

FULL PRESCRIBING INFORMATION

PROVEBLUE

I. BRAND NAME

PROVEBLUE

II. NON-PROPRIETARY NAME

Methylthioninium chloride

III. DOSAGE FORM AND FORMULATION

Solution.

Each ampoule contains:

Methylthioninium chloride	10 mg	50 mg
Vehicle q.s.	2 mL	10 mL

IV. THERAPEUTIC INDICATION

Acute symptomatic treatment for drug- and chemical-induced methaemoglobinaemia in paediatric and adult patients.

V. PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacodynamics:

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

In vivo, at low concentrations, methylthioninium chloride accelerates methaemoglobin conversion to haemoglobin.

Proveblue has been noted to selectively discolour tissues. Its (non-indicated) use in parathyroid surgery has induced adverse effects on the CNS when administered along with serotonergic drugs (see section X).

Paediatric population:

The efficacy of methylthioninium chloride to treat methaemoglobinaemia in the paediatric population was demonstrated in two retrospective studies and one randomized, open-label clinical trial. Also, clinical cases have been published that demonstrate its efficacy.

Please refer to section VII for important safety information.

Pharmacokinetics:

Following intravenous administration, Proveblue is rapidly taken up by the tissues. It is also well absorbed by oral route. The dose is primarily excreted in urine, usually as leucomethylthioninium chloride.

The estimated terminal half-life of methylthioninium chloride following intravenous administration is 26.7 h.

Proveblue is not an in vitro CYP2B6 or CYP3A4 inducer.

Proveblue is an in vitro P-gp inhibitor.

Proveblue is not an in vitro BCRP or OCT2 substrate nor is it an in vitro BCRP, OAT1 or OAT3 inhibitor.

VI. CONTRAINDICATIONS

- Hypersensitivity to the active ingredient or any other dyes that are thiazine derivatives.
- Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to the risk of haemolytic anaemia.
- Patients with nitrite-induced methaemoglobinaemia during treatment for cyanide poisoning.
- Patients with methaemoglobinaemia due to chlorate poisoning.
- NADPH (nicotinamide adenine dinucleotide phosphate) reductase deficiency.

VII. GENERAL PRECAUTIONS

General

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

It imparts a greenish blue colour to urine and stool and a blue colour to the 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 during administration of methylthioninium chloride as this treatment may exacerbate the formation of Heinz bodies and haemolytic anaemia. Therefore, a dose reduction should be considered, and the total cumulative dose should not exceed 4 mg/kg.

Proveblue may exacerbate dapsone-induced haemolytic anaemia as a result of the formation of hydroxylamine, the reactive dapsone metabolite that oxidizes haemoglobin. Exceeding a cumulative dose of 4 mg/kg is not recommended during treatment in patients with dapsone-induced methaemoglobinaemia.

In case of suspected methaemoglobinaemia, it is advisable to measure the oxygen saturation by co-oximetry, where this method is available, as pulse oximetry may provide a false estimation of oxygen saturation during the administration of methylthionium chloride.

Anaesthetists should be vigilant for the appearance of methaemoglobinaemia in patients treated with dapsone and monitor the BIS (bispectral index) during administration of Proveblue®.

The electrocardiogram (ECG) and blood pressure should be monitored during and after treatment with Proveblue, as hypotension and heart arrhythmias are potential adverse reactions (see section IX).

A lack of response to methylthionium chloride is suggestive of cytochrome b5 reductase deficiency, glucose-6-phosphate dehydrogenase deficiency, or sulfhaemoglobinaemia. Other alternative treatments should be considered.

Methylthionium chloride may cause severe or fatal serotonergic syndrome when used in combination with serotonergic drugs. Avoid concomitant use of methylthionium chloride and selective serotonin reuptake inhibitors (SSRI), serotonin and noradrenaline reuptake inhibitors (SNRI), and monoamine oxidase inhibitors (see section X).

Patients treated with methylthionium chloride in combination with serotonergic drugs should be monitored for potential appearance of serotonergic syndrome. In case of occurrence of serotonergic syndrome symptoms, discontinue treatment with methylthionium chloride and start supportive treatment.

Patients with hyperglycaemia or diabetes mellitus.

If diluted in glucose 5% (50 mg/mL) solution for injection, methylthionium chloride should be used with caution in patients with hyperglycaemia or diabetes mellitus, as these disorders may be exacerbated by the glucose solution.'

Paediatric population

Extreme caution should be exercised during administration to newborns and infants <3 months old, as lower NADPH-methaemoglobin reductase concentrations are required for methaemoglobin reduction to haemoglobin, and therefore these infants are more sensitive to the methaemoglobin produced by high doses of methylthionium chloride.

Photosensitivity

Methylthionium chloride may cause a cutaneous photosensitivity reaction from exposure to strong light sources such as phototherapy, light from operating rooms or lighting devices, e.g., pulse oximeters.

Advise patients to take protective measures against light exposure, since photosensitivity may be experienced following administration of methylthionium chloride.

VIII. PREGNANCY AND BREASTFEEDING RESTRICTIONS

Pregnancy

There is no sufficient data regarding the use of methylthioninium chloride in pregnant women. Animal studies have shown reproductive toxicity (see section XII). The potential risk for humans is unknown. Proveblue should not be used during pregnancy unless clearly required, e.g., in case of life-threatening methaemoglobinaemia.

Breastfeeding

It is unknown whether methylthioninium chloride is excreted in human breast milk. Excretion of methylthioninium chloride in milk has not been studied in animals. A risk for breastfed infants cannot be ruled out. Based on pharmacokinetic data, breastfeeding should be discontinued for 8 days after treatment with Proveblue.

IX. SIDE EFFECTS AND ADVERSE REACTIONS

Summary of the safety profile

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

Intravenous injection of methylthioninium chloride has occasionally caused hypotension and heart arrhythmias, and these disorders may be fatal in rare cases.

Table of adverse reactions

The adverse reactions listed in the table below have occurred in adults, children and adolescents (0-17 years old) following intravenous administration. Frequencies are unknown (cannot be estimated from the data available). If provided, the frequency is based on a very small sample.

System Organ Class	Adverse Reactions	Frequency
Blood and lymphatic system disorders	Methaemoglobinaemia	Unknown frequency
	Hyperbilirubinaemia ¹	Unknown frequency
	Haemolytic anaemia	Unknown frequency
Immune system disorders	Immune system disorders	Unknown frequency
Psychiatric disorders	Confusion	Unknown frequency
	Agitation	Unknown frequency
Nervous system disorders	Dizziness	Very frequent
	Headache	Frequent
	Anxiety	Frequent
	Tremor	Unknown frequency
	Fever	Unknown frequency
	Aphasia	Unknown frequency
	Paraesthesia	Very frequent
	Dysgeusia	Very frequent
	Serotonergic syndrome with concomitant use of serotonergic drugs (see sections VII and X)	Unknown frequency
	Eye disorders	Mydriasis
Cardiac disorders	Heart arrhythmia	Unknown frequency
	Tachycardia	Unknown frequency
Vascular disorders	Hypertension	Unknown frequency
	Hypotension	Unknown frequency
Respiratory, thoracic, and mediastinal disorders	Dyspnoea	Unknown frequency
	Tachypnoea	Unknown frequency
	Hypoxia	Unknown frequency
Gastrointestinal disorders	Nausea	Very frequent
	Vomiting	Frequent
	Abdominal pain	Frequent
	Stool discoloration (greenish blue)	Unknown frequency
Skin and subcutaneous tissue disorders	Skin discoloration (blue)	Very frequent
	Sweating	Very frequent
	Hives	Unknown frequency
	Phototoxicity/Photosensitivity	Unknown frequency
Renal and urinary disorders	Chromaturia (greenish blue)	Very frequent
General disorders and administration site conditions	Chest pain	Frequent
	Local tissue necrosis at the injection site	Unknown frequency
	Pain at the injection site	Frequent
Other investigations	Decreased haemoglobin	Unknown frequency
Musculoskeletal and connective tissue disorders	Extremity pain	Very frequent

¹ Reported in infants only.

Paediatric population

Adverse reactions are the same as those described for adults (except for hyperbilirubinaemia, which has been noted in infants only).

X. INTERACTION WITH OTHER DRUGS AND OTHER TYPES OF INTERACTION

Methylthioninium chloride should be avoided in patients treated with drugs that enhance serotonergic transmission due to the potential appearance of severe CNS reactions, including life-threatening serotonergic syndrome. These include: SSRI (selective serotonin reuptake inhibitors), bupropion, buspirone, clomipramine, mirtazapine, and venlafaxine. If intravenous administration of methylthioninium chloride in patients treated with serotonergic drugs cannot be avoided, the lowest possible dose should be selected, and the patient should be observed for 4 hours following administration for central nervous system (CNS) effects (see sections VII and IX).

Methylthioninium chloride is an in vitro inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5. Clinical consequences from increased plasma concentrations of co-administered drugs that are sensitive substrates of the CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A enzymes cannot be ruled out.

Methylthioninium chloride is an in vitro CYP1A2 inducer. Clinical consequences are unknown.

Proveblue administration may temporarily increase or decrease clearance of drugs that are primarily metabolized by these enzymes. However, the clinical consequences seem to be minimal, since Proveblue is usually administered only once and in extremely urgent situations.

Methylthioninium chloride is a potent inhibitor of the OCT2, MATE1, and MATE2-K transporters. Clinical consequences of the inhibition are unknown. Proveblue administration may temporarily increase exposure for drugs that are primarily eliminated by renal transport and that are OCT2/MATE-dependent, including cimetidine, metformin, and acyclovir.

Methylthioninium chloride is a P-glycoprotein (P-gp) substrate. The clinical consequences seem to be minimal as it is usually administered only once and temporarily as usual in urgent situations.

XI. CHANGES IN LABORATORY TEST RESULTS

In case of suspected methaemoglobinaemia, it is advisable to measure the oxygen saturation by co-oximetry, where this method is available, as pulse oximetry may provide a false estimation of oxygen saturation during the administration of methylthioninium chloride.

Bispectral index (BIS): methylthioninium chloride may interfere with BIS values.

XII. PRECAUTIONS RELATED TO CARCINOGENIC, MUTAGENIC, TERATOGENIC, AND FERTILITY EFFECTS

Repeat dose toxicity

One-month repeat dose toxicity studies in dogs showed no gross toxic effects.

Adverse reactions, seen at exposure levels similar to clinical exposure 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 blood bilirubin values and an increased incidence of moderate urine bilirubin.

Genotoxicity

Methylthioninium chloride was mutagenic in gene mutation assays performed in bacteria and mouse lymphoma cells, but not in the in vivo mouse micronucleus assay when administered by intravenous route at 62 mg/kg.

Carcinogenicity

Evidence of carcinogenic activity of methylthioninium chloride has been shown in male mice and male rats. Equivocal evidence of carcinogenic activity was observed in female mice. No evidence of carcinogenic activity was observed in female rats.

Reproductive toxicity

In vitro, methylthioninium chloride has been shown to reduce motility of human sperm in a dose-dependent manner. It has also been shown to inhibit growth of cultured two-cell mouse embryos and production of progesterone in cultured human luteal cells.

In rats and rabbits, teratogenic effects have been noted as foetal and maternal toxicity. In rats, increased resorption rates have been observed.

Fertility

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

XIII. DOSAGE AND ADMINISTRATION ROUTE

Proveblue should be administered by a healthcare professional.

Dosage

Adults

The usual dose is 1 to 2 mg per kg body weight, i.e., 0.2-0.4 ml per kg body weight, given over 5 minutes.

A repeat dose (1 to 2 mg/kg body weight, i.e., 0.2-0.4 ml/kg body weight) may be given one hour after the first dose in case of persistent or recurrent symptoms or if methaemoglobin levels remain significantly higher than the normal clinical range.

Treatment does not usually exceed one day.

The maximum recommended cumulative dose for the course of treatment is 7 mg/kg and should not be exceeded, since methylthionium chloride administered above the maximum dose may cause methaemoglobinaemia in susceptible patients.

In the case of aniline- or dapsone-induced methaemoglobinaemia, the maximum recommended cumulative dose for the course of treatment is 4 mg/kg (see section VII).

Too limited data is available to recommend a dosage for continuous infusion.

Special populations:

Elderly patients

No dose adjustment is required.

Patients with renal impairment

Methylthionium chloride should be used with caution in patients with moderate or severe renal impairment since there is limited data available and methylthionium chloride is primarily renally eliminated. Dose reduction may be required (<1 mg/kg).

Patients with hepatic impairment

There is no experience in patients with severe hepatic impairment.

Paediatric population

Infants >3 months old, children and adolescents:

Same dosage as for adults.

Infants ≤3 months old and newborns:

The recommended dose is 0.3-0.5 mg/kg body weight, i.e., 0.06 to 0.1 ml/kg body weight, given over 5 minutes.

A repeat dose (0.3 to 0.5 mg/kg body weight, i.e., 0.06-0.1 ml/kg body weight) may be given one hour after the first dose in cases of persistent or recurrent symptoms or if

methaemoglobin levels remain significantly higher than the normal clinical range (see section 4.4 for important safety information).

Treatment does not usually exceed one day.

Administration route

For intravenous use.

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

It should be injected very slowly over 5 minutes.

It should not be administered by subcutaneous or intrathecal injection.

This drug should not be mixed with other drugs. It must especially not be mixed with sodium chloride 9% (9 mg/ml) solution for injection as it has been demonstrated that chloride reduces the solubility of methylthioninium chloride.

XIV. OVERDOSE OR UNINTENTIONAL INGESTION SIGNS AND MANAGEMENT

Individuals without methaemoglobinaemia

Administration of large intravenous doses (≥ 7 mg/kg) of Proveblue® to individuals without methaemoglobinaemia induces nausea and vomiting, chest tightness, chest pain, tachycardia, restlessness, intense sweating, tremor, mydriasis, greenish blue urine discoloration, blue skin and mucous membrane colour, abdominal pain, dizziness, paraesthesia, headache, confusion, hypertension, mild methaemoglobinaemia (up to 7%) and electrocardiogram changes (T wave flattening or inversion). These characteristics usually resolve within 2-12 hours of the injection.

Individuals with methaemoglobinaemia

Cumulative doses of methylthioninium chloride may cause dyspnoea and tachypnoea, probably related to decreased oxygen availability due to methaemoglobinaemia, chest pain, tremor, cyanosis, and haemolytic anaemia.

Haemolytic anaemia has also been reported in cases 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 following administration of 20 mg/kg methylthioninium chloride.

Death occurred in two infants following administration of 20 mg/kg methylthioninium chloride. Both infants showed complex medical conditions and methylthioninium chloride was only partially responsible.

The patient must be observed, and methaemoglobin levels should be monitored, with supportive measures taken as required.

XV. HOW SUPPLIED

Carton with five 10 mL ampoules.
Carton with five 2 mL ampoules.

XVI. STORAGE RECOMMENDATIONS

Maintain the ampoule in the carton tightly closed.
Protect from light.
Store at no more than 25°C (10 mL size).
Store at no more than 30°C (2 mL size).

XVII. PRECAUTIONARY STATEMENTS

Literature for physicians only.
This drug may cause drowsiness and affect alertness, and therefore you should not drive or use heavy machinery while you are taking it.
The drug should be used immediately after opened or diluted.
Dispose of any remaining product if not completely administered.
Do not administer unless the solution is transparent and free of particles in suspension or precipitates.
Dispose of any remaining product if not completely administered.
In case of pregnancy or breastfeeding, talk to your doctor.
Please report suspected adverse reactions at: farmacovigilancia@cofepris.gob.mx and rfarmatecno@ackermanpharma.com.

XVIII. LABORATORY NAME AND ADDRESS

Ackerman Pharma, S.A. de C.V.
Avenida Jalisco No. 180 B, Primer Piso, Col. Tacubaya, C.P. 11870, Miguel Hidalgo, Mexico City, Mexico.

XIX. DRUG REGISTRATION NUMBER WITH THE MEXICAN SECRETARIAT OF HEALTH (SSA)

SSA No. 223300EL870108