Methylthioninium chloride Proveblue 5 mg/ml solution for injection.
Prescribing Information. Consult Summary of Product Characteristics before prescribing.

Marketing Authorisation number and basic NHS cost: PLGB 40051/0002 £196.89 per pack of 5 of 10ml ampoules. **Legal Category:** POM **Presentation:** Each ml of solution contains 5 mg methylthioninium chloride.. **Uses:** Proveblue is indicated for acute symptomatic treatment of medicinal and chemical products-induced methaemoglobinaemia in adults, children and adolescents (aged 0 to 17 years old). **Dosage and administration:** *Adults*-Usual dose is 1 to 2 mg per kg body weight, given over a period of 5 minutes. A repeat dose (1 to 2 mg/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. Maximum recommended cumulative dose is 7 mg/kg. In the case of aniline- or dapsone-induced methaemaglobinaemia, the maximum recommended cumulative dose is 4 mg/kg. Too limited data are available to support a continuous infusion dose recommendation. *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, given over a period of 5 minutes. A repeat dose (0.3 to 0.5 mg/kg body weight,) may be given one hour after the first dose. Treatment does not usually exceed one day. **Method of administration**: For intravenous use. for administration by a healthcare professional. Product 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. Must be injected very slowly over a period of 5 minutes to prevent high local concentrations of the compound from producing additional methaemoglobin. Must not be administered by subcutaneous or intrathecal injection. Must especially not be mixed with sodium chloride 9 mg/ml (0.9%) solution for injection because as chloride reduces the solubility of methylthioninium chloride. For instructions on handling and dilution of the medicinal product before administration, see SmPC. **Elderly:** No change in dose is required. **Hepatic impairment:** Safety and efficacy have not been established, no data are available.. **Renal impairment**: In patients > 3 months in moderate renal impairment dose is 1-2mg/ kg. If 1 mg/kg is given this can be repeated with a maximum cumulative dose of 2mg/kg. In severe renal impairment the dose is a single dose of 1mg/kg. **Paediatric population:** Infants 3 months old or younger and newborn infants: The recommended dose is 0.3-0.5 mg/kg body weight, given over a period of 5 minutes. A repeat dose (0.3 to 0.5 mg/kg body weight,) may be given one hour after the first dose. 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. **Pregnancy:** There are no adequate data from the use of methylthioninium chloride in pregnant women. Studies in animals have shown reproductive toxicity. 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. **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. **Special warnings and precautions for use:** 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. Can exacerbate dapsone-induced haemolytic anaemia 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.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. Electrocardiogram (ECG) and blood pressure should be monitored during and after treatment as hypotension and cardiac arrhythmia are potential adverse reactions. Failure to respond suggests cytochrome b5 reductase deficiency, glucose-6- phosphate dehydrogenase deficiency or sulfhaemoglobinemia. Alternative treatment options should be considered. 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. The lowest possible dose should be chosen and the patient observed closely for central nervous system (CNS) effects for up to 4 hours after. If symptoms of serotonin syndrome occur, discontinue use of methylthionine

chloride, and initiate supportive treatment. *Patients with hyperglycaemia or diabetes mellitus:* If diluted in glucose 50 mg/ml (5%) solution for injection, methylthionine chloride must be used with caution in patients with hyperglycaemia or diabetes mellitus. *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. **Side Effects:** Consult the summary of product characteristics for other side effects. 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. Other serious adverse reactions reported are, haemolytic anaemia, anaphylactic reactions. local tissue necrosis at the injection site.

Further information is available from: Provepharm UK Ltd, 450 Bath Road, Heathrow, UB7 0EB Tel: +44 20 8078 5235.
E-mail: safety-uk@provepharm.com
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Adverse reactions should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse reactions should also be reported to safety-uk@provepharm.com