

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 sections 4.

What is in this leaflet

1. What Methylthioninium chloride Proveblue is and what it is used for
2. What you need to know 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. Contents of the pack and other 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. 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 m²) 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 m²) 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 m²) since there is no data available and methylthioninium



28068953

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 m²).

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 (See details below). By reporting side effects you can help provide more information on the safety of this medicine.

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

or search for MHRA Yellow Card in the Google Play or Apple App Store

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.
- 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.

Marketing Authorisation Holder

Provepharm SAS

22 rue Marc Donadille, 13013 Marseille, France

Manufacturer responsible for batch release

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:

United Kingdom

Provepharm UK Limited

450 Bath Road

Longford Heathrow

UB7 0EB London

Greater London, UK

Tel: +44 20 8078 5235

This leaflet was last revised in 03/2024

Marketing Authorisation number : PLGB 40051/0002

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.



28068953

28068953