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

Methylthioninium chloride 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 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.

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

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 central nervous system (CNS) effects for up to 4 hours after administration.

Methylthioninium chloride is an in vitro inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5. The clinical consequences of increases plasma concentration of co-administered drugs which are sensitive 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 Proveblue has the potential to transiently increase or decrease the clearance of drugs that are primarily metabolized by these enzymes. The clinical consequences are however considered minimal since methylthioninium chloride Proveblue 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 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
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
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 estimated terminal half-life of methylthioninium chloride after intravenous administration is 26.7h.

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

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

3 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