ANNEX I

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 national reporting system listed in Appendix V.

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_{0-96h} 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/1.73m^2), and severe (eGFR 15-29 ml/min/1.73m^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_{0-96h} 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/1.73m^2), and severe (eGFR 15-29 ml/min/1.73m^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 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. 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)

EU/1/11/682/001
EU/1/11/682/002
EU/1/11/682/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 May 2011
Date of latest renewal: 08 February 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Cenexi
52, Rue Marcel et Jacques Gaucher
94120 Fontenay-sous-Bois
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURS)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Methylthioninium chloride Proveblue 5 mg/ml solution for injection
methylthioninium chloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
5 ampoules of 10 ml

50 mg/10 ml

5 ampoules of 2 ml
20 ampoules of 2 ml
10 mg/2 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use only
For slow intravenous injection

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The medicine must be used immediately after opening or dilution.

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.
Keep the ampoule in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only
Any solution remaining in the opened ampoules must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Provepharm SAS
22 rue Marc Donadille, 13013 Marseille, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/682/001
EU/1/11/682/002
EU/1/11/682/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Methylthioninium chloride Proveblue 5 mg/ml injection
methylthioninium chloride
Intravenous use only

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 mg/10 ml
10 mg/2 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Methylthioninium chloride Proveblue 5 mg/ml solution for injection
methylthioninium chloride

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Methylthioninium chloride Proveblue is and what it is used for

Methylthioninium chloride (also called methylene blue) belongs to a group of medicines called antidotes.

Methylthioninium chloride Proveblue will be given to you or your child (0-17 years old) to treat problems with your blood resulting from exposure to some medicines or chemicals that can cause a disease called methaemoglobinaemia.

In methaemoglobinaemia, your blood contains too much methaemoglobin (an abnormal form of haemoglobin that is not able to transport oxygen around your body effectively). This medicine will help your haemoglobin return to normal and restore the transport of oxygen in the blood.

2. What you need to know before you are given Methylthioninium chloride Proveblue

You must not be given Methylthioninium chloride Proveblue
- if you are allergic to methylthioninium chloride or other thiazine dyes
- if your body does not produce enough of the enzyme G6PD (glucose-6-phosphate dehydrogenase)
- if your body does not produce enough of the enzyme NADPH (nicotinamide adenine dinucleotide phosphate) reductase
- if your blood disorder has been caused by nitrite during treatment of cyanide poisoning
- if your blood disorder has been caused by chlorate poisoning.

Warnings and precautions
Talk to your doctor or nurse before you are given Methylthioninium chloride Proveblue
- if you have moderate or severe renal disease; lower single dose (1 to 2 mg/kg maximum) is needed
- if your blood disorder has been caused by a chemical called aniline, which is contained in dyes; lower doses may be needed and total cumulative dose should not exceed 4 mg/kg (see section 3 of this package leaflet)
- if your blood disorder has been caused by a medicine called dapsone (used to treat leprosy and other skin conditions); lower doses may be needed and total cumulative dose should not exceed 4 mg/kg (see section 3)

- if you suffer from hyperglycaemia or diabetes mellitus, as these conditions may be worsened by the glucose solution used for the dilution of the medicine
- your urine and stools may turn a blue-green colour; and skin may possibly turn a blue colour when you are treated with Methylthioninium chloride Proveblue. This discolouration is expected and will disappear after the treatment has ended

If any of the above applies to you, please consult your doctor.

Photosensitivity
Methylthioninium chloride may cause a photosensitivity reaction in the skin (sunburn-like reaction) when exposed to strong light sources, such as light therapy, lights in operating rooms and pulse oximeters.
Protective measures against exposure to light should be taken.

Monitoring tests
You will undergo monitoring tests during and after treatment with Methylthioninium chloride Proveblue.

Children
Special care must be taken with Methylthioninium chloride Proveblue:
- in newborns and infants 3 months old or younger, lower doses are recommended (see section 3 of this package leaflet).

Other medicines and Methylthioninium chloride Proveblue
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

You should not be given methylthioninium chloride at the same time you are taking certain medicines to treat depression or anxiety which affect a brain chemical called serotonin. When used in combination with these medicines methylthioninium chloride may cause serotonin syndrome, which can be potentially life-threatening. Such medicines include:
- Selective serotonin reuptake inhibitors (SSRIs) such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and zimelidine
- bupropion
- buspirone
- clomipramine
- mirtazapine
- venlafaxine
- Monoamine oxidase inhibitors

Opioids, for example, tramadol, fentanyl, pethidine, and dextromethorphan, may also increase the risk of developing serotonin syndrome, when used in combination with methylthioninium chloride.

However, if the intravenous use of methylthioninium chloride cannot be avoided, you should be administered the lowest possible dose and observed closely for up to 4 hours after administration.

If you have any doubts about whether this medicine should be given to you, consult your doctor.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

The use of Methylthioninium chloride Proveblue during pregnancy is not recommended unless it is clearly necessary, for example in a life-threatening situation.

Due to a lack of available data on whether methylthioninium chloride passes into human breast milk, breast-feeding should be discontinued for up to 8 days after treatment with this medicine.

Driving and using machines
Do not drive or use any tools or machines as methylthioninium chloride has moderate influence on the ability to drive and use machines.

3. How Methylthioninium chloride Proveblue is given

Your doctor will inject this medicine into a vein (intravenously) slowly over a period of 5 minutes.

Adults, children above 3 months and elderly
The usual dose is 1 to 2 mg per kilogram of your body weight, i.e. 0.2 to 0.4 ml per kilogram given over a period of 5 minutes. A second dose may be given after one hour if required.

The maximum recommended cumulative dose for the course of treatment is 7 mg/kg.
If your blood disorder has been caused by aniline or dapsone, total cumulative dose should not exceed 4 mg/kg (see section 2).

Usually, treatment should not exceed one day.

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.

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).

Infants 3 months old or younger
The recommended dose is 0.3 to 0.5 mg/kg body weight, i.e. 0.06 to 0.1 ml/kg, 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) may be given after one hour in case of persistence or recurrence of symptoms. Usually, treatment should not exceed one day.

This medicine may be diluted in 50 ml glucose 50 mg/ml (5%) solution for injection to avoid local pain, in particular in children.

If you are given more Methylthioninium chloride Proveblue than you should
As this medicine will be given to you whilst you are in hospital, it is unlikely that you will be given too much or too little, however, tell your doctor if you notice one of the following adverse reactions:
- feeling sick,
- stomach pain,
- chest pain,
- dizziness,

- headache,
- sweating,
- confusion,
- an increase in methaemoglobin (an abnormal form of haemoglobin in the blood),
- high blood pressure,
- shortness of breath,
- abnormally fast beating of the heart,
- tremor,
- skin discolouration. Your skin may turn blue
- reduction in red blood cells which may turn your skin pale and make you breathless and weak,
- jaundice (yellowing of the skin and eyes), this has only been reported in infants.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Methylthioninium chloride Proveblue can cause side effects, although not everybody gets them.

These effects are the same in adults and children except jaundice which has only been reported in infants.

- **Very common side effects** (may affect more than 1 in 10 people)
- pain in extremity
- dizziness
- sweating
- skin discolouration. Your skin may turn blue
- blue or green urine
- numbness and tingling
- abnormal taste in mouth
- nausea

- **Common side effects** (may affect up to 1 in 10 people):
- stomach pain
- chest pain
- headache
- anxiety
- injection site pain
- vomiting

- **Not known** (frequency cannot be estimated from the available data):
- serotonin syndrome when Methylthioninium chloride Proveblue has been taken with certain medicines to treat depression or anxiety, see section 2
- decreased haemoglobin (protein in red blood cells that carry oxygen in the blood) levels may be

reported during blood tests
- reduction in red blood cells which may turn your skin pale and make you breathless and weak
- local tissue damage at the injection site
- jaundice (yellowing of the skin and eyes) – this has only been reported in infants
- problems with speech
- high or low blood pressure
- agitation
- lack of oxygen
- irregular heartbeat, including an abnormally slow or fast beating of the heart
- severe allergic reactions (so called anaphylactic reaction which may cause your throat or face to swell, difficulty breathing or a severe rash)
- an increase in methaemoglobin (an abnormal form of haemoglobin in the blood)
- shortness of breath
- confusion
- shaking
- hives
- fever
- rapid breathing
- dilated pupils
- discoloured stools. They may appear green or blue
- increased sensitivity of your skin to light (photosensitivity)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Methylthioninium chloride Proveblue

Keep this medicine out of the sight and reach of children.

You should not be given this medicine after the expiry date which is printed on the carton and the ampoule labels after EXP. The expiry date refers to the last day of that month. The doctor or nurse will check that the expiry date on the label has not been passed before administering the injection to you.

Do not refrigerate or freeze. Keep the ampoule in the original package in order to protect from light.

The medicine must be used immediately after opening or dilution.

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.

6. Contents of the pack and other information

What Methylthioninium chloride Proveblue contains
- The active substance is methylthioninium chloride.

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.
- The other ingredient is water for injections.

What Methylthioninium chloride Proveblue looks like and contents of the pack

Methylthioninium chloride Proveblue is a clear dark blue solution for injection (injection) and is supplied in clear glass ampoules.
Each box contains a tray with 5 ampoules of 10 ml.
Each box contains a tray with 5 ampoules of 2 ml.
Each box contains a tray with 20 ampoules of 2 ml.

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Provepharm SAS
22 rue Marc Donadille, 13013 Marseille, France

Manufacturer
Cenexi
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

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The following information is intended for healthcare professionals only:

Preparation for intravenous administration

Use immediately on opening. Inject very slowly over a period of 5 minutes.

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 not be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection because it has been demonstrated that chloride reduces the solubility of methylthioninium chloride.

Additional information on how Methylthioninium chloride Proveblue can be given is provided in section 3 of the Package Leaflet.

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