**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Methylthioninium chloride Proveblue 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.
Each 2 ml ampoule contains 10 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

Acute symptomatic treatment of medicinal and chemical products-induced methaemoglobinaemia.
Methylthioninium chloride Proveblue is indicated in adults, children and adolescents (aged 0 to 17 years old).

### 4.2 Posology and method of administration

Methylthioninium chloride Proveblue is for administration by a healthcare professional.

Posology

*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 a period of 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 cases 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 Methylthioninium chloride administered above the maximum dose may cause methaemoglobinaemia in susceptible patients.

In the case of aniline- or dapsone-induced methaemaglobinaemia, the maximum recommended cumulative dose for the course of treatment is 4 mg/kg (see section 4.4).

Too limited data are available to support a continuous infusion dose recommendation.

Special populations

*Elderly*

No dose adjustment is necessary.

*Renal impairment*

In infants above 3 months, children and adolescents and in adults, the recommended dosage in patient with moderate renal impairment (eGFR 30-59 ml/min/1.73 $m^2$) is 1-2 mg/kg per body weight. If a 1 mg/kg dose is given, a repeat dose of 1 mg/kg 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. The maximum recommended cumulative dose for the course of treatment is 2 mg/kg (see section 5.2).

In infants above 3 months, children and adolescents and in adults, the recommended dosage in patient with severe renal impairment (eGFR 15-29 ml/min/1.73 $m^2$) is a single dose of 1 mg/kg per body weight. The maximum recommended cumulative dose for the course of treatment is 1 mg/kg.

Methylthioninium chloride should be used with caution in infants 3 months old or younger and newborn infants with moderate to severe renal impairment (eGFR 15-59 ml/min/1.73 $m^2$) since there is no data available and methylthioninium chloride is predominantly renally eliminated. Lower maximum cumulative doses (<0.5 mg/kg body weight) may be considered.

No dose adjustment is recommended in patients with mild renal impairment (eGFR 60-89 ml/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.

*Paediatric population*

Infants above 3 months, children and adolescents:
Same posology as for adults.

Infants 3 months old or younger and newborn infants:
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 a period of 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.

Method of administration

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

It must be injected very slowly over a period of 5 minutes.
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.

## 4.4 Special warnings and precautions for use

General

Methylthioninium chloride 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.

Methylthioninium chloride 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 Methylthioninium chloride Proveblue administration.

Electrocardiogram (ECG) and blood pressure should be monitored during and after treatment with Methylthioninium chloride 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), monoamine oxidase inhibitors and opioids (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

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 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 Interaction with other medicinal products and other forms of interaction

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. Opioids, for example, tramadol, fentanyl, pethidine, and dextromethorphan, may also increase the risk of developing serotonin syndrome, when used in combination with methylthioninium chloride. 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 a potent reversible inhibitor of monoamine oxidase (see section 4.4).

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 Proveblue 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 methylthioninium chloride 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. Methylthioninium chloride 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 Methylthioninium chloride 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 |
| 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Sheme at: www.mhra.gov.uk/yellowcard

### 4.9 Overdose

Individuals without methaemoglobinaemia

The administration of large intravenous doses (≥ 7 mg/kg) of Methylthioninium chloride 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.
Methylthioninium chloride Proveblue has been observed to stain tissues selectively. Its use in parathyroid surgery (not indicated) 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 Methylthioninium chloride 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.

After a single 1 mg/kg 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 $m^2$), moderate (eGFR 30-59 ml/min/1.73$m^2$), and severe (eGFR 15-29 ml/min/1.73$m^2$) renal impairment, respectively. Cmax 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. A longer mean half-life of 33 h were reported in subjects with severe renal impairment.

The $AUC_{0\text{-}96h}$ of Azure B after a single 1 mg/kg dose increased by 29%, 94%, and 339% in subjects with mild (estimated glomerular filtration rate (eGFR) 60 – 89 ml/min/1.73 $m^2$), moderate (eGFR 30-59 ml/min/1.73$m^2$), and severe (eGFR 15-29 ml/min/1.73$m^2$) renal impairment, respectively. Cmax increased by 23%, 13%, and 65% in subjects with mild, moderate, and severe renal impairment respectively.

Methylthioninium chloride Proveblue is an in vitro inhibitor of P-gp.

Methylthioninium chloride 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 methylthioniniul 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. 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

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.
Each carton contains a tray with 5 or 20 ampoules of 2 ml in blister.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

For single use only

Methylthioninium chloride Proveblue may be diluted in 50 ml glucose 50 mg/ml (5%) solution for injection to avoid local pain, in particular in paediatric population.
Before any administration, it is recommended to inspect the parenteral solutions to verify that they are free of particles. Do not use Methylthioninium chloride 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.

## 7. MARKETING AUTHORISATION HOLDER

PROVEPHARM SAS
22 rue Marc Donadille, 13013 Marseille, France

## 8. MARKETING AUTHORISATION NUMBER(S)

PLGB 40051/0002

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

## 10. DATE OF REVISION OF THE TEXT

23/05/2024