Package insert

Proveblue® 5 mg/ml, Solution for Injection

1. NAME OF THE MEDICINAL PRODUCT

Proveblue® (Methylthioninium chloride)
5 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 5 mg methylthioninium chloride.

Each 10 ml ampoule contains 50 mg methylthioninium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)
Clear dark blue solution with a pH value between 3.0 and 4.5
Osmolality is usually between 10 and 15 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Proveblue® is indicated:

- for the treatment of drug and chemical products-induced methaemoglobinaemia
- as a dye in diagnostic procedures such as fistula detection
- for the delineation of certain body tissues during surgery.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

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.

For the treatment of acute methaemoglobinaemia, 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

Renal impairment

In infants above 4 months , children and adolescents and in adults, the recommended dosage for the treatment of acquired methaemoglobinemia in patient with moderate or severe renal impairment (eGFR 15-59 mL/min/1.73 m^2) is a single dose of 1 to 2 mg/kg per body weight with a maximum recommended cumulative dose for the course of treatment of 2 mg/kg.

No dose adjustment is recommended in patients with mild renal impairment (eGFR 60-89mL/min/1.73 m^2).

The safety and efficacy of methylthioninium chloride in patients with end stage renal disease with and without dialysis has not yet been established. No data are available.

Hepatic impairment

The safety and efficacy of methylthioninium chloride in patients with hepatic impairment has not yet been established.

No data are available.

Treatment does not usually exceed one day.
It must not be administered by subcutaneous or intrathecal injection.
For instructions on handling and dilution of the medicinal product before administration, see section 6.6.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance, or to any other thiazine dyes
- Patients with Glucose-6-phosphate dehydrogenase deficiency (G6PD) due to the risk of haemolytic anaemia
- Patients with nitrite-induced methaemoglobinaemia during treatment of cyanide poisoning
- Patients with methaemoglobinaemia due to chlorate poisoning
- Deficiency in NADPH (nicotinamide adenine dinucleotide phosphate) reductase.

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

General

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

Methaemoglobin levels should be monitored throughout therapy

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.

Proveblue® must be injected very slowly over a period of 5 minutes to prevent high local concentrations of the compound from producing additional methaemoglobin.

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

In patients with aniline-induced methaemoglobinaemia, repeated doses of methylthioninium chloride may be required. Caution should be exercised in the course of treatment with methylthioninium chloride as this may exacerbate Heinz body formation and haemolytic anaemia. Lower doses should therefore be considered and total cumulative dose should not exceed 4 mg/kg.

Proveblue® can exacerbate dapsone-induced haemolytic anemia because 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.

In cases of suspected methaemoglobinaemia, 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 methylthioninium chloride.

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

Electrocardiogram (ECG) and blood pressure should be monitored during and after treatment with Proveblue® as hypotension and cardiac arrhythmia are potential adverse reactions (see section 4.8).

Failure to respond to methylthioninium chloride suggests cytochrome b5 reductase deficiency, glucose-6- phosphate dehydrogenase deficiency or sulfhaemoglobinemia. Alternative treatment options should be considered.

Methylthioninium chloride may cause serious or fatal serotonergic syndrome when used in combination 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 (see section 4.5).

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

Patients with hyperglycaemia or diabetes mellitus

If diluted in glucose 50 mg/ml (5%) solution for injection, methylthioninium chloride must be used with caution in patients with hyperglycaemia or diabetes mellitus, as these conditions may be exacerbated by the glucose solution.

Paediatric population

Safety and efficacy of methylthioninium chloride in infants have not been established. It has been reported that the metabolism of methylthioninium chloride 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 4 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 methylthioninium chloride.

Photosensitivity

Methylthioninium chloride 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 methylthioninium chloride.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Methylthioninium chloride should be avoided in patients receiving medicinal products that enhance serotonergic transmission because of the potential for serious CNS reactions, including potentially fatal serotonin syndrome. These include SSRIs (selective serotonin reuptake inhibitors), bupropion, buspirone, clomipramine, mirtazapine, and venlafaxine. If the intravenous use of methylthioninium chloride cannot be avoided in patients treated with serotonergic medicinal products, the lowest possible dose should be chosen and the patient observed closely for central nervous system (CNS) effects for up to 4 hours after administration (see sections 4.4 and 4.8).

Methylthioninium chloride is an in vitro inducer of CYP1A2. This interaction is not considered clinically relevant, since treatment with Methylthioninium chloride does not usually exceed one day.

In a drug interaction study, a single IV dose of 2 mg/kg Methylthioninium chloride did not have a clinically relevant effect on the pharmacokinetics of midazolam (CYP3A4), caffeine (CYP1A2), omeprazole (CYP2C19), warfarin (CYP2C9), and dextromethorphan (CYP2D6).

Methylthioninium chloride is a potent inhibitor of the transporters OCT2, MATE1 and MATE2-K. The clinical consequences of the inhibition are not known. The administration of Proveblue® 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.

Methylthioninium chloride 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no adequate data from the use of methylthioninium chloride in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Proveblue® should not be used during pregnancy unless clearly necessary, e.g. in life-threatening methaemoglobinaemia.

Breast-feeding

It is unknown whether methylthioninium chloride is excreted in human breast milk. The excretion of methylthioninium chloride in milk has not been studied in animals. A risk to the suckling child cannot be excluded. Based on kinetic data, breast-feeding should be discontinued for up to 8 days after treatment with Proveblue®.

Fertility

In vitro, methylthioninium chloride has been shown to reduce motility of human sperm in a dose dependant manner.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Methylthioninium chloride has moderate influence on the ability to drive and use machines. Indeed, driving can be affected due to confusional state, dizziness and possibly eye disturbances. However, the risk is limited as the medicinal product is intended for acute administration only in emergency situations at hospital.

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

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

Intravenous injection of methylthioninium chloride has occasionally caused hypotension and cardiac arrhythmias, and such disorders might prove fatal on rare occasions.

Tabulated list of adverse reactions

The adverse reactions listed in the table below occur in adults, children and adolescents (aged 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	Adverse reactions	Frequency
Blood and lymphatic system disorders	Methaemoglobinaemia	Not known
	Hyperbilirubinaemia[1]	Not known
	Haemolytic anaemia	Not known
Immune system disorders	Anaphylactic reactions	Not known
Psychiatric disorders	Confusional state	Not known
	Agitation	Not known
Nervous system disorders	Dizziness	Very common
	Headache	Common
	Anxiety	Common
	Tremor	Not known
	Fever	Not known
	Aphasia	Not known
	Paraesthesia	Very common
	Dysgeusia	Very common
	Serotonin Syndrome with concomitant use of serotonergic drugs (see section 4.4 and section 4.5)	Not known
Eye disorders	Mydriasis	Not known

System organ class	Adverse reactions	Frequency
Cardiac disorders	Cardiac arrhythmia	Not known
	Tachycardia	Not known
Vascular disorders	Hypertension	Not known
	Hypotension	Not known
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Not known
	Tachypnoea	Not known
	Hypoxia	Not known
Gastrointestinal disorders	Nausea	Very Common
	Vomiting	Common
	Abdominal pain	Common
	Faeces discoloration (blue-green)	Not known
Skin and subcutaneous tissue disorders	Skin discoloration (blue)	Very common
	Sweating	Very common
	Urticaria	Not known
	Phototoxicity / Photosensitivity	Not known
Renal and urinary disorders	Chromaturia (blue-green)	Very common
General disorders and administration site conditions	Chest pain	Common
	Local tissue necrosis at the injection site	Not known
	Injection site pain	Common
Investigations	Haemoglobin decreased	Not known
Musculoskeletal and connective tissue disorder	Pain in extremity	Very common

[1] Reported in infants only

Paediatric population

Adverse reactions are the same as in adults (except hyperbilirubinaemia, 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 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 to the National Competent Authority for pharmacovigilance.

4.9 OVERDOSE

Individuals without methaemoglobinaemia

The administration of large intravenous doses (≥ 7 mg/kg) of Proveblue® 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.

Individuals with methaemoglobinaemia

Cumulative doses of Methylthioninium chloride 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.

Paediatric population

Hyperbilirubinaemia has been observed in infants after administration of 20 mg/kg methylthioninium chloride.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

In vivo, in low concentration, methylthioninium chloride speeds up the conversion of methaemoglobin to haemoglobin.

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. Its use in parathyroid surgery has induced adverse CNS effects when administered concomitantly with serotonergic medicinal products (see section 4.5).

Paediatric population

The efficacy of methylthioninium chloride for the treatment of methaemoglobinaemia in peadiatric population was demonstrated in two retrospective studies and one open randomised clinical trial. Case reports of efficacy are also available in literature.

Please refer to section 4.4 for important safety information.

5.2 PHARMACOKINETIC PROPERTIES

After intravenous administration Proveblue® is rapidly taken up by the tissues. It is also well absorbed by the oral route. The majority of the dose is excreted in the urine, usually in the form of leucomethylthioninium chloride.

The mean (SD) terminal half-life of methylthioninium chloride after intravenous administration is 24.7 (7.2) h. 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.

After a single 1 mg/kg intravenous dose of methylthioninium chloride, $AUC_{0\text{-}96h}$ increased by 52%, 116%, and 192% in subjects with mild (estimated glomerular filtration rate (eGFR) 60 – 89 mL/min/1.73 m²), moderate (eGFR 30-59 mL/min/1.73 m²), and severe (eGFR 15-29 mL/min/1.73 m²) renal impairment, respectively. C_{max} increased by 42%, 34%, and 15% in subjects with mild, moderate, and severe renal impairment respectively. The half-life was unchanged in patients with mild to moderate renal impairment.

The $AUC_{0\text{-}96h}$ of Azure B after a single 1 mg/kg intravenous dose increased by 29%, 94%, and 339% in subjects with mild (estimated glomerular filtration rate (eGFR) 60 – 89 mL/min/1.73 m²), moderate (eGFR 30-59 mL/min/1.73 m²), and severe (eGFR 15-29 mL/min/1.73 m²) renal impairment, respectively. C_{max} increased by 23%, 13%, and 65% in subjects with mild, moderate, and severe renal impairment respectively.
Proveblue® is an in vitro inhibitor of P-gp.

Proveblue® is not an in vitro substrate for BCRP or OCT2 and is not an in vitro inhibitor of BCRP, OAT1 or OAT3.

5.3 PRECLINICAL SAFETY DATA

Repeated dose toxicity

One-month repeated dose toxicity in dogs showed no macroscopic toxic effects.

Adverse reactions, seen at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were moderate regenerative anaemia associated with increased mean platelet count and fibrinogen levels, a minimal increase in mean total bilirubin blood values and an increased incidence of moderate urine bilirubin levels.

Genotoxicity

Methylthioninium chloride was mutagenic in gene mutation assays in bacteria and mouse lymphoma cells but not in vivo mouse micronucleus assay when administered intravenously at 62 mg/kg.

Carcinogenicity

Some evidence of carcinogenic activity of methylthioninium chloride has been shown in male mice and male rats. An equivocal evidence of carcinogenic activity was observed in female mice. No evidence of carcinogenic activity was observed in female rats.

Reproductive Toxicology

In vitro, methylthioninium chloride has been shown to reduce motility of human sperm in a dose dependant manner. 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 rats and rabbits, teratogenic effects have been reported, with foetal and maternal toxicity. In rats, increased resorption rates have been observed.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Water for injections.

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. For an intravenous injection, it must especially not be mixed with sodium chloride 9 mg/ml (0.9%) solution for injection because it has been demonstrated that chloride reduces the solubility of methylthioninium chloride.

6.3 SHELF LIFE

4 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. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light. Do not refrigerate or freeze.

Keep the ampoule in the original package in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

Type I glass ampoules.

Each carton contains a tray with 5 ampoules of 10 ml in blister.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

For single use only.
For an intravenous injection:

- Proveblue® may be diluted in 50 ml glucose 50 mg/ml (5%) solution for injection to avoid local pain, in particular in paediatric population.
- 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).

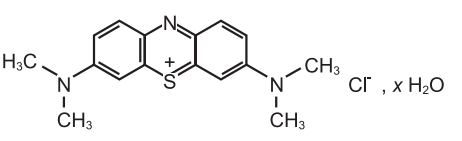
Before any administration, it is recommended to inspect the parenteral solutions to verify that they are free of particles. Do not use Proveblue® if the solution is discoloured, cloudy, turbid, or a precipitate or particles are present.

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

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. PRODUCT REGISTRATION HOLDER

Pharm-D Sdn. Bhd.
8B, Jalan 1/137C, Bedford Business Park,
Off Jalan Kelang Lama,
58000 Kuala Lumpur, Malaysia

8. MANUFACTURER

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9. DATE OF FIRST APPROVAL

05/01/2023

10. DATE OF REVISION

10/03/2025