American Regent Launches a New Vial Presentation

ProvayBlue®
(methylene blue) Injection, USP

ProvayBlue® is supplied as a 10 mL single-dose vial.

ProvayBlue®, the first and only FDA-approved, USP standard methylene blue injection, is now available in a 10 mL single-dose vial[1]

Melville, NY – June 28, 2022: American Regent, Inc. and Provepharm Life Solutions are pleased to announce the availability of ProvayBlue® (methylene blue) Injection, USP in a 10 mL single-dose vial. ProvayBlue® is indicated for the treatment of pediatric and adult patients with acquired methemoglobinemia. ProvayBlue® was approved by the US Food and Drug Administration (FDA) under accelerated approval. The new vial presentation joins the ampule that American Regent and Provepharm Life Solutions have been marketing since 2016. View more product specific information.

Provepharm has licensed exclusive rights to American Regent, Inc. to market and distribute ProvayBlue® in the United States. ProvayBlue® may cause serious or life-threatening side effects when used in combination with serotonergic drugs. Please see the Important Safety Information, including Boxed Warning, at the bottom of this press release and in the Full Prescribing Information.

"We are pleased that our continued partnership with Provepharm provides the opportunity to expand our line of ProvayBlue® products to better meet the needs of providers and patients," stated Joann Gioia, Vice President and Chief Commercial Officer at American Regent, Inc.

ProvayBlue® (methylene blue) Injection, USP is available for immediate shipment. Customers can order ProvayBlue® through their wholesaler/distributor, or by contacting our Customer Support Group at 1-800-645-1706.

ProvayBlue® (methylene blue) Injection, USP is supplied as follows:

Pack NDC#	Strength	Supplied as	Shelf pack
0517-0381-05 **NEW**	50 mg/10 mL	10 mL Single-dose vial	5
0517-0374-05	50 mg/10 mL	10 mL Single-dose ampule	5

Please see the Important Safety Information, including Boxed Warning, below. To view the Full Prescribing Information, please click here. For additional information on ProvayBlue® visit www.americanregent.com.

265 Broadhollow Road \\ 4th Floor \\ Melville, NY 11747
T 631.924.4000 \\ **F** 631.924.1731 \\ americanregent.com

A Daiichi Sankyo Group Company

References:
1. US Food and Drug Administration, Center for Drug Evaluation and Research. ProvayBlue® NDA 204630/s-011 Approval Letter, April 8, 2016.
2. ProvayBlue® (methylene blue) Injection, USP [package insert]. Shirley, NY: American Regent, Inc.; 12/2021.

ProvayBlue® (methylene blue) Injection, USP

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

INDICATIONS AND USAGE
ProvayBlue® (methylene blue) injection, USP is indicated for the treatment of pediatric and adult patients with acquired methemoglobinemia.
This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification of clinical benefit in subsequent trials.

IMPORTANT SAFETY INFORMATION

WARNING: SEROTONIN SYNDROME WITH CONCOMITANT USE OF SEROTONERGIC DRUGS

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

DOSAGE AND ADMINISTRATION

Preparation and Storage
ProvayBlue® is hypotonic and may be diluted before use in a solution of 50 mL 5% Dextrose Injection in order to avoid local pain, particularly in the pediatric population. Use the diluted solution immediately after preparation.
Avoid diluting with sodium chloride solutions, because it has been demonstrated that chloride reduces the solubility of methylene blue.

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

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

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

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

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

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

Hemolytic Anemia
Hemolysis can occur during treatment of methemoglobinemia with ProvayBlue®. Use the lowest effective number of doses of ProvayBlue® to treat methemoglobinemia. Discontinue ProvayBlue® and consider alternative treatments of methemoglobinemia if severe hemolysis occurs.

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

Interference with In Vivo Monitoring Devices
The presence of methylene blue in the blood may result in an underestimation of the oxygen saturation reading by pulse oximetry.

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

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

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

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

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

Other adverse reactions reported to occur following administration of methylene blue class products include, but are not limited to, the following: hemolytic anemia, hemolysis, hyperbilirubinemia, methemoglobinemia; palpitations, tachycardia; eye pruritus, ocular hyperemia, vision blurred; abdominal pain lower, dry mouth, flatulence, glossodynia, tongue eruption; death, infusion site extravasation, infusion site induration, infusion site pruritus, infusion site swelling, infusion site urticaria, peripheral swelling, thirst; elevated liver enzymes; myalgia; dysuria; nasal congestion, oropharyngeal pain, rhinorrhea, sneezing; necrotic ulcer, papule, phototoxicity; and hypertension.

USE IN SPECIFIC POPULATIONS

Pregnancy and Lactation

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

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

Renal Impairment

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

Hepatic Impairment

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

OVERDOSAGE

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

For additional safety information, including BOXED WARNING, please see Full Prescribing Information.

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

REF-0131 12/2021

You are encouraged to report adverse drug events (ADEs) to American Regent:
E pv@americanregent.com **F** 1-610-650-0170; **T** 1-800-734-9236

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

Drug information:
1-888-354-4855
(9:00 am – 5:00 pm Eastern Time, Monday – Friday)
www.americanregent.com/medical-affairs

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

About American Regent

American Regent, Inc., a Daiichi Sankyo Group company, is a leading injectable manufacturer. For over 50 years, American Regent has been developing, manufacturing and supplying quality generic and branded injectables for healthcare providers. For nearly 20 years, we have been a leader in IV iron therapy.

American Regent is committed to US based manufacturing. To that end, over the last several years, we have made significant investments in expanding and modernizing our manufacturing facilities in Ohio and New York. This expansion will nearly double our capacity and allow us to better serve our customers now and in the future.

Speed counts. Flexibility matters. Reliability and quality are paramount. Because patients should never have to wait for the medications they need.

For more information, please visit www.americanregent.com.

About Provepharm Life Solutions

Provepharm Life Solutions is a French private pharmaceutical company. With more than 20 years of experience, the company finds new uses for well-known, mature molecules, in particular antidotes and surgical dyes. The company's historic expertise in fine chemicals provides a platform for redefining purity requirements for active ingredients and maximizing their therapeutic potential, allowing it to explore new and untouched indications. Provepharm's strategy first bore fruit with the development of a new and patented method for synthesizing methylene blue. This new active ingredient enabled the company to obtain marketing authorizations in over 30 countries and to pursue its expansion internationally. Founded in 1998 and based in Marseille (France) and Philadelphia (USA), Provepharm Life Solutions has over 90 staff. The company recorded turnover of €66 million ($76M) in 2021. After raising €42.5 million ($49.8M) in 2019, it received a further investment of €120 million ($142.3M) in September 2021 from Tikehau Capital, which joined its group of historical banking investors, including Société Générale, BNP Paribas, Banque Populaire Méditerranée, Crédit Agricole Alpes Provence and Bpifrance. www.provepharm.com

About Daiichi Sankyo Group

Daiichi Sankyo is dedicated to creating new modalities and innovative medicines by leveraging our world-class science and technology for our purpose "to contribute to the enrichment of quality of life around the world." In addition to our current portfolio of medicines for cancer and cardiovascular disease, Daiichi Sankyo is primarily focused on developing novel therapies for people with cancer as well as other diseases with high unmet medical needs. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 16,000 employees around the world draw upon a rich legacy of innovation to realize our 2030 Vision to become an "Innovative Global Healthcare Company Contributing to the Sustainable Development of Society." For more information, please visit www.daiichisankyo.com.

Daiichi Sankyo, Inc., headquartered in Basking Ridge, New Jersey, is a member of the Daiichi Sankyo Group.

For more information on Daiichi Sankyo, Inc., please visit: www.dsi.com