CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204630Orig1s023

Trade Name:	**ProvayBlue**
Generic or Proper Name:	methylene blue
Sponsor:	PROVEPHARM SAS
Approval Date:	February 5, 2024
Indication:	**ProvayBlue** (methylene blue) is an oxidation-reduction agent indicated for the treatment of pediatric and adult parents with acquired methemoglobinemia.

CENTER FOR DRUG EVALUATION AND RESEARCH

204630Orig1s023

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 204630/S-023

SUPPLEMENT APPROVAL

Provepharm
c/o Provepharm Inc.
Attention: Melissa Henry
Director of Regulatory Affairs
100 Springhouse Drive
Suite 105
Collegeville, PA 19426

Dear Melissa Henry:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 3, 2023, and your amendments, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ProvayBlue (methylene blue) injection.

This Prior Approval Supplemental new drug application provides for changes to the design and the product strength description in the labeling for Provayblue (methylene blue) injection.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information) with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled *SPL Standard for Content of Labeling Technical Qs and As* at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and container labels (see table below), as soon as they are available, but no more than 30 days after they are printed.

Date of Submission	Carton and Container Labels
February 1, 2024	• 2ml Ampoule Box • 10ml Ampoule Box • 2ml Vial Box • 10ml Vial Box • 2ml Vial Label • 10ml Vial Label
February 2, 2024	• 2ml Ampule Label • 10ml Ampule Label

Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 204630/S-023.**" Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and

effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Mikee Aguirre, Regulatory Business Process Manager, at mikee.aguirre@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

For:
Ramesh Raghavachari, PhD
Supervisor, Div. of Product Quality Assessment IV
Office of Product Quality Assessment II
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

Rohit Kolhatkar

Digitally signed by Rohit Kolhatkar
Date: 2/05/2024 11:43:03AM
GUID: 57bf531500b52a2eccd5395bec77ebc2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204630Orig1s023

LABELING

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)*

----------RECENT MAJOR CHANGES ----------

Boxed Warning	11/2023
Indications and Usage (1)	01/2024
Warnings and Precautions (5)	11/2023

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

PROVAYBLUE (methylene blue) is an oxidation-reduction agent indicated for the treatment of pediatric and adult patients with acquired methemoglobinemia.

----------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) (0.5%) single-dose ampule. (3)
- 10 mg/2 mL (5 mg/mL) (0.5%) single-dose ampule. (3)
- 50 mg/10 mL (5 mg/mL) (0.5%) single-dose vial. (3)
- 10 mg/2 mL (5 mg/mL) (0.5%) 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 (≥2%) included headache, hypokalemia, diarrhea, hypomagnesemia, myoclonus, nausea, and seizure-like phenomena. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact American Regent at 1-800-734-9236, 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: 02/2024

FULLPRESCRIBINGINFORMATION:CONTENTS.*

***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

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 is indicated for the treatment of pediatric and adult patients with acquired methemoglobinemia.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage and Administration

- Ensure patent venous access prior to administration of PROVAYBLUE. Do not administer PROVAYBLUE subcutaneously.
- 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

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.

Discard unused portion.

3 DOSAGE FORMS AND STRENGTHS

PROVAYBLUE (methylene blue) injection, USP: 50 mg/10 mL (5 mg/mL) (0.5%) or 10 mg/2 mL (5 mg/mL) (0.5%) 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 in adults with acquired methemoglobinemia was assessed in 31 patients who received at least 1 dose of PROVAYBLUE *[see Clinical Studies (14)]*. Most doses administered were 1 mg/kg (82.9%), but doses from 0.78 mg/kg to 2 mg/kg were administered. All patients received at least one dose of PROVAYBLUE; two received two doses, and one received three doses. Serious adverse reactions occurred in 3.2% of patients who received PROVAYBLUE. A serious adverse reaction of seizure-like phenomenon was reported in one patient. Adverse reactions (≥2%) included headache, hypokalemia, diarrhea, hypomagnesemia, myoclonus, nausea, and seizure-like phenomena.

The safety of PROVAYBLUE in pediatric patients with acquired methemoglobinemia was assessed in two retrospective case series that included two pediatric patients treated with PROVAYBLUE and 12 treated with another methylene blue product. The case series included patients in the following age groups: 3 neonates (<1 month), 4 infants (1 month to <2 years), 4 children (2 years to <12 years), and 3 adolescents (12 years to <17 years). The safety profile in pediatric patients was similar to that in adult patients.

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

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

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 for the treatment of acquired methemoglobinemia 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

Clinical studies of PROVAYBLUE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. PROVAYBLUE 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.

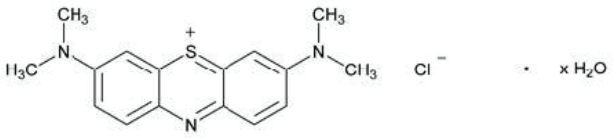
A severe overdosage (single dose of 20 mg/kg or more) of a methylene blue class product caused severe intravascular hemolysis, hyperbilirubinemia and death.

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 USP is a sterile solution intended for intravenous administration. Each mL of solution contains 5 mg methylene blue and water for injection. PROVAYBLUE **(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. 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 in the treatment of patients with methemoglobinemia was evaluated in 31 adult patients with acquired methemoglobinemia across two studies: NCT03395223, a prospective, interventional, open-label, single-arm study, and NCT03542760, a prospective, multicenter, observational registry. Of the 31 subjects enrolled 90% were white, 10% were black, 58% were female, and 42% were male. Hispanic or Latino was 9.7%; non-Hispanic or Latino was 67.7%, and ethnicity data were missing for 22.6%. The mean age was 45.6 years, and the ages ranged from 19 to 72 years. Each individual received at least 1 intravenous dose of PROVAYBLUE; two received 2 doses and one received 3 doses. Most doses administered were 1 mg/kg (82.9%), but doses from 0.78 mg/kg to 2 mg/kg were administered. The recommended PROVAYBLUE dose is 1 mg/kg; lower or greater doses are not recommended. The maximum recommended number of doses is two *[see Dosage and Administration (2.1)]*.

In total, 29 of the 31 (93.5%) subjects had post treatment methemoglobin (metHb) assessment; 28 of the 29 subjects had baseline metHb with a mean concentration of 18.4% and a range of 4.1% to 74.4%. Twenty-six of the 28 (92.9%) subjects who had baseline metHb had at least a 50% reduction in metHB from baseline in their first assessment post baseline. This first post dosing assessment occurred from 0.2 to 27.3 hours from the end of first PROVAYBLUE infusion with a median time of 2.7 hours. There were 12 subjects that had baseline metHb and had metHb assessed within 2 hours of the end of the first PROVAYBLUE treatment; 9 of the 12 (75%; 95% CI (42.8%,93.3%)) had at least a 50% reduction in metHb at 1 hour postdosing.

Available vital sign data including blood pressure, heart rate and respiratory rate were reviewed at baseline and compared to data collected within 2 hours post PROVAYBLUE infusion. Prior to treatment with PROVAYBLUE, 16 of the 23 (70%) of patients had a respiratory rate exceeding the upper limit of normal (≥ 20 bpm). Of these, 10 of the 16 (63%) experienced a normalization of respiratory rate within 2 hours post ProvayBlue infusion. There was minimal impact on other vital signs.

At baseline, the most common prespecified signs and symptoms of methemoglobinemia (reported by ≥2 subjects [6.5%] overall) were cyanosis (32.3%), dyspnea (25.8%), fatigue (25.8%), depressed CNS (9.7%), headache (6.5%), weakness (6.5%), and dizziness (6.5%). Following treatment with PROVAYBLUE, signs and symptoms of methemoglobinemia improved.

The efficacy of PROVAYBLUE in the treatment of methemoglobinemia in pediatric patients was assessed in 14 patients in two retrospective case series (2 patients received PROVAYBLUE and 12 who received another methylene blue product). The ages ranged from 6 days to 16 years. The efficacy outcomes were consistent across the pediatric and adult populations.

16 HOW SUPPLIED/STORAGE AND HANDLING

PROVAYBLUE (methylene blue) injection, USP: 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 (0.5%): NDC 0517-0374-05

Box of 5 ampules of 10 mg/2 mL (0.5%): NDC 0517-0125-05

Box of 5 vials of 50 mg/10 mL (0.5%): NDC 0517-0381-05

Box of 5 vials of 10 mg/2 mL (0.5%): 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

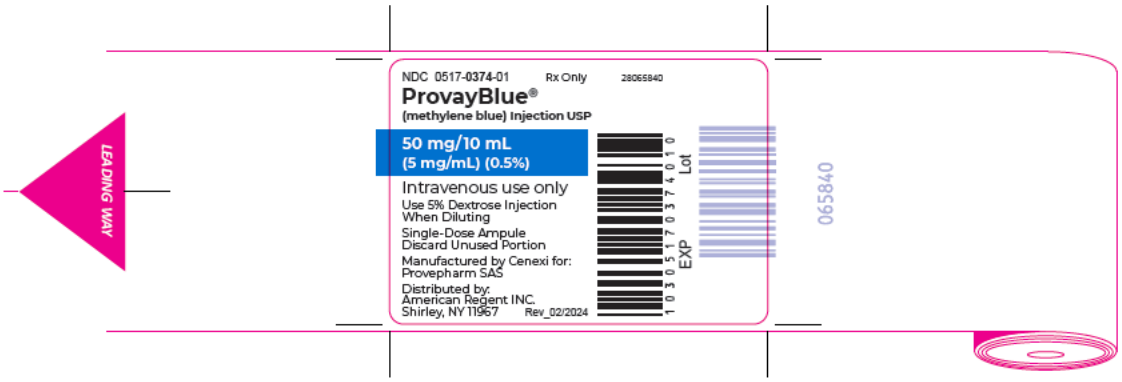
Ampules manufactured
by: CENEXI
52 rue Marcel et Jacques Gaucher
94120 Fontenay sous Bois, France

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

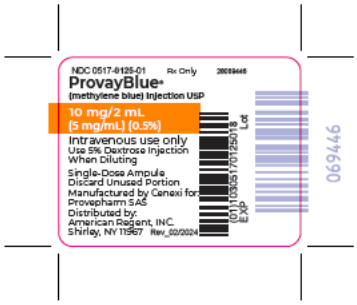
Distributed by:
American Regent, Inc.
Shirley, NY 11967
Questions? : 1-800-734-9236

[controlled part number code]

(b) (4)

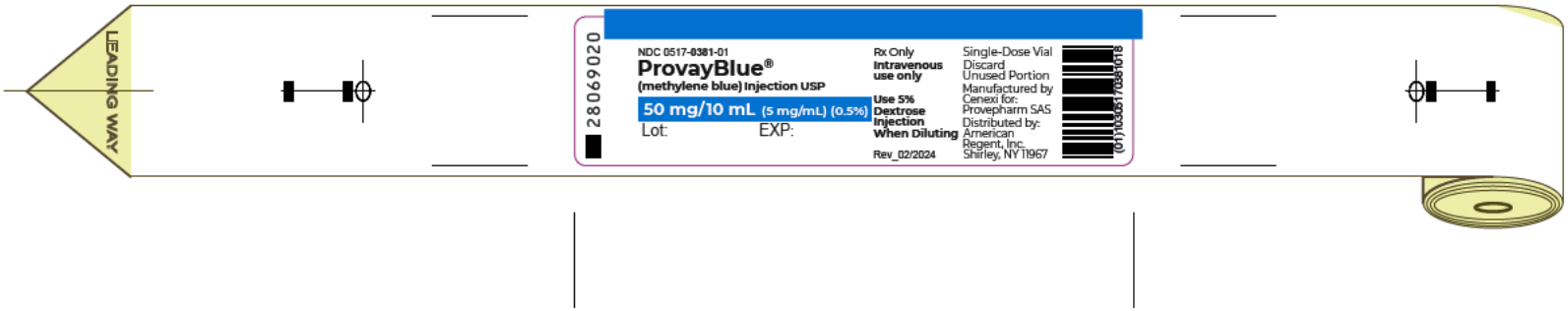

LEADING WAY
NDC 0517-0374-01 Rx Only 28065840
ProvayBlue®
(methylene blue) Injection USP
50 mg/10 mL
(5 mg/mL) (0.5%)
Intravenous use only
Use 5% Dextrose Injection
When Diluting
Single-Dose Ampule
Discard Unused Portion
Manufactured by Cenexi for:
Provepharm SAS
Distributed by:
American Regent INC.
Shirley, NY 11967
Rev_02/2024
(10) 05170374010
Lot
EXP
065840

(b) (4)


NDC 0517-6125-01 Rx Only 20069446
ProvayBlue®
(methylene blue) Injection USP
10 mg/2 mL
(5 mg/mL) (0.5%)
Intravenous use only
Use 5% Dextrose Injection
When Diluting
Single-Dose Ampule
Discard Unused Portion
Manufactured by Cenexi for
Provepharm SAS
Distributed by
American Regent, INC.
Shirley, NY 11967 Rev_02/2024
(01)10305170125018
Lot
EXP
069446


LEADING WAY
28069018
NDC 0517-0371-01
ProvayBlue®
(methylene blue) Injection USP
10 mg/2 mL (5 mg/mL) (0.5%)
Lot:
EXP:
Rx Only
Intravenous use only
Use 5% Dextrose Injection When Diluting
Single-Dose Vial. Discard Unused portion
Manufactured by Cenexi for:
Provepharm SAS
Distributed by:
American Regent, INC.
Shirley, NY 11967
Rev_02/2024
(01) 10305170371019

(b) (4)


LEADING WAY
28069020
NDC 0517-0381-01
ProvayBlue®
(methylene blue) Injection USP
50 mg/10 mL (5 mg/mL) (0.5%)
Lot:
EXP:
Rx Only
Intravenous use only
Use 5% Dextrose Injection When Diluting
Rev_02/2024
Single-Dose Vial
Discard Unused Portion
Manufactured by Cenexi for: Provepharm SAS
Distributed by: American Regent, Inc. Shirley, NY 11967
(01)10305170381018

(b) (4)

Rx only

NDC 0517-**0374**-05

ProvayBlue®
(methylene blue) Injection USP

5 Single-Dose Ampules.
Discard Unused Portion

50 mg/10 mL (5 mg/mL) (0.5%)

Intravenous use only
For slow intravenous injection
Use 5% Dextrose Injection When Diluting

Distributed by:

AMERICAN REGENT™

PROVEPHARM

Manufactured by:
CENEXI
52 rue Marcel et Jacques Gaucher
94120 Fontenay sous Bois
France

PROVEPHARM

28065839

ProvayBlue®
(methylene blue) Injection USP
50 mg/10 mL (5 mg/mL) (0.5%)
Intravenous use only
For slow intravenous injection
Use 5% Dextrose Injection When Diluting

5 Single-Dose Ampules
Discard Unused Portion
PROVEPHARM

ProvayBlue®
(methylene blue) Injection USP
50 mg/10 mL (5 mg/mL) (0.5%)
Intravenous use only
For slow intravenous injection
Use 5% Dextrose Injection When Diluting

5 Single-Dose Ampules
Discard Unused Portion
PROVEPHARM

Patented : US 8,765,942; US 9,227,945

Each 10 mL ampule contains 50 mg methylene blue dissolved in Water for Injection, USP **- Intravenous use only.**

See package insert for full prescribing information.

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].

Do not refrigerate or freeze.

Keep the ampule in the original package. Protect from light.

For single dose only.

Any solution remaining in the opened ampule must be discarded.

Manufactured by CENEXI for:
Provepharm SAS
13013 Marseille, France

Distributed by:
American Regent, Inc.
Shirley, NY 11967

www.provayblue.com

Rev_02/2024

ProvayBlue is a registered trademark of Provepharm.

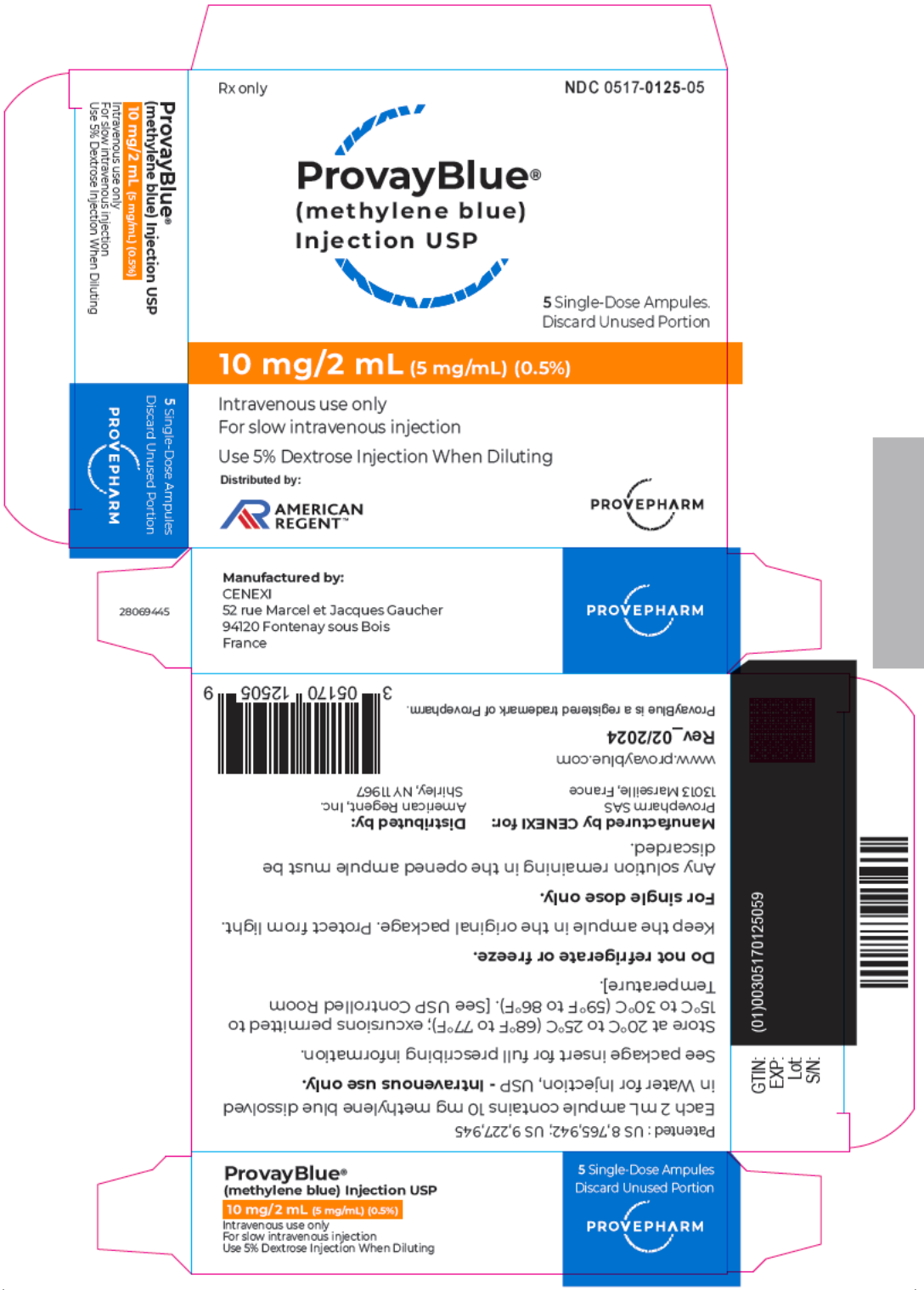
3 05170 37405 1

GTIN:
EXP:
Lot:
S/N:

(01) 00305170374051

28065839

(b) (4)


Rx only
NDC 0517-0125-05
ProvayBlue®
(methylene blue)
Injection USP
5 Single-Dose Ampules.
Discard Unused Portion
10 mg/2 mL (5 mg/mL) (0.5%)
Intravenous use only
For slow intravenous injection
Use 5% Dextrose Injection When Diluting
Distributed by:
AMERICAN REGENT™
PROVEPHARM
ProvayBlue® (methylene blue) Injection USP
10 mg/2 mL (5 mg/mL) (0.5%)
Intravenous use only
For slow intravenous injection
Use 5% Dextrose Injection When Diluting
5 Single-Dose Ampules
Discard Unused Portion
PROVEPHARM
28069445
Manufactured by:
CENEXI
52 rue Marcel et Jacques Gaucher
94120 Fontenay sous Bois
France
PROVEPHARM
3 05170 12505 9
ProvayBlue is a registered trademark of Provepharm.
Rev_02/2024
www.provayblue.com
Manufactured by CENEXI for:
Provepharm SAS
13013 Marseille, France
Distributed by:
American Regent, Inc.
Shirley, NY 11967
Any solution remaining in the opened ampule must be discarded.
For single dose only.
Do not refrigerate or freeze.
Keep the ampule in the original package. Protect from light.
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].
See package insert for full prescribing information.
Each 2 mL ampule contains 10 mg methylene blue dissolved in Water for Injection, USP - Intravenous use only.
Patented : US 8,765,942; US 9,227,945
ProvayBlue®
(methylene blue) Injection USP
10 mg/2 mL (5 mg/mL) (0.5%)
Intravenous use only
For slow intravenous injection
Use 5% Dextrose Injection When Diluting
5 Single-Dose Ampules
Discard Unused Portion
PROVEPHARM
GTIN:
EXP:
Lot:
S/N:
(01)00305170125059
28069445
(b) (4)
(b) (4)

Bar prints 100mm @ 100%

ProvayBlue®
(methylene blue) Injection USP

50 mg/10 mL (5 mg/mL) (0.5%)

Intravenous use only
For slow intravenous injection
Use 5% Dextrose Injection When Diluting

5 Single-Dose Vials
Discard Unused Portion

PROVEPHARM

28069019

(01)00305170381059

Each 10 mL vial contains 50 mg methylene blue dissolved in Water for Injection, USP

Intravenous use only.

See package insert for full prescribing information.

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].

Do not refrigerate or freeze.

Keep the vial in the original package. Protect from light.

For single dose only. Any solution remaining in the opened vial must be discarded.

Manufactured by:
Cenexi HSC
2 rue Louis Pasteur
14200 Hérouville-Saint-Clair, France

Manufactured by CENEXI for:
Proveplharm SAS
13013 Marseille, France

Distributed by:
American Regent, Inc.
Shirley, NY 11967

ProvayBlue is a registered trademark of Proveplharm.
www.provayblue.com

Rev_02/2024

Patented: US 8,765,942; US 9,227,945

GTIN
(01)00305170381059
S/N
EXP
LOT

Rx only

NDC 0517-**0381**-05

ProvayBlue®
(methylene blue) Injection USP

50 mg/10 mL (5 mg/mL) (0.5%)

Intravenous use only
For slow intravenous injection
Use 5% Dextrose Injection When Diluting

5 Single-Dose Vials
Discard Unused Portion

PROVEPHARM

Distributed by:
AMERICAN REGENT™


ProvayBlue®
(methylene blue) Injection USP
10 mg/2 mL (5 mg/mL) (0.5%)
Intravenous use only
For slow intravenous injection
Use 5% Dextrose Injection When Diluting
5 Single-Dose Vials
Discard Unused Portion
PROVEPHARM
28069017
[01)00305170371050
Patented: US 8,765,942; US 9,227,945
Each 2 mL vial contains 10 mg methylene blue dissolved in Water for Injection, USP
intravenous use only.
See package insert for full prescribing information.
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].
Do not refrigerate or freeze.
Keep the vial in the original package. Protect from light.
For single dose only. Any solution remaining in the opened vial must be discarded.
Manufactured by:
Cenexi HSC
2 rue Louis Pasteur
14200 Hérouville-Saint-Clair, France
Manufactured by CENEXI HSC for:
Proveplarm SAS
13013 Marseille, France
Distributed by:
American Regent, Inc.
Shirley, NY 11967
www.provayblue.com
ProvayBlue is a registered trademark of Proveplarm.
Rev_02/2024
S/N
EXP
LOT
(01)00305170371050
GTIN
Rx only
NDC 0517-0371-05
ProvayBlue®
(methylene blue)
Injection USP
10 mg/2 mL (5 mg/mL) (0.5%)
Intravenous use only
For slow intravenous injection
Use 5% Dextrose Injection When Diluting
Distributed by:
AMERICAN REGENT
5 Single-Dose Vials
Discard Unused Portion
PROVEPHARM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204630Orig1s023

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 2, 2024
Requesting Office or Division:	Office of Pharmaceutical Quality (OPQ)
Application Type and Number:	NDA 204630 S-023
Product Name, Dosage Form, and Strength:	ProvayBlue (methylene blue) Injection Ampule: 50 mg/10 mL (5 mg/mL) (0.5%) and 10 mg/2 mL (5 mg/mL) (0.5%) Vial: 50 mg/10 mL (5 mg/mL) (0.5%) and 10 mg/2 mL (5 mg/mL) (0.5%)
Applicant/Sponsor Name:	Provepharm SAS (Provepharm)
TTT ID #:	2023-6089-3
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on February 2, 2024 for ProvayBlue. We reviewed the revised container labels for ProvayBlue (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

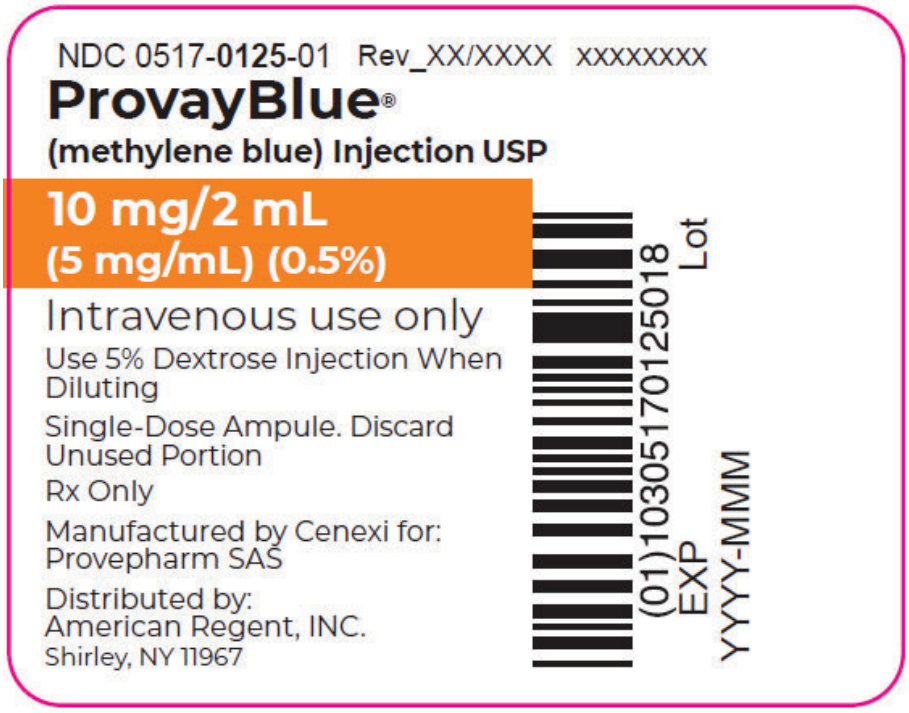
2 CONCLUSION

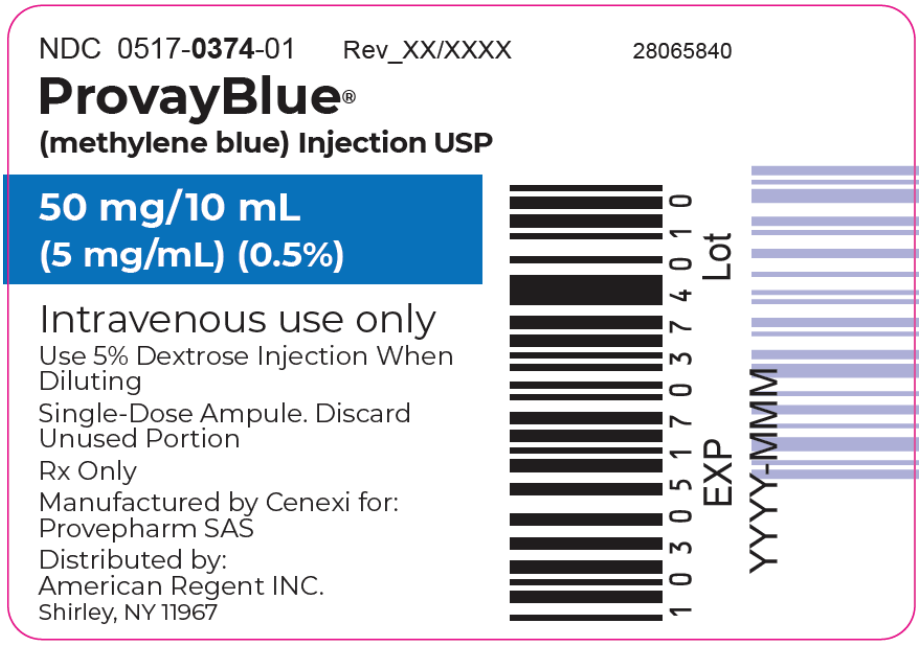
The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Black, S. Label and Labeling Review for ProvayBlue (NDA 204630 S-023). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 FEB 01. TTT ID No.: 2023-6089-2.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 2, 2024

Container label – Ampules





This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUE L BLACK
02/05/2024 12:22:19 PM

NICOLE F IVERSON
02/05/2024 01:53:27 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 1, 2024
Requesting Office or Division:	Office of Pharmaceutical Quality (OPQ)
Application Type and Number:	NDA 204630/S-023
Product Name, Dosage Form, and Strength:	ProvayBlue (methylene blue) Injection Ampule: 50 mg/10 mL (5 mg/mL) (0.5%) and 10 mg/2 mL (5 mg/mL) (0.5%) Vial: 50 mg/10 mL (5 mg/mL) (0.5%) and 10 mg/2 mL (5 mg/mL) (0.5%)
Applicant/Sponsor Name:	Provepharm SAS (Provepharm)
TTT ID #:	2023-6089-2
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on February 1, 2024 for ProvayBlue. We reviewed the revised container labels and carton labeling for ProvayBlue (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations for the container labels and carton labeling. In addition, the Applicant further revised the following:

- Relocated "Single-Dose Vial. Discard Unused portion" (b) (4) to the side right panel (vial labels)

[a] Black, S. Label and Labeling Review for ProvayBlue (NDA 204630/S-023). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 JAN 19. TTT ID No.: 2023-6089-1.

- Relocated the revision date (b) (4) to the middle panel (50 mg vial label)

We find the revised vial container labels and carton labeling (vial and ampule) acceptable from a medication error perspective. However, the revised ampule container labels are unacceptable from a medication error perspective as the (b) (4) (b) (4) not prominent.

3 RECOMMENDATIONS FOR PROVEPHARM SAS (PROVEPHARM)

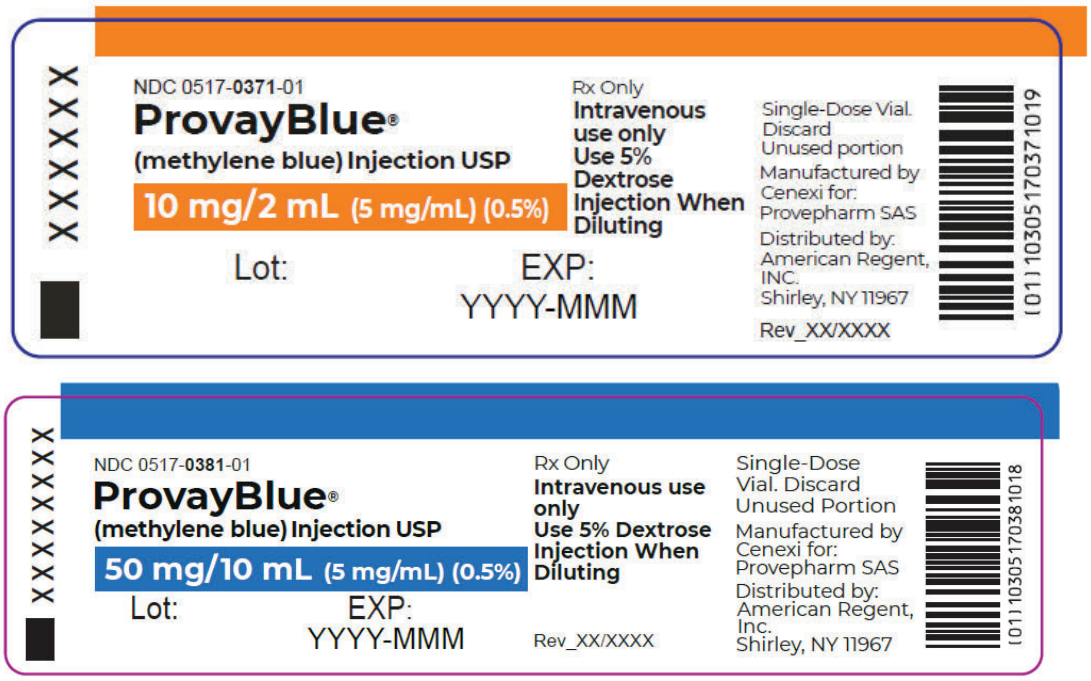
We recommend the following be implemented prior to approval of this NDA supplement:

A. Container label - Ampules

1. As currently presented, the (b) (4) lacks prominence. Lack of prominence of the (b) (4) may contribute to product selection medication errors. See 21CFR201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter. Increase the prominence (b) (4) in accordance with 21 CFR 201.15(a)(6). Take into account all pertinent factors including font size, type, and color; background contrast; and statement location. For (b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Container label – Vials



Carton labeling – Ampules

4 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUE L BLACK
02/01/2024 09:46:23 PM

NICOLE F IVERSON
02/02/2024 01:21:22 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 19, 2024
Requesting Office or Division:	Office of Pharmaceutical Quality (OPQ)
Application Type and Number:	NDA 204630/S-023
Product Name, Dosage Form, and Strength:	ProvayBlue (methylene blue) Injection Ampule: 50 mg/10 mL (5 mg/mL) and 10 mg/2 mL (5 mg/mL) Vial: 50 mg/10 mL (5 mg/mL) and 10 mg/2 mL (5 mg/mL)
Applicant/Sponsor Name:	Provepharm SAS (Provepharm)
TTT ID #:	2023-6089-1
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on November 2, 2023 for ProvayBlue. We reviewed the revised container labels and carton labeling for ProvayBlue (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented most of our recommendations. We note the format of the expiration date as YYYY-MMM-DD (carton labeling) and YYYY-MMM (container labels).

The below recommendations were not implemented; however, we find these acceptable.

[a] Black, S. Label and Labeling Review for ProvayBlue (NDA 204630/S-023). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 OCT 06. TTT ID No.: 2023-6089.

- Relocation of the route of administration and dilution information to the PDP under the strength (as the lot number and expiration date couldn't be moved to any other location on the label). We note this information was bolded for prominence. (Vial Label)
- "Single-Dose Vial. Discard Unused Portion" statement was not relocated to the PDP of the vial label (but rather to the middle panel and the barcode was relocated to the far right). (Vial label)

Lastly, our recommendation to remove the percentage (0.5%) strength was not implemented as the Applicant believes the expression of the percentage strength in addition to the quantity per total volume is necessary to differentiate from and minimize medication errors with the unapproved methylene blue 1% products. The Office of Pharmaceutical Quality (OPQ) disagreed with ProvePharm's rationale to include the percentage strength based on an unapproved product, however, they deferred to the Clinical team in the Office of New Drugs (OND) and DMEPA to determine if including the percentage strength can minimize the potential for errors.

We reached out to the Clinical team to clarify the clinical consequences of overdose if the 1% product is used to prepare a dose of 0.5% product or underdose if the 0.5% product is used to prepare a dose of 1% product. Clinical confirmed that the both overdose and underdose errors may have serious clinical consequences (i.e., underdose may be life threatening if methemoglobinemia is not treated; overdose may result in hypotension, wheezing and reduced oxygenation).

We conducted a FAERS search (see Appendix B) and did not identify any postmarketing reports of mix-ups between ProvayBlue (5 mg/mL) and the unapproved methylene blue products (10 mg/mL). In addition, with guidance from the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) Postmarket Medication Error Team (PMET), we sent an information request (IR) to ProvePharm to request postmarket medication error and adverse event cases and complaints related to confusion between ProvayBlue and the unapproved 1% methylene blue products, as well as wrong dose medication errors due to lack of the percentage strength. See Appendix C for the full information request. In response, ProvePharm did not identify any reports with the 1% unapproved methylene blue products and provided two related medical inquiries (i.e., question regarding difference between discontinued old methylene blue product and new the FDA ProvayBlue and question if this solution is 1% or 0.5%). Given this additional information, we reached out to Clinical to get their input if the percentage strength of 0.5% should be added to the labels and labeling in addition to total quantity/total volume. In response, Clinical agreed with the Applicant that adding 0.5% to the label would help decrease errors.

We considered if adding the percentage strength of 0.5% to the labels and labeling would decrease the risk of selection errors. In the event that the wrong product strength was selected, an overdose (double dose) and underdose (half the dose) error may occur. As noted by Clinical,

both overdose and underdose errors may have serious clinical consequences. Therefore, in this case, despite the absence of postmarketing medication error reports between ProvayBlue and the unapproved methylene products, we find adding the percentage strength of 0.5% offers an incremental layer of safety and differentiation which may help to mitigate selection errors. On January 10, 2024, we informed OPQ of our conclusion and confirmed the presentation of the percentage as 10 mg/2 mL (5 mg/mL) (0.5%) and 50 mg/10 mL (5 mg/mL) (0.5%) is acceptable on the container labels and carton labeling. We also informed OPQ that similar changes to the strength presentation is needed in the Prescribing Information for consistency with the container labels and carton labeling.

3 RECOMMENDATIONS FOR OFFICE OF PHARMACEUTICAL QUALITY (OPQ)

A. Highlights of Prescribing Information

1. Dosage Forms and Strengths

a. For consistency with the container labels and carton labeling, we recommend adding the percentage strength of 0.5% and presenting as follows:

i. 50 mg/10 mL (5 mg/mL) (0.5%) single-dose ampule. (3)
ii. 10 mg/2 mL (5 mg/mL) (0.5%) single-dose ampule. (3)
iii. 50 mg/10 mL (5 mg/mL) (0.5%) single-dose vial. (3)
iv. 10 mg/2 mL (5 mg/mL) (0.5%) single-dose vial. (3)

B. Prescribing Information

1. Dosage Forms and Strengths

a. For consistency with the container labels and carton labeling, we recommend adding the percentage strength of 0.5% and presenting as follows:

i. Injection: 50 mg/10 mL (5 mg/mL) (0.5%) or 10 mg/2 mL (5 mg/mL) (0.5%) clear dark blue solution in single-dose ampules or single-dose vials.

2. How Supplied/Storage and Handling

a. For consistency with the container labels and carton labeling, we recommend adding the percentage strength of 0.5% and presenting as follows:

i. 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 (0.5%): NDC 0517-0374-05
Box of 5 ampules of 10 mg/2 mL (0.5%): NDC 0517-0125-05
Box of 5 vials of 50 mg/10 mL (0.5%): NDC 0517-0381-05

Box of 5 vials of 10 mg/2 mL (0.5%): NDC 0517-0371-05

4 RECOMMENDATIONS FOR PROVEPHARM SAS (PROVEPHARM)

We recommend the following be implemented prior to approval of this NDA supplement:

A. General Comments (Container Labels and Carton Labeling)

1. Upon further consideration, we agree with your proposal to include the percentage strength of 0.5% on the container labels and carton labeling to mitigate selection errors. As currently proposed, (b) (4) (b) (4) (b) (4). Therefore, we recommend presenting the percentage strength as:
    a. 10 mg/2 mL (5 mg/mL) (0.5%)
    b. 50 mg/10 mL (5 mg/mL) (0.5%)

5 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

On 11/21/2023, we searched FAERS using the criteria in the table below and identified 29 cases. We individually reviewed the cases and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[b] We excluded 26 because they described medication errors not related to methylene blue (n=12), lack of effect (n=2), off label use (n=4), drug-drug interaction (n=5) and wrong drug (n=3).

Table 2. Criteria Used to Search FAERS	
Active Ingredient:	methylene blue
Drug Role	Suspect
Event:	SMQ *Medication errors* (Narrow)
Country (Derived):	USA

B.2 Results

Our search identified 29 cases, of which 3 cases described errors relevant for this review.

Wrong Technique (n=1)

- One case (FAERS 13786289) describes seven patients who received ProvayBlue diluted in 0.9% Sodium Chloride Injection, which was the hospital's standard diluent for vasoplegia syndrome. The institution did not have reports of precipitation although they acknowledge it cannot be ruled out. To mitigate wrong technique errors they have rebuilt their dilutions in 5% Dextrose Injection and updated their guidelines. Root causes include drug shortage, knowledge deficit of practitioner – unfamiliar/ inexperienced as with the dilution requirements for a drug shortage product manufactured in France by another company. Although the error reached the patient, there was no patient harm.

Potential wrong drug error (n=1)

- One case (FAERS 13409207) states "the old methylene blue in a concentration of 10 mg/mL is not available and what can be purchased is a newer FDA approved product with a brand name of Provayblue. The problem is that the new product comes in a concentration of 5 mg/mL. Seems like there might be a potential for error." No additional information provided.

[b] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

Wrong dose (n=1)

- One case (FAERS 4251520) describe an overdose (e.g., child receives 100 mg of methylene blue vs. a normal dose for a child weighing 26 lbs is 20 mg-30 mg). Outcomes include "vomited blue material and had blue urine (Day 1 of overdose), hemolysis of red blood cells secondary to the methylene blue and heinz body formation, anemic (Day 2 of overdose), temporary renal shutdown (Day 3 of overdose), and urine green, stool was blue-green (Day 4 of overdose)." No contributing factors were provided.

We reviewed the Prescribing Information and note that Section 2.3 *Preparation* (b) (4) states "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. Avoid diluting with sodium chloride solutions, because it has been demonstrated that chloride reduces the solubility of methylene blue." In addition, the container labels (side panel) and carton labeling (principal display panel) contain a statement "Use 5% Dextrose in Water when Diluting". We also note the recommended dose is clearly stated in Section 2.1 *Dosage and Administration* of the Prescribing Information as "Administer PROVAYBLUE 1 mg/kg intravenously over 5-30 minutes." Therefore, we have no recommendations at this time.

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case numbers and manufacturer control numbers for the cases relevant for this review.

FAERS Case **Number**	Manufacturer Control **Number**	**Version Number**
4251520	Not provided	1
13409207	Not provided	1
13786289	Not provided	1

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX C. INFORMATION REQUEST

DMEPA FDA Information Request sent on November 7, 2023:

We refer to your response received on November 2, 2023. We are reviewing your response and have the following information request. We are unaware of any postmarketing reports of mix-ups between ProvayBlue and the unapproved 1% methylene blue products, or any wrong dose administration errors related to the lack of the percentage strength (0.5%) on ProvayBlue labels and labeling. To assist us in our evaluation of your request to add the percentage strength (0.5%), please submit an analysis of your U.S. postmarket serious and non-serious medication error and adverse event cases and complaints related to confusion between your product and the unapproved 1% methylene blue products, as well as wrong dose medication errors due to lack of the percentage strength. Additionally, provide a line listing of the cases and complaints that includes the product strength, contributing factors to the errors, adverse events, and outcomes.

Applicant response received on November 21, 2023:

- See Cover Letter: \\CDSESUB1\evsprod\NDA204630\0238\m1\us\12-cover-letters\0238-cover-letter-response-to-ir-for-s023-labeling-update-21.pdf
- Line listing: \\CDSESUB1\EVSPROD\nda204630\0238\m1\us\111-information-amendment\0238-line-listings-may-2020.pdf

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUE L BLACK
01/19/2024 11:27:31 AM

NICOLE F IVERSON
01/19/2024 02:18:43 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204630Orig1s023

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 204630 SUPPL # 021 HFD #

Trade Name ProVay Blue

Generic Name methylene blue

Applicant Name Provepharm SAS

Approval Date, If Known: January 8, 2024

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)/SE7

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (c) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 1795 B&R #328 Tab

NDA# 001049 Rinatin Tab

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to

3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

- Interventional Study, PVP-2016003
- Observational Study, HQF-METHB-2018001

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

- Interventional Study, PVP-2016003
- Observational Study, HQF-METHB-2018001

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 118156	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☒
		! Explain: This was an observational study and not carried out under an IND.

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☒	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☒
Explain:	! Explain: Study HQF-METHB-2018001, was an academically sponsored, real-world registry to collect data.

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

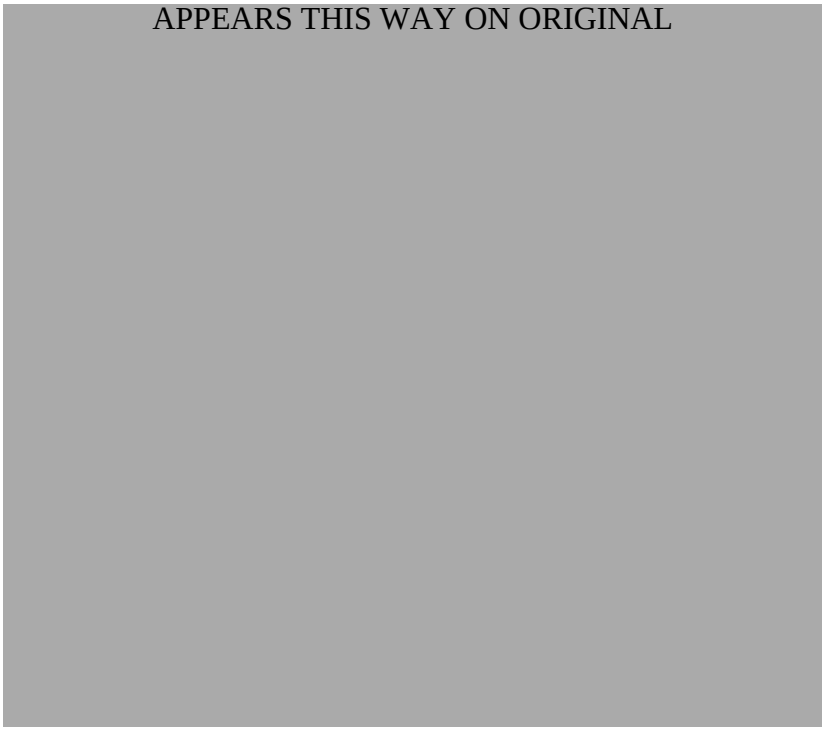
If yes, explain:

==========

Name of person completing form: Courtney Hamilton
Title: Senior Regulatory Project Manager
Date: 1/12/2024

Name of Division Director signing form: Tanya Wroblewski
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12



This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

COURTNEY V HAMILTON
01/17/2024 08:51:18 AM

TANYA M WROBLEWSKI
01/17/2024 10:38:20 AM