

AUSTRALIAN PRODUCT INFORMATION

METHYLENE BLUE INJECTION

(METHYLENE BLUE)

1 NAME OF THE MEDICINE

Methylene blue (also known as methylthioninium chloride)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Methylene blue is a dark blue or dark green crystalline powder with a metallic sheen. It is soluble in water, alcohol and chloroform. Methylene Blue Injection is a sterile solution of methylene blue trihydrate 50 mg.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Methylene Blue Injection is a sterile solution for oral/intravenous use. The pH of the solution ranges between 3.0 and 4.5.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Methylene Blue Injection is indicated:

- for the treatment of drug-induced methaemoglobinaemia
- for the treatment of idiopathic methaemoglobinaemia (in which a 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

Methylene Blue Injection may be administered orally or by intravenous injection. In the treatment of acute methaemoglobinaemia, the intravenous 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 a 1% solution in doses of 1 mg to 2 mg per kg bodyweight injected over a period of several 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.

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.

Methylene Blue Injection 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 5-10 mL of the 1% 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 bodyweight.

Use immediately following dilution.

4.3 CONTRAINDICATIONS

Methylene Blue Injection is contraindicated in the following circumstances:

- known hypersensitivity to the drug or to 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 result (see Section 4.3 Contraindications). 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.

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.

Due to the potential risk of cardiac arrhythmia and hypotension, electrocardiographs (ECG) and blood pressure should be monitored during and after treatment with methylene blue.

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.

Potent monoamine oxidase inhibition and serotonin syndrome

Methylene blue has 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 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.

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 (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

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 Injection is contraindicated in patients with severe renal impairment. Caution should be exercised when administering methylene blue to patients with mild to moderate renal impairment.

Use in the elderly

No data available.

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 efficacy of NADP-diaphorase in this age group. The use of Methylene Blue Injection in infants up to 4 months of age is not recommended.

Extreme caution should be exercised when administering to 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

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

Pulse oximetry: methylene blue may result in an underestimation of oxygen saturation reading. It is advisable to check the oxygen saturation by co-oximetry 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

An in vitro study showed that methylene blue is a potential inhibitor of CYP450 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5. The clinical relevance of this finding is unknown, but it cannot be excluded that the systemic exposure of medical products being substrates for these isozymes may be increased on concomitant administration with methylene blue.

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 Injection may interact with any drug that acts as an SRI including, amongst others, SSRIs such as fluvoxamine, fluoxetine, paroxetine, sertraline, escitalopram and citalopram, and SNRIs like venlafaxine and duloxetine. 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 Special Warnings and Precautions for Use).

Serotonin syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of methylene blue and serotonergic agents, including antidepressants such as 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. Opioids, for example tramadol, pethidine, and dextromethorphan, may also increase the risk of developing serotonin syndrome when used in combination with methylene blue.

Methylene blue has been demonstrated to be a potent MAOI and may cause potentially fatal serotonin toxicity (serotonin syndrome) when combined with SRIs (see section 4.4 Special Warnings and Precautions for Use).

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 fetal intestinal atresia.

Category D. Methylene blue should not be administered to pregnant women.

Australian categorisation definition of Category D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Use in lactation

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

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 adverse effects listed in the table below occur in adults, children, and adolescents (age 0 to 17 years old) after intravenous administration.

System Organ Class	Adverse reactions
<i>Gastrointestinal</i>	Nausea, vomiting, diarrhoea, abdominal pain, blue colour of faeces and saliva
<i>Blood and lymphatic system disorders</i>	haemolysis (in glucose-6-phosphate dehydrogenase deficiency, or high doses), methaemoglobinaemia (after high doses), hyperbilirubinemia [^]
<i>Cardiovascular</i>	hypertension, hypotension*, arrhythmia*, chest pain, tachycardia
<i>Respiratory, thoracic and mediastinal disorders</i>	dyspnoea, tachypnoea, hypoxia
<i>Body as a whole</i>	profuse sweating
<i>Dermal</i>	rash (blue macules, severe burning pain), skin discolouration (blue), urticaria, phototoxicity/photosensitivity
<i>Nervous system</i>	headache, dizziness, paraesthesia, dysgeusia, anxiety, tremor, fever, aphasia, serotonin syndrome with concomitant use of serotonergic drugs (see section 4.4 Special Warnings and Precautions for Use and section 4.5 Interactions with Other Medicines and Other Forms of Interactions)
<i>Psychiatric disorders</i>	mental confusion, agitation
<i>Injection site</i>	injection site pain, thrombophlebitis (resulting from high doses, if not adequately diluted – not more than 350 mg of methylene blue should be diluted in each 500 mL of infusion fluid), necrosis (if extravasation occurs)
<i>Renal</i>	blue colour of urine
<i>Immune system disorders</i>	anaphylactic reactions
<i>Ocular disorders</i>	mydriasis
<i>Investigational</i>	haemoglobin decrease
<i>Musculoskeletal and connective tissue disorder</i>	pain in extremity

*might prove fatal on rare occasions

[^]Hyperbilirubinaemia has been reported in infants only.

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.

Reporting suspected adverse effects

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 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 an 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 methaemoglobinaemia levels have returned to normal.

Treatment of overdose

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 on 131126 (Australia).

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 the red blood cells. It activates a normally dormant reductase enzyme system that reduces the methylene blue to leucomethylene blue, which in turn is 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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES**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

Methylene Blue Injection contains water for injections, sodium hydroxide and/or hydrochloric acid may be used for pH adjustment.

6.2 INCOMPATIBILITIES

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

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).

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG)¹. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Methylene Blue Injection is presented as 5 mL of solution in a 7 mL glass vial as a pack of 10.

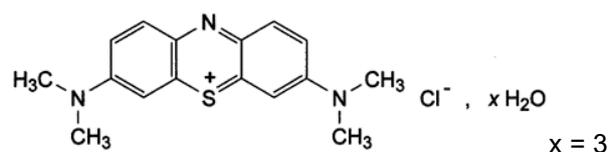
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The active ingredient of Methylene Blue Injection USP is methylene blue trihydrate (3, 7- bis (dimethylamino) phenazathionium chloride trihydrate). The molecular formula of methylene blue trihydrate is $C_{16}H_{18}ClN_3S \cdot 3H_2O$. It has a molecular weight of 373.9.

¹ AUST R 223583

Chemical structure**CAS number**

7220-79-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Phebra² Pty Ltd
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9 DATE OF FIRST APPROVAL

8 OCT 1991

10 DATE OF REVISION

14 September 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4, 4.5, 4.6, 4.8, 6.1, 6.5, 10	MEC to improve the quality and readability of the PI
4.4	Updated: existing precautions Added: separate sub-sections on Monoamine oxidase inhibition and Photosensitivity
4.5	Updated: interactions with enzymes, serotonin reuptake inhibitors, serotonin syndrome
4.8	Updated: adverse effects

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