonergic drugs and opioids. Avoid concomitant use of methylene blue with selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and opioids. (*5.1, 7.1*)

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

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)
- Administer a single dose of 1 mg/kg in patients with moderate or severe renal impairment. (2.2)

--DOSAGE FORMS AND STRENGTHS-

- 5 mg/mL single-dose vial. (3)
- 50 mg/10 mL (5 mg/mL) single-dose vial. (3)
- 10 mg/2 mL (5 mg/mL) single-dose vial. (3)

----------CONTRAINDICATIONS----------

Methylene blue 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 methylene blue, 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 methylene blue 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 Zydus Pharmaceuticals (USA) Inc. at 1-877-993-8779 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).
- Hepatic Impairment: Monitor patients longer for toxicity and drug interactions due to delayed clearance. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 01/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SEROTONIN SYNDROME WITH CONCOMITANT USE OF SEROTONERGIC DRUGS

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- 2.1 Dosage and Administration
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3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SEROTONIN SYNDROME WITH CONCOMITANT USE OF SEROTONERGIC DRUGS AND OPIOIDS

Methylene blue may cause serious or fatal serotonergic syndrome when used in combination with serotonergic drugs and opioids. Avoid concomitant use of methylene blue with selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs) and opioids ***[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]***

1 INDICATIONS AND USAGE

Methylene blue injection 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 methylene blue injection. Do not administer methylene blue injection subcutaneously.
- Monitor vital signs, electrocardiogram and methemoglobin levels during treatment with methylene blue injection and through resolution of methemoglobinemia.
- Administer methylene blue injection 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 methylene blue injection 1 mg/kg may be given one hour after the first dose.
- If methemoglobinemia does not resolve after 2 doses of methylene blue injection, consider initiating alternative interventions for treatment of methemoglobinemia.

2.2 Recommended Dosage for Renal Impairment

- The recommended dosage of methylene blue injection in patients with moderate or severe renal impairment (eGFR 15 - 59 mL/min/1.73 m^2) is a single dose of 1 mg/kg.
- If the methemoglobin level remains greater than 30% or if the clinical symptoms persist 1 hour after dosing, consider initiating alternative interventions for the treatment of methemoglobinemia.

2.3 Preparation and Storage

Each mL of methylene blue injection contains 5 mg methylene blue.

Each 1 mL vial of methylene blue injection contains 5 mg methylene blue. of Each 10 mL vial of methylene blue injection contains 50 mg methylene blue. Each 2 mL vial of methylene blue injection contains 10 mg methylene blue.

Methylene blue injection 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.

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

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

Discard unused portion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 5 mg/mL or 50 mg/10 mL (5 mg/mL) or 10 mg/2 mL (5 mg/mL) clear dark blue solution in single-dose vials.

4 CONTRAINDICATIONS

Methylene blue 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 and Opioids

The development of serotonin syndrome has been reported with the 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 (MAOIs). Opioids and dextromethorphan may increase the risk of developing serotonin syndrome. 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 methylene blue with serotonergic drugs and opioids.

Patients treated with methylene blue should be monitored for the emergence of serotonin syndrome. If symptoms of serotonin syndrome occur, discontinue use of methylene blue, 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 methylene blue injection *[see Drug Interactions (7), Patient Counseling*

Information (17)].

5.2 Hypersensitivity

Anaphylactic reactions to methylene blue class products have been reported. Patients treated with methylene blue should be monitored for anaphylaxis. If anaphylaxis or other severe hypersensitivity reactions (e.g., angioedema, urticaria, bronchospasm) should occur, discontinue use of methylene blue and initiate supportive treatment. Methylene blue 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 methylene blue in patients with methemoglobinemia due to aryl amines such as aniline or sulfa drugs such as dapsone. Monitor response to therapy with methylene blue through resolution of methemoglobinemia. If methemoglobinemia does not respond to 2 doses of methylene blue injection 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 methylene blue to its active form in vivo. Methylene blue 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 methylene blue. 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 methylene blue injection. The anemia may require red blood cell transfusions *[see Adverse Reactions (6.1)]*. Use the lowest effective number of doses of methylene blue injection to treat methemoglobinemia. Discontinue methylene blue and consider alternative treatments of methemoglobinemia if severe hemolysis occurs. Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with methylene blue may result in severe hemolysis and severe anemia. Methylene blue 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 methylene blue 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 methylene blue 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 methylene blue 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 methylene blue have resolved.

5.7 Interference with Laboratory Tests

Methylene blue 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 and Opioids *[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 methylene blue 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 methylene blue 2 mg/kg intravenously. There was one serious adverse reaction reported (syncope due to sinus pauses of 3-14 seconds). The most common (≥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 methylene blue.

Table 1
Adverse Reactions Following Infusion of Methylene Blue Injection 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	

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

Clinically significant drug interactions with methylene blue are described below:
The concomitant use of methylene blue with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. Although the mechanism is not clearly understood, literature reports suggest methylene blue is a potent reversible inhibitor of monoamine oxidase. Avoid concomitant use of methylene blue with medicinal products that enhance serotonergic transmission including antidepressants like SSRIs (selective serotonin reuptake inhibitors), SNRIs (serotonin and norepinephrine reuptake inhibitors), MAOIs (monoamine oxidase inhibitors), bupropion, buspirone, clomipramine, mirtazapine, linezolid, opioids, and dextromethorphan because of the potential for serious CNS reactions, including potentially fatal serotonin syndrome. If the intravenous use of methylene blue cannot be avoided in patients treated with serotonergic medicinal products, choose the lowest possible dose and observe the patient closely for CNS effects for up to 4 hours after administration *[see Warning and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Methylene blue 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 methylene blue 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/m^2) 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/m^2) 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 methylene blue *[see Clinical*

Pharmacology (12.3)].

8.4 Pediatric Use

The safety and effectiveness of methylene blue have been established in pediatric patients. Use of methylene blue is supported by two retrospective case series that included 2 pediatric patients treated with methylene blue 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 methylene blue injection (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

Methylene blue concentrations increased in subjects with renal impairment (eGFR 15 to 89 mL/min/1.73m^2) significantly *[see Clinical Pharmacology (12.3)]*. Adjust methylene blue dosage in patients with moderate or severe renal impairment (eGFR 15 to 59 mL/min/1.73 m^2) *[see Dosage and Administration (2.2)]*. No dose adjustment is recommended in patients with mild renal impairment (eGFR 60 - 89 mL/min/1.73 m^2).

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 methylene blue.

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.

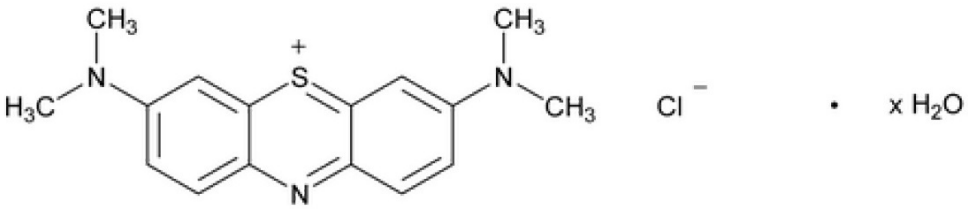
A severe overdosage (single dose of 20 mg/kg or more) of a methylene blue class product caused severe intravascular hemolysis, hyperbilirubinemia and death.

In case of overdose of methylene blue, 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

Methylene blue, USP is an oxidation-reduction agent.

Its chemical name is 3,7-bis(dimethylamino)phenothiazin-5-ium, chloride hydrate. The molecular formula of methylene blue is $C_{16}H_{18}ClN_3S\ xH_2O$ and its molecular weight of 319.86 g/mol for the anhydrous form. The structural formula of methylene blue, USP is:



Methylene blue injection, USP is a sterile solution intended for intravenous administration. Each mL of solution contains 5 mg methylene blue USP and water for injection USP. Additionally, it contains the excipients sodium citrate dihydrate USP and citric acid anhydrous USP in single dose glass vial.

Methylene blue injection, USP 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. Methylene blue injection, USP strength is expressed in terms of trihydrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylene blue is a water soluble thiazine dye that promotes a non-enzymatic redox conversion of metHb 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 metHb 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 methylene blue 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%) Cmax 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 ± standard deviation steady state volume of distribution of a 2 mg/kg dose of methylene blue was 255 L ± 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±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 in humans.

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 into the urine unchanged.

Specific Populations

Renal Impairment

After a single 1 mg/kg dose of methylene blue, $AUC_{0\text{-}96h}$ increased by 52%, 116%, and 192% in subjects with mild (estimated glomerular filtration rate (eGFR) 60 - 89 mL/min/1.73m^2), moderate (eGFR 30 - 59 mL/min/1.73m^2), and severe (eGFR 15 - 29 mL/min/1.732m^2) renal impairment, respectively. C_{max} increased by 42%, 34%, and 15% in subjects with mild, moderate, and severe renal impairment respectively *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*. The half-life was unchanged in patients with mild to moderate renal impairment.

The $AUC_{0\text{-}96h}$ of Azure B after a single 1 mg/kg dose increased by 29%, 94%, and 339% in subjects with mild (estimated glomerular filtration rate (eGFR) 60 - 89 mL/min/1.73 m^2), moderate (eGFR 30 - 59 mL/min/1.73 m^2), and severe (eGFR 15 - 29 mL/min/1.732 m^2) renal impairment, respectively. C_{max} increased by 23%, 13%, and 65% in subjects with mild, moderate, and severe renal impairment, respectively *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)].*

Drug Interactions Studies

Clinical Studies:

The coadministration of 2 mg/kg dose of methylene blue with midazolam (a CYP3A4 substrate), caffeine (a CYP1A2 substrate), warfarin (a CYP2C9 substrate), and dextromethorphan (a CYP2D6 substrate) in a cocktail study did not affect the exposure of these substrates compared to their exposure without methylene blue administration.

In Vitro Studies:
Cytochrome P450 (CYP450) Enzymes:
Methylene blue inhibits CYP isozymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5. Possible time-dependent inhibition of CYP2C9, CYP2D6 and CYP3A4/5 (testosterone as substrate) was also observed. Methylene blue induces CYP1A2 but does not induce CYP2B6 or CYP3A4.

UDP-Glucuronosyltransferase (UGT):
Methylene blue inhibits UGT1A9 and UGT1A4, but did not significantly inhibit UGTs 1A1, 1A3, 1A6, 2B7 or 2B15.

Transporter:
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. Methylene blue inhibits OCT2, MATE1 and MATE2-K.

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 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 methylene blue was assessed on the basis of a methemoglobin decrease of at least 50% within 1 hour after intravenous administration of 1 - 2 mg/kg methylene

blue (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 methylene blue (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

Methylene blue injection, USP is supplied in 10 mL, 2 mL and 1 mL single-dose vials. Each 10 mL vial contains 50 mg of methylene blue, USP as a clear dark blue solution. Each 2 mL vial contains 10 mg of methylene blue, USP as a clear dark blue solution. A box contains five vials.
Each 1 mL vial contains 5 mg of methylene blue, USP as a clear dark blue solution.

Box of 10 vials of 5 mg/1 mL: NDC 70710-xxxx-x
Box of 5 vials of 50 mg/10 mL: NDC 70710-1838-5
Box of 5 vials of 10 mg/2 mL: NDC 70710-1837-5

Storage:
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°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 vial 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 methylene blue: 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 methylene blue during pregnancy *[see Use in Specific populations (8.1)]*.

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

Driving and Using Machines
Advise patients to avoid driving and use of machines during treatment with methylene blue. 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 methylene blue may cause a blue discoloration of the skin and body fluids *[see Adverse Reactions (6.1)]*.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Please address medical inquiries to, MedicalAffairs@zydususa.com or Tel.: 1-877-993-8779.

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