

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.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for 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 Proveblue 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

Methylthioninium chloride Proveblue should be used with caution in patients with moderate to severe renal disease since there is limited data available and methylthioninium chloride is predominantly renally eliminated. Lower doses (<1 mg/kg) may be needed.

Hepatic impairment

There is no experience in patients with severe hepatic impairment.

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 of 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 sodium nitrite-induced methaemoglobinaemia
- Patients with methaemoglobinaemia due to chlorate poisoning
- Deficiency in NADPH 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.

Electrocardiograph (ECG) and blood pressure should be monitored during and after treatment with Methylthioninium chloride Proveblue as hypotension and cardiac arrhythmia are potential adverse effects (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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Methylthioninium chloride should be avoided in patients receiving medicinal products that enhance serotonergic transmission including 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 CNS effects for up to 4 hours after administration.

An *in vitro* study showed that methylthioninium chloride is a potent inhibitor of CYP450 1A2, 2B6, 2C9 and 2C19. The clinical relevance of this finding is unknown but it cannot be excluded that the systemic exposure of medicinal products being substrates for these isoenzymes may be increased on concomitant administration with methylthioninium chloride.

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 6 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 Proveblue 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

The most commonly reported adverse reactions are nausea, abdominal and chest pain, headache, dizziness, tremors, anxiety, confusional state, dyspnoea, tachycardia, hypertension, the formation of methaemoglobinaemia and hyperhidrosis.

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

The adverse reactions listed in the table below occur in adults, children and adolescents (aged 0 to 17 years old) after intravenous administration (except hyperbilirubinaemia, reported in infants only). The frequencies are not known (cannot be estimated from the available data).

SYSTEM ORGAN CLASS	ADVERSE REACTION
Blood and lymphatic system disorders	Methaemoglobinaemia, hyperbilirubinaemia ¹
	Haemolytic anaemia
Immune system disorders	Anaphylactic reactions
Psychiatric disorders	Confusional state
	Agitation
Nervous system disorders	Dizziness, headache, anxiety, tremor
	Fever
	Aphasia
Eye disorders	Mydriasis
Cardiac disorders	Cardiac arrhythmia
	Tachycardia
Vascular disorders	Hypertension
	Hypotension
Respiratory, thoracic and mediastinal disorders	Dyspnoea
	Tachypnoea
	Hypoxia
Gastrointestinal disorders	Nausea, vomiting, abdominal pain, faeces discoloration (blue-green)
Skin and subcutaneous tissue disorders	Skin discoloration (blue), sweating
	Urticaria
Renal and urinary disorders	Cromaturia (blue-green)
General disorders and administration site conditions	Chest pain
	Local tissue necrosis at the injection site
Investigations	Haemoglobin decreased

¹ Reported in infants only

Paediatric population

Adverse reactions are the same as in adults (except hyperbilirubinaemia, reported in infants only).

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 paediatric 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 estimated terminal half-life of methylthioninium chloride after intravenous administration is 18.5h.

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 sodium chloride 0.9 mg/ml (0.9%) solution for injection because it has been demonstrated that chloride reduces the solubility of methylthioninium chloride.

6.3 Shelf life

3 years

From a microbiological point of view, unless the method of opening 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 box contains a tray with 5 ampoules of 10 ml in blister pack.

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

Hôtel Technologique, Technopôle de Château-Gombert

45 rue Frédéric Joliot Curie

13013 Marseille, France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/682/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 May 2011

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. Manufacturing authorisation holder responsible for batch release**
- B. Conditions of the marketing authorisation**

A. Manufacturing authorisation holder responsible for batch release

Name and address of the manufacturer responsible for batch release

Pierrel S.p.A.
s.s. Appia 7 bis, 46/48
IT-81043 Capua (CE)
Italy

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 of the marketing authorisation

- **Conditions or restrictions regarding supply and use imposed on the marketing authorisation holder**

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

- **Conditions or restrictions with regard to the safe and effective use of the medicinal product**

Not applicable

- **Other conditions**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1 dated September 2010 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached

- At the request of the EMA

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX/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

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. 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 reach and sight 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
Hôtel Technologique, Technopôle de Château-Gombert
45 rue Frédéric Joliot Curie
13013 Marseille, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/682/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

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

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.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

In this leaflet:

1. What Methylthioninium chloride Proveblue is and what it is used for
2. Before you are given Methylthioninium chloride Proveblue
3. How Methylthioninium chloride Proveblue is given
4. Possible side effects
5. How to store Methylthioninium chloride Proveblue
6. Further information

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. BEFORE YOU ARE GIVEN METHYLTHIONINIUM CHLORIDE PROVEBLUE

You must not be given Methylthioninium chloride Proveblue:

- if you are allergic (hypersensitive) 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 sodium nitrite
- if your blood disorder has been caused by chlorate poisoning.

Special care must be taken with Methylthioninium chloride Proveblue:

- if you have moderate or severe renal disease; lower doses (< 1 mg/kg) may be 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

Monitoring tests

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

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

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).

Taking other medicines

Please tell your doctor, pharmacist or nurse if you are taking or have recently taken any other medicine, including medicines obtained without a prescription.

You should not be given Methylthioninium chloride Proveblue at the same time you are taking certain medicines to treat depression or anxiety which affect a brain chemical called serotonin. Such medicines include:

- Selective serotonin reuptake inhibitors (SSRIs) such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and zimelidine
- bupropion
- buspirone
- clomipramine
- mirtazapine
- venlafaxine.

However, if the intravenous use of Methylthioninium chloride Proveblue 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

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 6 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 METHYLTHIONIUM CHLORIDE PROVEBLUE WILL BE GIVEN

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

Adults, children above 3 months and the 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.

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 Methylthionium 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, Methylthionium 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.

The frequencies of these side effects are not known (cannot be estimated from the available data):

- high or low blood pressure
- 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)
- blue or green urine
- discoloured stools. They may appear green or blue
- skin discolouration. Your skin may turn blue
- feeling and being sick
- stomach pain
- chest pain
- headache
- dizziness
- confusion
- anxiety
- shaking
- sweating
- shortness of breath
- 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
- agitation
- lack of oxygen
- hives
- fever
- rapid breathing
- dilated pupils

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE METHYLTHIONINIUM CHLORIDE PROVEBLUE

Keep out of the reach and sight of children.

You should not be given this medicine after the expiry date which is printed on the carton, the blister 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. The solution is normally a clear dark blue liquid.

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

6. FURTHER 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.
- 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 in blister pack.

Marketing Authorisation Holder

Provepharm SAS

Hôtel Technologique, Technopôle de Château-Gombert, 45 rue Frédéric Joliot Curie, 13013 Marseille, France

Manufacturer

Pierrel S.p.A.

s.s. Appia 7 bis, 46/48 - 81043 Capua, Italy

Cenexi

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

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

België/Belgique/Belgien: Lamepro B.V., Tél/Tel: +31 (0) 76-5600030

България: Provepharm SAS, Тел. +33 (0)4 91 11 87 59

Česká republika: Provepharm SAS, Tel: +33 (0)4 91 11 87 59

Danmark: NordMedica International A/S, Tlf: +45 33 33 76 33

Deutschland: Dr. Franz Köhler Chemie GmbH, Tel: +49 (0) 6251-1083-373

Eesti: Provepharm SAS, Tel: +33 (0)4 91 11 87 59

Ελλάδα: a VIPharma International AE, Τηλ. +30-210-6194170

España: Laboratorios Farmacéuticos ROVI, S.A., Tel: +34 913756230

France: Inresa, Tél: +33 (0)3 89 70 76 60

Ísland: NordMedica International A/S, Simi: +45 33 33 76 33

Italia: Italfarmaco S.p.A., Tel: +39-02-6443 1

Κύπρος: Isangen Pharma Cyprus Ltd, Τηλ. +357-24-638833

Latvija: Provepharm SAS, Tel: +33 (0)4 91 11 87 59

Lietuva: Provepharm SAS, Tel: +33 (0)4 91 11 87 59

Luxembourg/Luxemburg: Lamepro B.V., Tél/Tel: +31 (0) 76-5600030

Magyarország: Provepharm SAS, Tel: +33 (0)4 91 11 87 59

Malta: Provepharm SAS, Tel: +33 (0)4 91 11 87 59

Nederland: Lamepro B.V., Tel: +31 (0) 76-5600030

Norge: NordMedica International A/S, Tlf: +45 33 33 76 33

Österreich: KAIROS Life Sciences GmbH, Tel: +43 699 18955731

Polska: Provepharm SAS, Tel: +33 (0)4 91 11 87 59

Portugal: Labesfal - Laboratórios Almiro, S.A., Tel : + 351 232 831100

România: Provepharm SAS, Tel: +33 (0)4 91 11 87 59

Slovenija: Provepharm SAS, Tel: +33 (0)4 91 11 87 59

Slovenská republika: Provepharm SAS, Tel: +33 (0)4 91 11 87 59

Suomi/Finland: NordMedica International A/S, Puh/Tel: +45 33 33 76 33

Sverige: NordMedica International A/S, Tel: +45 33 33 76 33

United Kingdom and the Republic of Ireland: Martindale Pharmaceuticals, Tel: + 44 (0)1277 266600

This leaflet was last approved 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 medical or 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. Methylthioninium chloride Proveblue must not be diluted with sodium chloride (NaCl) 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.