Press Release

Hikma launches Methylene Blue Injection, USP in the US

London, 25 June 2025 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Methylene Blue Injection, USP in a 50mg/10mL dose in the US. The product is indicated for the treatment of pediatric and adult patients with acquired methemoglobinemia. Hikma will be the third generic on the market and we are pleased to expand our portfolio with this launch, increasing patients access in the US.

According to IQVIA, US sales of Methylene Blue Injection, USP in, 50mg/10mL, were approximately $36 million in the 12 months ending April 2025.

Hikma is a top three supplier of generic injectable medicines by volume in the US[1], with a growing portfolio of more than 170 products. We are continuously expanding our portfolio of essential medicines and introducing new dosage forms that enhance patient care.

- ENDS –

This product has been approved for marketing in the United States by the US FDA. This product approval does not confer the right on Hikma, or any other party, to market this product outside the United States.

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About Hikma
(LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated BBB/stable S&P and BBB/stable Fitch)

Hikma helps put better health within reach every day for millions of people around the world. For more than 45 years, we've been creating high-quality medicines and making them accessible to the people who need them. Headquartered in the UK, we are a global company with a local presence across North America, the Middle East and North Africa (MENA) and Europe, and we use our unique insight and expertise to transform cutting-edge science into innovative solutions that transform people's lives. We're committed to our customers, and the people they care for, and by thinking creatively and acting practically, we provide them with a broad range of branded and non-branded generic medicines. Together, our 9,500 colleagues are helping to shape a healthier world that enriches all our communities. We are a leading licensing partner, and through our venture capital arm, are helping bring innovative health technologies to people around the world. For more information, please visit: www.hikma.com

[1] Source: IQVIA MAT April 2025, generic injectable volumes by eaches, excluding branded generics and Becton Dickinson

hikma.

Important Safety Information for Methylene Blue Injection, USP, 50mg/10mL:

Please see package insert for referenced section/section numbering, where appropriate.

BOXED WARNING

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

Methylene blue injection may cause serious or fatal serotonergic syndrome when used in combination with serotonergic drugs and opioids. Avoid concomitant use of Methylene blue injection 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)*].

CONTRAINDICATIONS

Methylene blue is contraindicated in the following conditions:

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

WARNINGS & PRECAUTIONS

- **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.
- **Hypersensitivity –** Anaphylactic reactions to methylene blue class products have been reported. Methylene blue 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 may not resolve or may rebound after response to treatment with methylene blue in patients with methemoglobinemia due to aryl amines such as aniline or sulfa drugs such as dapsone. Patients with glucose-6-phosphate dehydrogenase deficiency may not reduce methylene blue to its active form in vivo. Methylene blue may not be effective in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- **Hemolytic Anemia –** Hemolysis can occur during treatment of methemoglobinemia with methylene blue. Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with methylene blue may result in severe hemolysis and severe anemia. Methylene blue is contraindicated for use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- **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.
- **Effects on Ability to Drive and Operate Machinery –** Treatment with Methylene blue injection 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 Methylene blue injection have resolved.
- **Interference with Laboratory Tests –** Methylene blue injection 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 following adverse reactions are discussed in greater detail in other sections of the labeling:

- Serotonin Syndrome with Concomitant Use of Serotonergic Drugs and Opioids [see *Warnings and Precautions (5.1)*]
- Anaphylaxis [see *Warnings and Precautions (5.2)*]
- Lack of Effectiveness [see *Warnings and Precautions (5.3)*]

- Hemolytic Anemia [see *Warnings and Precautions (5.4)*]
- Interference with In-Vivo Monitoring Devices [see *Warnings and Precautions (5.5)*]
- Effects on Ability to Drive and Operate Machinery [see *Warnings and Precautions (5.6)*]
- Interference with Laboratory Tests [see *Warnings and Precautions (5.7)*]

Clinical Trials Experience
The safety of methylene blue in adults with acquired methemoglobinemia was assessed in 24 patients who received at least 1 dose of methylene blue. Most doses administered were 1 mg/kg (88.5%), but doses from 1 mg/kg to 2 mg/kg were administered. All patients received at least one dose of methylene blue; two received two doses. Serious adverse reactions occurred in 4.2% of patients who received methylene blue. 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 Methylene blue injection in pediatric patients with acquired methemoglobinemia was assessed in two retrospective case series that included two pediatric patients treated with Methylene blue injection 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 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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
Methylene blue may cause fetal harm when administered to a pregnant woman. Intra-amniotic injection of pregnant women with a methylene blue class product during the second trimester was associated with neonatal intestinal atresia and fetal death.

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.

Lactation
Risk Summary
There is no information regarding the presence of methylene blue in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions, including genotoxicity discontinue breast-feeding during and for up to 8 days after treatment with Methylene blue injection.

Pediatric Use
The safety and effectiveness of methylene blue for the treatment of acquired methemoglobinemia have been established in pediatric patients. Use of methylene blue is supported by two retrospective case series that included 2 pediatric patients treated with methylene blue and 12 treated with another methylene blue class product. The case series included pediatric patients in the following age groups: 3 neonates (less than 1 month), 4 infants (1 month up to less than 2 years), 4 children (2 years up to less than 12 years), and 3 adolescents (12 years to less than 17 years). The efficacy outcomes were consistent across pediatric and adult patients in both case series.

Geriatric Use
Clinical studies of Methylene blue injection 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. Methylene blue 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.

Renal Impairment
Methylene blue concentrations increased in subjects with renal impairment significantly. Adjust Methylene blue injection dosage in patients with moderate or severe renal impairment. 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 Methylene blue injection.

DOSAGE AND ADMINISTRATION

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

Recommended Dosage for Renal Impairment
- The recommended dosage of Methylene blue injection in patients with moderate or severe renal impairment 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.

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Keep the vials in the original package to protect from light. Discard unused portion.

OVERDOSAGE

Hypotension, wheezing and reduced oxygenation have been reported in patients who received methylene blue

class products in single doses of 3 mg/kg or more.

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

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

In case of overdose of Methylene blue injection, maintain the patient under observation until signs and symptoms have resolved, monitor for cardiopulmonary, hematologic and neurologic toxicities, and institute supportive measures as necessary.

INDICATIONS AND USAGE

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

HOW SUPPLIED/STORAGE AND HANDLING

Methylene Blue Injection, USP is supplied in 10 mL single-dose vials. Each 10 mL vial contains 50 mg of methylene blue as a clear dark blue solution. A box contains five vials placed in a tray.
Box of 5 vials of 50 mg/10 mL (0.5%): NDC 0143-9094-05

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 vials in the original package to protect from light.

ENDING INFORMATION

Patient Counseling Information should be shared with the patient prior to administration.
For additional information, please refer to the Package Insert for full prescribing information, available on www.hikma.com.

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or FDA at 1-800 FDA-1088 or www.fda.gov/medwatch.

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