SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methylthioninium Chloride 10 mg/ml Sterile Concentrate for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate for solution for injection contains 10 mg Methylthioninium Chloride (trihydrate).

Each 5 ml vial contains 50 mg of Methylthioninium Chloride (trihydrate).

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for injection

A clear, blue coloured sterile solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Methylthioninium Chloride is primarily used in the treatment of medicinal and chemical induced and genetic methaemoglobinaemia that are not due to a structural abnormality of haemoglobin.

Methylthioninium Chloride is indicated in adults, and children and adolescents (aged 0 to 17 years old).

4.2 Posology and method of administration

Methylthioninium Chloride is for administration by a healthcare professional.

Methylthioninium Chloride should be administered orally or by intravenous (IV) injection. In the treatment of acute methaemoglobinaemia, the IV route of administration is usually preferred because it provides a more rapid onset of effect. However, in large doses, Methylthioninium Chloride can itself produce methaemoglobinaemia and the methaemoglobin concentration should therefore be closely monitored during treatment.

Intravenous Use

The usual IV dose of Methylthioninium Chloride for adults and children over 3 months of age is as a 1% solution in doses of 1 to 2 mg/kg bodyweight (i.e. 0.1-0.2 ml/kg body weight) injected over a period of at least five minutes. A repeat dose may be given not less than 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 7 mg/kg and should not be exceeded.

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

The available data are insufficient to support a dose recommendation for continuous infusion.

Oral Use

When treatment is less urgent, and for chronic dosing of genetic methaemoglobinaemia, Methylthioninium Chloride 3-6 mg/kg (generally 300 mg daily in adults) is given orally in divided doses over 24 hours with ascorbic acid 500 mg daily. A suitable dilution for oral dosing would be 5-10 ml of the 1% solution diluted to 100-200 ml with water for injection. The high volume is suggested to reduce the degree of gastrointestinal disturbance and dysuria.

The dosage of Methylthioninium Chloride should be calculated on the basis of lean bodyweight.

Special populations

Elderly

No dose adjustment is necessary.

Renal impairment

Methylthioninium Chloride should be used with caution in patients with moderate renal disease since there is limited data available and Methylthioninium Chloride is predominantly eliminated renally. Lower doses (<1 mg/kg) may be needed. (see also section 4.3).

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: Birth to 3 months (inclusive):

The recommended dose for IV administration is 0.3-0.5 mg/kg body weight, i.e. 0.03 to 0.05 ml/kg body weight, given over a period of at least five minutes.

A repeat dose (0.3 to 0.5 mg/kg body weight, i.e. 0.03-0.05 ml/kg body weight) may be given not less than 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).

Method of administration

Intravenous use:

Methylthioninium Chloride may be diluted in 50 ml glucose 50 mg/ml (5%) solution for injection to avoid local pain, in particular in the paediatric population.

It must be injected very slowly over a period of at least five 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.

Oral Use:

A suitable dilution for oral dosing would be 5-10 ml of the 1% solution diluted to 100-200 ml with water for injection. The high volume is suggested to reduce the degree of gastrointestinal disturbance and dysuria.

4.3 Contraindications

- Use in pregnancy and lactation is contraindicated as its safe use during pregnancy has not yet been established.
- Patients with severe renal impairment
- Hypersensitivity to the active substance, or to any other thiazine dyes
- Patients with methaemoglobinaemia due to chlorate poisoning as Methylthioninium Chloride may convert the chlorate to hypochlorite which is an even more toxic compound.
- Patients with methaemoglobinaemia as a direct consequence of treating cyanide poisoning with sodium nitrite
- Patients with glucose-6-phosphate dehydrogenase deficiency, due to the risk of haemolytic anaemia
- Deficiency in NAPDH reductase
- Intrathecal injection of Methylthioninium Chloride which can result in neural damage

4.4 Special warnings and precautions for use

Long term administration of Methylthioninium Chloride may result in marked anaemia due to accelerated destruction of erythrocytes; haemoglobin concentrations should be checked frequently.

If Methylthioninium Chloride is injected subcutaneously or if extravasation occurs, necrotic abscesses may result.

Methylthioninium Chloride must be injected very slowly over a period of at least five minutes to prevent high local concentrations of the compound from producing additional methaemoglobin.

It imparts a blue-green colour to urine and 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 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.

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.

Anaesthetists should be vigilant for methaemoglobinaemia in patients receiving dapsone therapy and for BIS (Bispectral Index) interference with Methylthioninium Chloride administration.

Electrocardiograph (ECG) and blood pressure should be monitored during and after treatment with Methylthioninium Chloride 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.

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 reupdate inhibitors (SSRIs), serotonin and norepinephrine reupdate inhibitors (SNRIs), and monoamine oxidase inhibitors (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. 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 (see sections 4.4 and 4.8).

Methylthioninium Chloride is an *in vitro* inhibitor of CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5. The clinical consequences of increases in plasma concentration of co-administered drugs which are sensitive to CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A substrates cannot be ruled out.

Methylthioninium chloride is an *in vitro* inducer of CYP1A2. The clinical consequence is not known.

The administration of methylthioninium chloride has the potential to transiently increase or decrease the clearance of drugs that are primarily metabolised by the enzymes. The clinical consequences are however considered minimal since methylthioninium chloride is used often only once and in an acute emergency setting.

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 has the potential to transiently increase the exposure of drugs primarily cleared by renal transport involving the OCT2/MATE pathway, including cimetidine, metformin and aciclovir.

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

Use in 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 should not be used during pregnancy unless clearly necessary, e.g. in life-threatening methaemoglobinaemia.

Although intra-amniotic injection of Methylthioninium Chloride has been used to diagnose premature rupture of foetal membranes or to identify separate amniotic sacs in twin pregnancies, there have been several reports of haemolytic anaemia and hyperbilirubinaemia in neonates exposed to Methylthioninium Chloride in the amniotic cavity.

Use in Lactation

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, unless the clinical need clearly outweighs the potential risk.

Fertility

In vitro, Methylthioninium Chloride has been shown to reduce motility of human sperm in a dose dependent manner.

4.7 Effects on ability to drive and use machines

Methylthioninium Chloride has a 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 observed during clinical trials are dizziness, paraesthesia, dysgeusia, nausea, skin discoloration, chromaturia, sweating, injection site pain and pain in extremity.

Oral Administration

Oral administration may cause gastrointestinal disturbances (nausea, vomiting and diarrhoea) and dysuria.

Intravenous Administration

After intravenous administration, Methylthioninium Chloride may cause nausea, vomiting, abdominal and chest pain, headache, dizziness, mental confusion and profuse sweating.

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 REACTION	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 4.4 and 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

SYSTEM ORGAN CLASS	ADVERSE REACTION	FREQUENCY
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Not known
	Tachypnoea	Not known
	Hypoxia	Not known
Gastrointestinal disorders	Nausea	Very common
	Abdominal pain	Common
	Vomiting	Common
	Faeces discolouration (blue-green)	Not known
Skin and subcutaneous tissue disorders	Skin discolouration (blue)	Very common
	Sweating	Very common
	Urticaria	Not known
	Phototoxicity / Photosensitivity	Not known
Renal and urinary disorders	Cromaturia (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

Use of Methylthioninium Chloride for endoscopic tattoo (not an approved indication) has been associated with vascular necrosis, mucosal ulceration, mural necrosis, extramural fat necrosis and inflammatory changes in the colon.

Injection of Methylthioninium Chloride into joint space (not an approved indication) has resulted in effusion in the treated joint.

Paediatric population

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

High Doses

With very high doses methaemoglobinaemia and haemolysis may occur. Infants and patients with glucose-6-phosphate dehydrogenase deficiency are particularly susceptible to haemolysis from treatment with Methylthioninium Chloride.

High doses, if not adequately diluted, could cause thrombophlebitis. Not more than 350 mg of Methylthioninium Chloride should be diluted in each 500 ml of infusion fluid.

Blue Colouration

Methylthioninium Chloride imparts a blue colour to the skin, saliva, oral mucosa and teeth, and a blue-green colour to urine and faeces.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal

product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme;

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In high concentrations, Methylthioninium Chloride can oxidise haemoglobin to methaemoglobin, thus increasing methaemoglobinaemia. Nonspecific side effects seen with high doses included precordial pain, dyspnoea, restlessness, apprehension, tremors, and a sense of oppression. Large doses are irritant to the urinary tract. In addition, it can produce a mild haemolysis with moderate hyperbilrubinaemia, reticulosis and slight anaemia. Rarely, however, a severe haemolytic anaemia with Heinz body formation has resulted. Methylthioninium Chloride in large doses could cause a blue discolouration to the skin after methaemoglobin levels had returned to normal.

More specifically:

Individuals without methaemoglobinaemia

The administration of large intravenous doses (≥ 7 mg/kg) of Methylthioninium Chloride 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.

Treatment of Overdosage

General supportive care and removal of the toxin should be carried out. Depending on the severity of the poisoning and the causative agent, this may include removal of contaminated clothing, rinsing the skin with water, ipecac-induced emesis or gastric lavage, charcoal, cathartics, and even haemodialysis.

There is no specific antidote. The patient should be maintained under observation, the methaemoglobin level should be monitored and appropriate supportive measures taken as necessary.

In severe and refractory cases methaemoglobinaemia, blood transfusions and even exchange transfusions, and (possibly) hyperbaric oxygen therapy may be the only

alternative available. Ascorbic acid works slowly and is probably no benefit in the acute situation. Removal of the toxic compound and supportive therapy are essential.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: All other therapeutic products, antidotes, ATC code: V03AB17.

In patients with methaemoglobinemia, therapeutic doses of Methylthioninium Chloride can lower the levels of methaemoglobin in the red blood cells. It activates a normally dormant reductase enzyme system which reduces the Methylthioninium Chloride to leucomethylthioninium chloride, which in turn is able to reduce methaemoglobin to haemoglobin. However, in large doses, Methylthioninium Chloride can itself produce methaemoglobinemia and the methaemglobin concentration should therefore be closely monitored during treatment. Methylthioninium Chloride is not effective for the treatment of methaemoglobinemia in patients with glucose-6-phosphate dehydrogenase deficiency as these patients have a diminished capacity to reduce Methylthioninium Chloride to leucomethylthioninium chloride. It is also potentially harmful as patients with glucose-6-phosphate dehydrogenase deficiency are particularly susceptible to the haemolytic anaemias induced by Methylthioninium Chloride.

Methylthioninium Chloride also possesses weak antiseptic and bacteriological staining properties and is reported to inhibit amine oxidase in tissues. The drug appears to bind irreversibly to viral nucleic acid and cause disruption of the virus molecule upon exposure to light.

Methylthioninium Chloride 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 the 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

Intravenous Administration

After intravenous administration Methylthioninium Chloride is rapidly taken up by the tissues. 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 26.7 h.

Oral Administration

Methylthioninium Chloride is well absorbed from the human gastrointestinal tract and is rapidly reduced to leucomethylthioninium chloride.

About 75% of a single 10 mg oral dose of Methylthioninium Chloride is recovered from the urine, mainly (80%) as leucomethylthioninium chloride. This metabolite is

colourless but turns green or blue on exposure to air due to presence of the oxidation product methylene azure (methylthioninium chloride sulphone).

Oral and Intravenous administration

Methylthioninium chloride is not an *in vitro* inducer of CYP2B6 and CYP3A4.

Methylthioninium chloride is an *in vitro* inhibitor of P-gp

Methylthioninium chloride is not an *in vitro* substrate for BCRP or OCT2 and is not an in vitro inhibitor of BRCP, 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 *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.

Methylthioninium Chloride is reported to be incompatible with caustic alkalis, iodides, dichromates and oxidising and reducing substances.

6.3 Shelf life

Prior to first use: 36 months.

In use: 24 hours

6.4 Special precautions for storage

Prior to first use: Do not store above 25°C

In use: Following dilution with 5% dextrose solution, chemical and physical in-use stability has been demonstrated for 24 hours at temperature not above 25°C.

However, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

50 mg/5ml - Clear Type I glass vial with a rubber stopper and flip off seal in packs of 5 vials.

6.6 Special precautions for disposal

For single use only.

Methylthioninium Chloride may be diluted in 50 ml glucose 50 mg/ml (5%) solution for injection to avoid local pain, in particular in the 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 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

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8 MARKETING AUTHORISATION NUMBER(S)

PL 42973/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/12/1993

10 DATE OF REVISION OF THE TEXT

10/09/2024