
NEW ZEALAND DATA SHEET

1. PROVEBLUE® METHYLENE BLUE 50 mg/10 mL SOLUTION FOR INJECTION

PROVEBLUE® METHYLENE BLUE 50 mg/ 10mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Methylthioninium choride hydrate (Methylene blue) 50 mg/10 mL.

1 mL of solution contains 5 mg of methylthioninium chloride hydrate (also known as methylene blue hydrate), equivalent to 4.277 mg of methylthioninium chloride anhydrous (also known as methylene blue anhydrous).

Each 10 mL ampoule contains 50 mg methylthioninium chloride hydrate (also known as methylene blue trihydrate), equivalent to 42.77 mg of methylthioninium chloride anhydrous (also known as methylene blue anhydrous).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear blue solution. The pH of the solution ranges between 3.0 and 4.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PROVEBLUE® METHYLENE BLUE is indicated in adults and children over 4 months:

- 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 Dosage and method of administration

Dose

Treatment of methaemoglobinaemia (drug-induced or idiopathic): 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 7 mg/kg bodyweight is recommended.

The use of methylene blue is not recommended in infants under 4 months of age.

Delineation of certain body tissues during surgery: 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. Elderly population

No dose adjustment is necessary.

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.

Hepatic impairment

There is no experience in patients with severe hepatic impairment.

Method of Administration

PROVEBLUE® METHYLENE BLUE may be administered orally or by intravenous (IV) injection. It must not be administered by subcutaneous or intrathecal injection, as it can result in neural damage (intrathecal administration) and necrotic abscess (subcutaneous administration).

In the treatment of acute methaemoglobinaemia, the IV route of administration is usually preferred because it provides a more rapid onset of effect. The injection should be very slowly, over a period of 5 minutes.

PROVEBLUE® METHYLENE BLUE 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). (See section 6.2)

PROVEBLUE® METHYLENE BLUE is hypotonic and may be diluted in glucose 50 mg/mL (5%) solution for injection.

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.

For instructions on handling and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

PROVEBLUE® METHYLENE BLUE is contraindicated in the following circumstances:

- known hypersensitivity to the active substance 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 (see section 4.8).

Failure to respond to methylene blue suggests cytochrome b5 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 (serotonergic syndrome) when combined with serotonergic drugs. Avoid concomitant use of methylthionium chloride with selective serotonin inhibitors (SSRIs). If methylene blue is judged to be indicated serotonin reuptake inhibitors (SRIs) must be ceased, prior to treatment/ procedure/ surgery (See section 4.5).

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.

Paediatric population

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.

Use in renally impaired patients

See section 4.2, Renal impairment.

4.5 Interactions with other medicines and other forms of interaction

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 inhibitors (SSRIs) such as fluvoxamine, fluoxetine, 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 co-administered with any drug that acts as 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. Co-administration 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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category D

Methylene Blue Injection caused ileal abnormalities including foetal intestinal atresia.

PROVEBLUE® METHYLENE BLUE should not be administered to pregnant women.

Category D definition: Medicines 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 medicines may also have adverse pharmacological effects. Accompanying references should be consulted for further details.

Breast-feeding

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® METHYLENE BLUE.

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.

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 Undesirable effects

a. Summary of the safety profile

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.

b. Tabulated list of adverse reactions

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 Class	Organ	Frequency	Adverse reactions
<i>Blood and lymphatic system disorders</i>		Not known	Methaemoglobinaemia (after high doses), hyperbilirubinemia, haemolysis (in glucose-6-phosphate dehydrogenase deficiency, or high doses).
<i>Immune system disorders</i>		Not known	Anaphylactic reactions
<i>Psychiatric disorders</i>		Not known	Mental confusion, agitation
<i>Nervous system disorders</i>		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)
<i>Eye disorders</i>		Not known	Mydriasis
<i>Cardiac disorders</i>		Not known	Cardiac arrhythmia*, tachycardia
<i>Vascular disorders</i>		Not known	Hypertension, hypotension*
<i>Respiratory, thoracic and mediastinal disorders</i>		Not known	Dyspnoea, tachypnoea, hypoxia
<i>Gastrointestinal disorders</i>		Very common Common Not known	Nausea Vomiting, abdominal pain Diarrhoea, blue colour of faeces and saliva
<i>Skin and subcutaneous tissue disorders</i>		Very common Not known	Skin discolouration (blue), sweating Rash (blue macules, severe burning pain), urticaria, phototoxicity/photosensitivity
<i>Renal and urinary disorders</i>		Very common	Blue colour of urine
<i>General disorders and administration site conditions</i>		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)
<i>Investigations</i>		Not known	Haemoglobin decreased
<i>Musculoskeletal and connective tissue disorder</i>		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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

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.

Signs

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

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.

The patient should be maintained under observation, the methaemoglobin level should be monitored and appropriate supportive measures taken as necessary.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: All other therapeutic products, antidotes, ATC code: V03AB17

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-6-phosphate 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.

5.2 Pharmacokinetic properties

Absorption

No data available.

Distribution

No data available.

Biotransformation

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.

Elimination

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

Carcinogenicity

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

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

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

3 years.

After opening or dilution: from a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product must be used immediately.

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

10 mL borosilicate type 1 clear glass ampoule. It is presented as a pack of 5 ampoules.

6.6 Special precautions for disposal and other handling

PROVEBLUE® METHYLENE BLUE is hypotonic and may be diluted in glucose 50 mg/mL (5%) solution for injection in order to avoid local pain, in particular in paediatric population. Before any administration, it is recommended to inspect the parenteral solution to verify that it is free of particles.

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

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

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

PROVEBLUE® is sponsored in New-Zealand for Provepharm SAS by:

Clinect NZ Pty Limited

C/- Ebos Group Limited

108 Wrights Road

Christchurch 8024

New Zealand

Free Call New Zealand: 0800 138 803

9. DATE OF FIRST APPROVAL

28 July 2016

10. DATE OF REVISION OF THE TEXT

4 July 2019

Summary Table of Changes

Section Changed	Summary of New Information
8	Addition that PROVEBLUE® is sponsored in New Zealand for Provepharm SAS by Clinect Pty Ltd