Australian Product Information - PROVEBLUE® (methylene blue solution for injection)

1. NAME OF THE MEDICINE

Methylene blue (also known as methylthioninium chloride)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROVEBLUE® injection is a sterile solution containing 50 mg methylene blue trihydrate (equivalent to 42.77 mg of methylene blue anhydrous) in water for injections to 10 mL. The pH of the solution ranges between 3.0 and 4.5.

Methylene blue is a dark blue, crystalline powder with a copper-coloured sheen, or green crystals with a bronze-coloured sheen. It is slightly soluble in water and slightly soluble in ethanol.

3. PHARMACEUTICAL FORM

PROVEBLUE® is a clear blue solution and contains methylene blue trihydrate 50 mg/10 mL.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PROVEBLUE® is indicated:

- for the treatment of drug-induced methaemoglobinaemia
- for the treatment of idiopathic methaemoglobinaemia (in which structural abnormality of haemoglobin is not present)
- as a bacteriological stain
- as a dye in diagnostic procedures such as fistula detection
- for the delineation of certain body tissues during surgery.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

PROVEBLUE® may be administered orally or by intravenous (IV) injection.

In the treatment of acute methaemoglobinaemia, the IV route of administration is usually preferred because it provides a more rapid onset of effect.

Adults and children: In the treatment of methaemoglobinaemia, methylene blue is administered intravenously as the 0.5 % solution in doses of 1 to 2 mg per kg bodyweight injected over a period of 5 minutes. A repeat dose may be given after one hour if required. A maximum dose of 7mg/kg bodyweight is recommended. The use of methylene blue is not recommended in infants under 4 months of age.

A dose of 5 mg/kg diluted in 500 mL of glucose 5% infused over 1 hour has been used successfully to stain and identify the parathyroid glands.

PROVEBLUE® should not be diluted with sodium chloride 0.9% (saline) as precipitation may occur (due to presence of chloride ions which have been shown to reduce the solubility of methylene blue).

A suitable dilution for oral dosing would be 10-20 mL of the 0.5 % solution diluted to 100-200 mL with water for injections. The high volume is suggested to reduce the degree of gastrointestinal disturbances and dysuria. The dosage of methylene blue should be calculated on the basis of lean body weight.

Use immediately following dilution.

The PROVEBLUE® ampoules should be inspected visually prior to administration. The product should not be used if the solution is discoloured, cloudy, turbid or if a precipate or particles are present.

Each ampoule is for single use in one patient only. Discard any residue. PROVEBLUE® contains no antimicrobial agents

4.3 CONTRAINDICATIONS

PROVEBLUE® is contraindicated in the following circumstances:

- known hypersensitivity to the drug or any other thiazide dyes
- patients with severe renal impairment
- patients with glucose-6-phosphate dehydrogenase deficiency
- methaemoglobinaemia due to chlorate poisoning
- methaemoglobinaemia during treatment of cyanide poisoning

Intrathecal and subcutaneous injection of methylene blue are also contraindicated as they can result in neural damage (intrathecal administration) and necrotic abscess (subcutaneous administration).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Long term administration of methylene blue may result in marked anaemia due to accelerated destruction of erythrocytes; haemoglobin concentrations should be checked frequently.

If methylene blue is injected subcutaneously or if extravasation occurs, necrotic abscesses may occur (See section 4.3). Slow injection rates are recommended to prevent high local concentration of the compound.

Methylene blue imparts a blue-green colour to urine, faeces and a blue colour to skin which may hinder a diagnosis of cyanosis.

Caution should be exercised in the course of treating aniline-induced methaemoglobinaemia. The repeated doses, that may be required, may exacerbate Heinz body formation and haemolytic anaemia. Lower doses should be considered.

Exacerbation of dapsone-induced haemolytic anaemia has been reported as a result of the formation of the dapsone reactive metabolite hydroxylamine which oxidises haemoglobin. It is recommended not to exceed a cumulative dose for the course of treatment of 4 mg/kg in patients with dapsone-induced methaemoglobinaemia.

Anaesthesiologists should be vigilant for methaemoglobinaemia in patients receiving dapsone therapy and for BIS (Bispectral Index) interference.

Due to the potential risk of cardiac arrhythmia and hypotension, electrocardiographs (ECG) and blood pressure monitoring is recommended.

Failure to respond to methylene blue suggests cytochrome b_5 reductase deficiency, glucose-6-phosphate dehydrogenase deficiency or sulfhaemoglobinemia. Alternative treatment options should be considered.

Patients with hyperglycaemia or diabetes mellitus: if diluted in glucose 5% (50 mg/mL) solution for injection, Methylene Blue Injection must be used with caution in patients with hyperglycaemia or diabetes mellitus, as these conditions may be exacerbated by the glucose solution.

Patient monitoring

Full blood count, including reticulocyte count should be undertaken to ensure haemolysis has not occurred. Electrocardiograph (ECG) and blood pressure should be monitored during and after treatment with methylene blue as hypotension and cardiac arrhythmia are potential adverse effects

Long term administration of methylene blue may result in anaemia. Haemoglobin levels should be monitored during long term therapy.

Methaemoglobin levels should be monitored throughout therapy.

Methylene blue is a potent monoamine oxidase inhibitor

Methylene blue has recently been demonstrated to be a potent monoamine oxidase inhibitor (MAOI) and may cause serious or fatal serotonin toxicity (serotoninergic syndrome) when combined with serotonergic drugs.(1) Avoid concomitant use of methylthioninium chloride with selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors. If methylene blue is judged to be indicated serotonin reuptake inhibitors (SRIs) must be ceased, prior to treatment/procedure/surgery (See section 4.5).

Patients treated with methylene blue in combination with serotonergic drugs should be monitored for the emergence of serotonin syndrome. If symptoms of serotonin syndrome occur, discontinue use of methylene blue, and initiate supportive treatment.

Photosensitivity

Methylene blue may cause a cutaneous photosensitivity reaction when exposed to strong light sources, such as phototherapy, those found in operating theatres or locally from illuminating devices such as pulse oximeters.

Advise patients to take protective measures against exposure to light, because photosensitivity may occur after administration of methylene blue.

Use in renal impairment

Methylene blue is excreted mainly via the urine, primarily as leucomethylene blue. Methylene blue is contraindicated in patients with severe renal impairment. Caution should be exercised when administering methylene blue to patients with mild to moderate renal impairment.

Paediatric use

Safety and efficacy of methylene blue in infants have not been established. It has been reported that the metabolism of methylene blue to leucomethylene blue is likely to be less efficient in neonates, due to reduced efficiency of NADPH-diaphorase in this age group. The use of methylene blue in infants up to 4 months of age is not recommended.

Extreme caution should be exercised when administering to the newborns and infants below the age of 3 months due to lower concentrations of NADPH-methaemoglobin reductase necessary for reducing methaemoglobin to haemoglobin, making these infants more susceptible to methaemoglobinaemia produced by high doses of methylene blue.

Effects on laboratory tests

Phenolsulphthalein excretion test: methylene blue may cause false positive test results.

Pulse oximetry: methylene blue may result in an underestimation of the oxygen saturation reading. It is advisable to check the oxygen saturation by cooximetry when available since pulse oximetry may provide a false estimation of oxygen saturation during administration of methylene blue.

Bispectral Index (BIS): methylene blue may interfere with BIS values.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Methylene blue is an *in vitro* inhibitor of CYP450 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5. The clinical consequences of increased plasma concentration of co-administered drugs which are sensitive CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A substrates cannot be ruled out. Methylene blue is an *in vitro* inducer of CYP1A2. The clinical consequence is not known.

The administration of methylene blue has the potential to transiently increase or decrease the clearance of drugs that are primarily metabolised by these enzymes. The clinical consequences are however considered minimal since methylene blue is used often only once and in an acute emergency setting.

Methylene blue is a potent inhibitor of the transporters OCT2, MATE1 and MATE2-K. The clinical consequences of the inhibition are not known. The administration of methylene blue has the potential to transiently increase the exposure of drugs primarily cleared by renal transport involving the OCT2/MATE pathway, including cimetidine, metformin and acyclovir.

Methylene blue is a substrate of P-glycoprotein (P-gp). The clinical consequences are considered likely to be minimal due to the transient and single dose use that normally occurs in the emergency setting.

Serotonin reuptake inhibitor

Methylene blue may interact with any drug that acts as a serotonin reuptake inhibitor (SRI) including, amongst others, selective serotonin reuptake inhibits (SSRIs) such as fluvoxamine, fluoxetin, paroxetine, sertraline, escitalopram and citalopram, serotonin and noradrenaline reuptake inhibitors (SNRIs) like clomipramine, venlafaxine, duloxetine and sibutramine; such combinations have the consequence of potential serious CNS reactions, including potentially fatal serotonin toxicity (serotonin syndrome). Methylene blue should not be coadministered with any drug that acts an SRI. (See section 4.4)

Serotonin Syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of methylene blue and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been reported. Coadministration of methylene blue and serotonergic agents is therefore not recommended except where administration of methylene blue and concomitant serotonergic agents is essential. In those cases the lowest possible dose should be used and patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia, clonus and incoordination. If signs or symptoms occur physicians should consider discontinuing either one or both agents; if the concomitant serotonergic agent is withdrawn, discontinuation symptoms can occur. Opioids, for example, tramadol, pethidine, and dextromethorphan, may also increase the risk of developing serotonin syndrome when used in combination with methylene blue.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

In vitro methylene blue has been shown to reduce motility of human sperm. It has also been shown to inhibit the growth of cultured two-cell mouse embryos and the production of progesterone in cultured human luteal cells. *In vivo* effects on fertility and reproduction are not known.

Use in Pregnancy

Methylene Blue Injection caused ileal abnormalities including foetal intestinal atresia.

Category D. PROVEBLUE® should not be administered to pregnant women.

Category D, Australian definition: Drugs which have caused, are suspected to have caused, or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying references should be consulted for further details.

Use in Lactation

There is no information on whether or not methylene blue crosses into breast milk. Safety in the newborn has not been established, and hence, it is recommended that breastfeeding is discontinued prior to administration of PROVEBLUE®.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Driving can be affected due to confusional state, dizziness and possibly eye disturbances. However, the risk is limited as the medical product is intended for acute administration only in emergency situations at hospital.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most commonly reported adverse reactions observed during clinical trials following intravenous administration are dizziness, paresthesia, dysgeusia, nausea, skin discoloration, chromaturia, sweating, injection site pain and pain in extremity.

The adverse effects listed in the table below occur in adults, children and adolescents (age 0 to 17 years old) after intravenous administration. The frequencies are not known (cannot be estimated from the available data). When indicated, the frequency is based on a very small sample size.

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Not known	Methaemoglobinaemia (after high doses), hyperbilirubinemia, haemolysis (in glucose-6-phosphate dehydrogenase deficiency, or high doses).
Immune system disorders	Not known	Anaphylactic reactions
Psychiatric disorders	Not known	Mental confusion, agitation
Nervous system disorders	Very common Common Not known	Dizziness, paraesthesia, dysgeusia Headache, anxiety Tremor, fever, aphasia, serotonin syndrome with concomitant use of serotonergic drugs (See sections 4.4 and 4.5)
Eye disorders	Not known	Mydriasis
Cardiac disorders	Not known	Cardiac arrhythmia*, tachycardia
Vascular disorders	Not known	Hypertension, hypotension*
Respiratory, thoracic and mediastinal disorders	Not known	Dyspnoea, tachypnoea, hypoxia
Gastrointestinal disorders	Very common Common Not known	Nausea Vomiting, abdominal pain Diarrhoea, blue colour of faeces and saliva
Skin and subcutaneous tissue disorders	Very common Not known	Skin discolouration (blue), sweating Rash (blue macules, severe burning pain), urticaria, phototoxicity/photosensitivity
Renal and urinary disorders	Very common	Blue colour of urine
General disorders and administration site conditions	Common Not known	Injection site pain, chest pain Thrombophlebitis (resulting from high doses, if not adequately diluted – not more 350 mg of methylene blue should be diluted in each 500 mL of infusion fluid), necrosis (if extravasation occurs)
Investigations	Not known	Haemoglobin decreased
Musculoskeletal and connective tissue disorder	Very common	Pain in extremity

*might prove fatal on rare occasions

Oral administration may cause gastrointestinal disturbances and dysuria.

Use of methylene blue for endoscopic tattoo has been associated with vascular necrosis, mucosal ulceration, mural necrosis, extramural fat necrosis and inflammatory changes in the colon.

Injection of methylene blue into joint space has resulted in effusion in the treated joint.

Hyperbilirubinaemia has been reported in infants only.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms: No specific information is available. However, large doses of methylene blue can produce methaemoglobinaemia. Side effects seen with high doses include chest pain, dyspnoea, restlessness, apprehension, tremors and a sense of oppression. Large doses are irritant to the urinary tract. In addition it can produce a mild haemolysis with moderate hyperbilirubinaemia, reticulosis and slight anaemia. Rarely, however, severe haemolytic anaemia with Heinz body formation has resulted. Methylene blue in large doses could cause a blue discolouration of the skin after methaemoglobin levels have returned to normal.

Individuals with methaemoglobinaemia

Cumulative doses of methylene blue may lead to dyspnoea and tachypnoea, presumably related to reduced oxygen availability caused by methaemoglobinaemia, chest pain, tremor, cyanosis and haemolytic anaemia.

Haemolytic anaemia has also been reported in case of severe overdose (20-30 mg/kg) in infants and adults with methaemoglobinaemia caused by aniline or chlorates. Haemodialysis may be used in patients with severe haemolysis.

Individuals without methaemoglobinaemia

The administration of large intravenous doses (≥ 7 mg/kg) of methylene blue to individuals without methaemoglobinaemia induces nausea and vomiting, chest tightness, chest pain, tachycardia, apprehension, severe sweating, tremor, mydriasis, blue-green staining of the urine, blue staining of the skin and mucous membranes, abdominal pain, dizziness, paraesthesia, headache, confusion, hypertension, mild methaemoglobinaemia (up to 7%) and electrocardiogram changes (T wave flattening or inversion). These features resolve generally within 2-12 hours of the injection.

Paediatric population

Hyperbilirubinaemia has been observed in infants after administration of 20 mg/kg methylene blue.

Death occurred in 2 infants after administration of 20 mg/kg methylene blue. Both infants had complex medical circumstances and methylene blue was only partially responsible.

Treatment of Overdosage: There is no specific antidote for methylene blue overdose. Treatment is symptomatic and supportive. In severe and refractory cases of methaemoglobinaemia, blood transfusions and even exchange transfusions and (possibly) hyperbaric oxygen may be the only alternative available.

For information on the management of overdose contact the Poisons Information Centre: **13 11 26 (Australia). If you are in New Zealand, please call 0800 POISON or 0800 764766.**

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

In patients with methaemoglobinaemia, therapeutic doses of methylene blue can lower the levels of methaemoglobin in red blood cells. It activates a normally dormant reductase enzyme system that reduces the methylene blue to leucomethylene blue, which is then able to reduce methaemoglobin to haemoglobin. However, in large doses, methylene blue can itself produce methaemoglobinaemia and the methaemoglobin concentration should therefore be closely monitored during treatment. Methylene blue is not effective for the treatment of methaemoglobinaemia in patients with glucose-6-phosphate dehydrogenase deficiency as

these patients have a diminished capacity to reduce methylene blue to leucomethylene blue. It is also potentially harmful as patients with glucose-6phosphate dehydrogenase deficiency are particularly susceptible to the haemolytic anaemia induced by methylene blue.

Methylene blue also possesses weak antiseptic and bacteriological staining properties and is reported to inhibit amine oxidase in tissues. The drug appears to bind irreversibly to viral nucleic acid and cause disruption of the virus molecule upon exposure to light.

The use of methylene blue as a diagnostic aid is based on its ability to stain tissue. Any skin discolouration can be removed with hypochlorite solution.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

No data available.

Distribution

No data available.

Metabolism

In tissues, methylene blue is rapidly reduced to leucomethylene blue, which is stabilised as an undetermined salt, complex, or combination form in the urine but not in the blood.

Excretion

About 75% of an oral dose of methylene blue is excreted in the urine, a small proportion of which is the unchanged drug, while some is excreted via the bile.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Methylene blue was positive to gene mutation assays in bacteria and mouse lymphoma cells, but was negative in the in vivo mouse micronucleus test.

Carcinogenicity

There is no information on the carcinogenic potential of methylene blue.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Water for injections.

6.2 INCOMPATIBILITIES

Precipitation has been reported in cases where methylene blue has been diluted with sodium chloride 0.9%, saline (due to presence of chloride ions which have been shown to reduce the solubility of methylene blue).

Methylene blue is reported to be incompatible with caustic alkalis, iodides and dichromates, and oxidising and reducing substances.

6.3 SHELF LIFE

4 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light. Do not refrigerate or freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

10mL clear glass ampoule. It is presented as a pack of 5 ampoules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

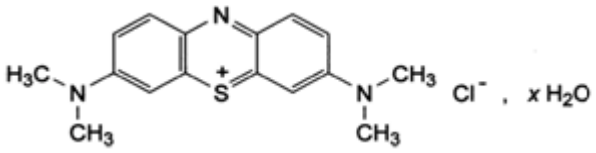
Each ampoule is for single use in one patient only. Discard any residue.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Name: 3,7-Bis(dimethylamino)phenothiazin-5-ylium trihydrate

Chemical Structure

The molecular weight of methylene blue trihydrate is 373.9. The molecular formula of hydrated methylene blue is $C_{16}H_{18}ClN_3S,xH_2O$ (where x=3,4 or 5) and its structure is as follows:



CAS Number

CAS registry number of methylene blue trihydrate is 7220-79-3

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription only medicine

8. SPONSOR

PROVEBLUE® is sponsored in Australia for Provepharm SAS by:

Clinect Pty Ltd,
120-132 Atlantic Drive,
Keysborough, VIC 3173,
Australia

Free Call Australia: 1800 899 005

Free Call New Zealand: 0800 138 803

9. DATE OF FIRST APPROVAL

23 July 2015

10. DATE OF REVISION

28 July 2026

Summary table of changes

Section changed	Summary of new information
6.3	Shelf Life Extension to 4 years