EU Risk Management Plan for Methylthioninium chloride Proveblue

RMP version to be assessed as part of this application:

RMP Version number: 3.4

Data lock point for this RMP: 11/03/2025

Date of final sign off: 11/03/2025

Rationale for submitting an updated RMP: Submission to the EMA the final Clinical Study Report from the clinical study (PVP-20160005): An open-label, Parallel group, Population-matched, Single-Dose Study To Investigate the Influence of Hepatic Impairment on the Pharmacokinetics and safety of ProvayBlue® (methylene blue) – (PMR-3065-3)

Summary of significant changes in this RMP v3.4:

- Part II: Module SV – Post-autorisation experience – SV.1 Post-autorisation exposure : update of post- authorisation exposure data
- Part II : Module SIV – Populations not studied in clinical trials and Part IV: Plans for post-authorisation efficacy studies : update of the completed and on-going clinical studies ; PVP-2016005 from on-going to complete

Other RMP versions under evaluation: N/A

Details of the currently approved RMP:

Version number: 3.3

Approved with procedure: EMEA/H/C/PSUSA/00002029/202305

Date of approval (opinion date): 11/01/2024

QPPV name: Sabine Baron

QPPV Deputy name: Polina Amato

QPPV signature:

QPPV oversight declaration: The content of this EU RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Methylthioninium chloride (Methylene blue)
Pharmacotherapeutic group(s) (ATC Code)	V03AB17
Marketing Authorisation <Holder> <Applicant>	Provepharm SAS
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Methylthioninium chloride Proveblue 5 mg/ml solution for injection
Marketing authorisation procedure	centralised
Brief description of the product	Chemical class: CAS number [61-73-4] (anhydrous) [122965-43-9] (monohydrate) [7220-79-3] (trihydrate) [32680-41-4] (pentahydrate)
	Summary of mode of action: Methylthioninium chloride reduces the heme from methaemoglobin to haemoglobin. It acts as a co-factor of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) reductase. Generated by the pentose phosphate pathway, NADPH reduces Methylthioninium chloride to leucomethylene blue; this reaction is catalysed by NADPH reductase. In turn, Methylthioninium chloride allows a non-enzymatic redox reaction from methaemoglobin to haemoglobin.
	Important information about its composition: Methylthioninium chloride Proveblue contains methylthioninium chloride and water for injections.
Hyperlink to the Product Information	European SmPC
Indication(s) in the EEA	Current (if applicable): 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).
	Proposed (if applicable): N/A

Dosage in the EEA	Current (if applicable): Methylthioninium chloride Proveblue 5 mg/ml solution for injection should be administered by intravenous injection. 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 higher than normal. The maximum recommended cumulative dose is 7 mg/kg.
	Proposed (if applicable): N/A
Pharmaceutical form(s) and strengths	Current (if applicable): Solution for injection, 5 mg/ml
	Proposed (if applicable): N/A
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Acute symptomatic treatment of medicinal and chemical products-induced methaemoglobinaemia

Incidence: <100 cases per year,

Prevalence: around = 0.013 per 100,0001

The exact prevalence rate of this rare disease is difficult to assess from the available data sources. There is a low level of consistency between studies, a poor documentation of methods used, continuous or intermittent dosing, underlying cause, severity and mean duration of treatment. In the absence of readily available prevalence or incidence data, the number of cases reported in the literature is acceptable.

The main existing treatment options:

Methylthioninium chloride Proveblue is a first-line acute symptomatic treatment for medicinal and chemical products-induced methaemoglobinaemia. It is intended to provide curative treatment. It is one of few therapeutic antidotes for this condition.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Unknown. Methaemoglobinaemia is a serious clinical condition that requires immediate emergency treatment. In cases of severe poisoning (methaemoglobinaemia >70%) the condition can be life-threatening. If left untreated, the condition can be fatal.

Important co-morbidities:

Methaemoglobinaemia may arise from a variety of aetiologies including genetic, dietary, idiopathic, and toxicologic sources. Treatment with Methylthioninium chloride is usually within a critical care setting (as an antidote) and therefore aetiologies may not always be apparent. Accordingly, to ascertain and review co-morbidities within the general population is not practical. Nevertheless, several potential co-morbidities of relevance are considered below.

Table Part I.2 – Important co-morbidities of relevance

Indication/target population	**Important co-morbidity in the target population.**
Treatment of medicinal and chemical product-induced methaemoglobinaemia	*Kidney Disease (Renal Impairment)* At least 10% of the population of Europe currently have some degree of Chronic Kidney Disease (CKD) and so it is estimated that at least 70 million people in the EU are affected. Furthermore, this figure is increasing each year and, if the present trend is to continue, the number of people with CKD will double over the next decade (EKHA 2015). In the presence of moderate or severe renal impairment, toxic blood concentrations may occur with conventional doses, since methylthioninium chloride is eliminated predominantly by the kidney (Dollery 1999). ADRs in these patients, in particular haemolytic anaemia, can be pronounced. Therefore, methylthioninium chloride should be used with caution in patients with moderate or severe renal impairment (Therapeutic Drugs 1999; Martindale 2007; Bradberry 2001). Lower doses (<1 mg/kg) may be needed.
Treatment of medicinal and chemical product-induced methaemoglobinaemia	*Anaemic Patients* Methaemoglobin is generally expressed as a percent of total haemoglobin; levels may not correspond with symptoms in some patients. An anaemic patient may have greater symptoms at a level of 20% than a non-anaemic patient, because the oxygen-carrying capacity is lower and more easily compromised (Wright 1999). High blood levels of methaemoglobin may put patients' life at risk because of an important decrease in oxygen-carrying capacity and an increase of oxygen affinity with haemoglobin. Methaemoglobin levels above 50% may lead to arrhythmias, seizures, coma and acidosis. At levels 70% or greater, death can occur. Therefore, methaemoglobinaemia should be closely monitored at high concentrations since it can lead to life-threatening disease, especially when the condition is associated with a co-morbidity affecting oxygen delivery (Hersch 2004; Bradberry 2003; Beutler 2005; Camp 2007). Drug induced anaemia (e.g. Dapsone-

	induced anaemia) may exacerbate the underlying condition.
Treatment of medicinal and chemical product-induced methaemoglobinaemia	*Cardiac, Pulmonary, or Hematologic Diseases* Patients with underlying cardiac, pulmonary, or hematologic disease may exacerbate the toxicity of methaemoglobin. Therefore, diagnosis in these patient groups may be complicated by the effect of methaemoglobin on arterial blood gas and pulse oximeter oxygen saturation results (Wright 1999).
Treatment of medicinal and chemical product-induced methaemoglobinaemia	*Diabetes Mellitus or Hyperglycaemic Patients* Methylthioninium chloride Proveblue is hypotonic and may be diluted in 50 ml glucose 50 mg/ml (5%) solution for injection. Therefore, Methylthioninium chloride when diluted in glucose 5% solution for injection may exacerbate underlying conditions in patients with hyperglycaemia or diabetes mellitus. If treated with a glucose solution diluent, patients may experience excessive thirst or an increase in the volume or frequency of urination.

Part II: Module SII - Non-clinical part of the safety specification

Toxicity

- Key issues identified from acute or repeat-dose toxicity studies

Single dose toxicity

Single-dose toxicity data has been generated for a number of species including rat, mouse, rabbit, guinea pig, monkey, sheep, dog and cat.

Methylthioninium chloride was administered via a range of routes and the median lethal dose (LD_{50}) or the lethal dose low (LDL_o) was established. In those studies where Methylthioninium chloride was given intravenously, the LD_{50} ranged from 77 mg/kg in mice to 1250 mg/kg in rats. The LDL_o ranged from 10 mg/kg in the monkey to 50 mg/kg in dogs.

In a pharmacokinetic study in sheep, a toxicological assessment was conducted using LD50 determination, Methaemoglobin (MetHb) production and haematological effects as evaluation parameters. The results of the study indicated that the dosage of Methylthioninium chloride may be safely increased up to at least 15 mg/kg in sheep in the treatment of severe methaemoglobinaemia (Burrows 1984).

Relevance to human usage: The maximum recommended dose in Human is known and is 7 mg/kg per kilo weight.

Repeat dose toxicity

The US National Toxicology Program (NTP) studied the effects of Methylthioninium chloride trihydrate on male and female rats and mice to identify potential toxic or cancer-related hazards (NTP TR540 2008).

In the one month trial, doses of 0, 125, 250, 500, 1000, 2000 mg/kg body weight/day were administered orally five days per week for five weeks. None of the mice in the 500, 1000 or 2000 mg/kg/d groups survived to the end of the study and in rats treated with doses of 500 mg/kg and above, early deaths were observed. In both mouse and rat, lesions to the spleen and liver were seen with Methylthioninium chloride treatment. Of the animals which survived the study, methaemoglobinaemia followed by anaemia, haemosiderin pigment deposition in the liver and kidney and subsequent hepato- and nephro-toxicity were observed.

In the three month study, much lower doses of 0, 25, 50, 100 or 200 mg/kg/day were administered orally five days per week for 14 weeks. In both rat and mouse, there was a dose-dependent increase in spleen weights and a reduction in thymus weights. Methaemoglobinaemia and regenerative Heinz body anaemia were also experienced. In the mouse only, there was decreased sperm motility and increased epididymal sperm counts in male at 200 mg/kg.

Provepharm conducted a 1-month repeat-dose toxicity study in dogs. The test item, Methylthioninium chloride Proveblue 5 mg/ml, was administered by slow intravenous administration to beagle dogs at dose-levels of 0.25, 0.50 and 1.00 mg/kg. A reference item, Methylene Blue injection USP 1% w/v was administered at a dose-level of 1.00 mg/kg under the same experimental conditions. No unscheduled death occurred. No treatment related-effect on clinical signs, body weight and food consumption was observed during the study period. No relevant findings on ophthalmology and electrocardiography were noted at the end of the treatment period.

Repeated daily intravenous dosing for one month in dogs showed no macroscopic toxic effects up to the highest dose tested: 1 mg/kg/day. The greater apparent sensitivity seen in dogs relative to humans was considered to be related to species differences in pharmacokinetics. Exposure at 1 mg/kg in the dog was significantly greater than that following a similar dose in healthy human volunteers. Adverse reactions, seen at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were moderate regenerative anemia 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. Increased spleen weights correlated with increased hemopoiesis and congestion in the spleen, compensatory to the anemia. Green/brown pigment seen in the spleen, kidneys and liver of treated animals was also consistent with hemosiderosis and increased cellularity of the bone marrow related to regenerative anemia was noted in all treated dogs. Inflammatory findings at the injection sites indicated a minimal irritant effect of the test item.

Relevance to human usage: Usually the treatment for methemoglobinemia is a unique dose of methylthioninium chloride. A repeat dose may be given one hour after the first dose without exceeding 7 mg/kg.

Treatment does not usually exceed one day.

Therefore there is a limited risk regarding repeat dose toxicity.

Moreover, haemolytic anaemia has been observed in dogs. It has also been observed in human usage and is therefore listed as an important identified risk.

- reproductive/developmental toxicity

Methylthioninium chloride is currently classified by FDA as a category C drug: "*Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks*. "(Drug Facts and Comparisons 2004).

The TGA *classified Methylthioninium Chloride in Category D: "Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details*."

Methylthioninium chloride has been shown to reduce motility of human sperm in a dose dependent manner. At the lowest concentration studied (0.0005% = 5 ng/ml) motility was reduced from a normal level of >85% sperm motile to less than 15% motile after 45 min (Coddington 1989).

In the 3-month rat and mouse toxicity studies reported in the NTP report for Methylthioninium chloride administered by oral gavage, sperm motility and vaginal cytology (to assess oestrus cycle) were assessed. In the rat study no significant reductions in sperm motility or oestrus cycle were observed. In the mouse study there was a statistically significant but small reduction in sperm motility at the high dose of 200 mg/kg/d, with no effect on oestrus cycle (NTP report TER92124; NTP report TER92125).

A poorly described study by Telford (1962) assessed foetal resorption in rats administered 500 mg Methylthioninium chloride in the diet. It was clear from the study that there was an effect of Methylthioninium chloride on foetal resorptions. In the Methylthioninium chloride treated group 90% had one or more foetal resorptions compared with 40.8% in the control group.

Two oral gavage developmental toxicity studies are reported by the NTP, one in Sprague-Dawley rats (NTP report TER92124) and the other in New Zealand White rabbits (NTP report TER92125). Daily administration in both studies was during the period of organogenesis (day 6-15 of pregnancy in rats

and day 6-19 of pregnancy in rabbits). The rat study confirmed the results of the Telford study with an increase in the percentage of foetal resorptions per litter at the high dose of 200 mg/kg/d, although litter size was unaffected. The NOAEL for developmental toxicity in rats was 125 mg/kg/d and maternal toxicity was observed at all dose levels tested (50, 125 and 200 mg/kg/d).

There were no significant effects on developmental endpoints (indicators of embryo/foetal growth, viability and morphological development) up to the high dose of 150 mg/kg/d in the rabbit developmental toxicity study. However, the report suggested that 150 mg/kg/d was approaching the Lowest Observed Adverse Effect Level (LOAEL) for developmental effects (not teratogenic effects) on the basis of dose-related trends for development endpoints seen in the study and an increase in foetal abortions and resorptions at 200 mg/kg/d in a dose range finding study.

Relevance to human usage: The potential risk for humans is unknown. Methylthioninium chloride Proveblue should not be used during pregnancy unless clearly necessary.

Methylthioninium chloride has been shown to reduce motility of human sperm in a dose dependent manner.

- genotoxicity

Methylthioninium chloride was mutagenic in gene mutation assays in bacteria and mouse lymphoma cells but not in an *in vivo* mouse micronucleus assay with and without S9 activation when administered intravenously at 62 mg/kg (Wagner 1995).

None of the genotoxicity studies reported looked at the effects of light on the genotoxic effect of Methylthioninium chloride. As Methylthioninium chloride has been shown to be an *in vitro* genotoxin/clastogen, in vitro photogenotoxicity studies are unlikely to add significantly to the risk/benefit analysis for the product and so a case might be reasonably be made for their omission.

Relevance to human usage: No impact for the acute treatment of acquired methemoglobinemia.

- carcinogenicity

Some evidence of carcinogenic activity of Methylthioninium chloride has been shown in male mice based on increased incidences of carcinoma and of adenoma or carcinoma (combined) in the small intestine and in male rats based on increased incidence of pancreatic islet cell adenoma and adenoma or carcinoma (combined). Equivocal evidence of carcinogenic activity was observed in female mice based on marginally increased incidences of malignant lymphoma. No evidence of carcinogenic activity has been observed in female rats.

Relevance to human usage: According to ICH S1A, carcinogenicity studies should be performed if the pharmaceutical drug is continuously used for more than 6 months. Methylthioninium chloride Proveblue 5 mg/ml solution for injection will be used for short durations in emergency situation, thus no further carcinogenicity studies are needed.

Safety pharmacology

- cardiovascular system, including potential effect on the QT interval

Following bolus intravenous injections of Methylthioninium chloride in rats (5 and 50 mg/kg) Vutskits et al. reported that blood pressure and heart rate remained within the normal physiologic ranges. Oktay

reported an increase in blood pressure followed by hypotension following administration of Methylthioninium chloride at 10 and 20 mg/kg IV. These results may suggest that *in vivo* guanylate cyclase inhibition by Methylthioninium chloride leads to an increase in blood pressure (Oktay 1993). In addition, Methylthioninium chloride (100 µM) has been shown to directly activate large conductance BKCa channels providing a mechanism whereby Methylthioninium chloride can cause both contraction and relaxation of smooth muscle. These actions may explain some of the paradoxical effects of vascular cells to relaxing agents (Stockland 1996). The effects on blood pressure appear to be transient however and are seen at doses that are higher than intended therapeutic doses.

Relevance to human usage: Clinical experience with Methylthioninium chloride indicates that at therapeutic doses (1mg/kg) there are no significant cardiovascular effects of Methylthioninium chloride.

The QT study PVP-2014002 demonstrated that at a dose of 2 mg/kg methylthioninium chloride did not have a clinically relevant effect on any of the studied ECG parameters (cf. PVP-2014002 study report).

However with higher dose (7 mg/kg IV, the maximum daily recommended dose), electrocardiogram changes (T wave flattening or inversion) have been reported in humans without methaemoglobinaemia (Bradberry 2001). These features resolved within 2–12 hours of the injection.

There are no reports that Methylthioninium chloride affects hERG channels and its lack of effect on the ECG in dogs supports a lack of interaction with cardiac ion channels.

Methylthioninium chloride therefore has little direct effect on the cardiovascular system although it has been associated with modulation of smooth muscle relaxation but has no marked effects on haemodynamics.

- central nervous system

Neurotoxic effects after administration of Methylthioninium chloride in vitro and in vivo have been reported in the literature. Garthwaite et al. (1988) investigated the neurotoxic effect of Methylthioninium chloride (10 to 100 µM) on slices of young rat cerebellum and showed that there was a progressive destruction of the differentiating cells. Similarly Vutskits et al. (2008) reported an increase in dying hippocampal cells at doses of 10 and particularly 100 µM Methylthioninium chloride over 2-48 hours.

A study in which a single bolus IV administration of Methylthioninium chloride (at 5 mg/kg and 50 mg/kg) was given to anaesthetised rats, led to a significant increase in the number of degenerating neurons, with the effects being dose dependent with a more marked effect following a dose of 50 mg/kg.

Intrathecal administration of Methylthioninium chloride in cats resulted in neuronal damage and inflammation, and associated paraplegia, indicating that its concomitant use with prilocaine in humans via this route may not be safe.

Extrapolation from in vitro data and in vivo data in animals to humans requires some caution and the doses or concentrations where marked neurological effects were noted are higher than therapeutic doses of Methylthioninium chloride used for treatment of methaemoglobinaemia. In humans, doses of 5-10 mg/kg IV during parathyroidectomy may induce prolonged post-operative disorientation and are associated with serotonin toxicity (Khan 2007).

Relevance to human usage: CNS effects of methylthioninium chloride are only seen with higher doses and so may be of concern when used, for example, in parathyroid surgery or in people who have increased sensitivity. Lower doses of methylthioninium chloride (~1mg/kg) used in the treatment of methaemoglobinaemia however, are not associated with any neurological effects of concern. Overdose could result in a significant effect on the central nervous system and so should be avoided.

Other toxicity-related information or data

Methylthioninium chloride Proveblue is indicated for use in neonates and children. Clinical literature data collected show that treatment with Methylthioninium chloride is effective in very young children of this age.

Extreme caution should be exercised when administering to newborns and infants below the age of three 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.

No non-clinical data relating to the use of Methylthioninium chloride in infants has been provided. Since the product is well established and clinical data is available for the use of Methylthioninium chloride in infants, no non-clinical studies are deemed necessary.

Part II: Module SIII - Clinical trial exposure

Table SIII.1: Duration of exposure

Cumulative for all indications (person time)		
Duration of exposure	Patients	Person time
1 Day	118	118
Total person time	118 person-days	
Acute symptomatic treatment of medicinal and chemical products-induced methaemoglobinaemia		
Duration of exposure	Patients	Person time
2 mg/kg	118	118
Total person time for indication	118	

Table SIII.2: Age group and gender

Age group	Patients		Person time	
	M	F	M	F
Adults (19-55 years)	59	59	59	59
Total	59	59	59	59
Acute symptomatic treatment of medicinal and chemical products-induced methaemoglobinaemia				
Age group	Patients		Person time	
	M	F	M	F
Adults (19-55 years)	59	59	59	59
Total	59	59	59	59

Table SIII.3: Dose

Dose of exposure	Patients	Person time
2 mg/kg	118	118
Total	118	118

Acute symptomatic treatment of medicinal and chemical products-induced methaemoglobinaemia		
Dose of exposure		
2 mg/kg	118	118
Total	118	118

Table SIII.4: Ethnic origin

Ethnic origin	Patients	Person time
Acute symptomatic treatment of medicinal and chemical products-induced methaemoglobinaemia		
Not Hispanic or Latino	70	70
Hispanic or Latino	48	48
Total	118	118

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

As the Marketing Authorisation Application for Methylthioninium chloride Proveblue was submitted according to Article 10(3) of Directive 2001/83/EC as amended (hybrid application), no pivotal clinical study takes part to the development programme.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The Marketing Authorisation Application for Methylthioninium chloride Proveblue was submitted according to Article 10(3) of Directive 2001/83/EC as amended (hybrid application), consequently the clinical and safety database for Methylthioninium chloride Proveblue is limited.

Provepharm have conducted two post-marketing clinical trials (PVP-2014001 and PVP-2014002) since Marketing Authorisation in the EU was granted, however both of these trials involved the enrollment and treatment of healthy volunteers.

Furthermore, in response to the FDA's request of post-marketing requirements for NDA 20-4630, four (4) clinical trials have been initiated: a Safety and Efficacy Study, a Clinical Drug Interaction Study, a pharmacokinetic study on renal impairment population and a pharmacokinetic study hepatic impairment population. These four (4) clinical trials are completed.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3.1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development program
Breastfeeding women	

Patients with relevant comorbidities: • Patients with hepatic impairment	Hepatic impairment: a clinical study had been conducted. A total of 78 subjects with hepatic impairment had been enrolled and treated 78 patients had been enrolled and treated (30 healthy subjects comprised the control group, 16 patients each comprised the 3 groups of mild, moderate, and severe hepatic-impaired function) in the Safety Population and 37 patients in the PK Population (13 healthy subjects and 8 patients each in the 3 hepatic impairment groups).
• Patients with renal impairment	Renal impairment: a clinical study had been conducted. A total of 34 subjects with renal impairment had been included.
• Patients with cardiovascular impairment	Not included in the clinical development program
• Immunocompromised patients	Not included in the clinical development program
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Not included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	Not included in the clinical development program

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Although an estimate of the number of persons exposed to Methylthioninium chloride Proveblue from marketing use cannot be made, exposure by number of packs sold can be provided. Total worldwide sales of Methylthioninium chloride Proveblue since International Birth Date (IBD) are 3 845 820 10 ml ampoules and 215 435 2 ml ampoules which corresponds to 194 445,35 grams of active medicinal product (see Table in section SV.1) (or approximately 194,45 kg).

SV.1.2 Exposure

Table SV.1.1: Exposure table by region

Indication	Region	
Overall	EU country	Non EU country
Acute symptomatic treatment of medicinal and chemical products-induced methaemoglobinaemia (the indication is	5 ampoules of 10 ml boxes: 231 741 boxes, which correspond to 1 158 705 ampoules	5 ampoules of 10 ml boxes: 537 423 boxes, which correspond to ampoules 2 687 115 ampoules
	5 ampoules of 2 ml boxes:	5 ampoules of 2 ml boxes:

slightly different depending on the country out of Europe).	34 413 boxes, which correspond to 172 065 ampoules	8 674 boxes, which correspond to 43 370 ampoules

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Clinical use of methylthioninium chloride has provided no evidence to suggest a potential for misuse including the sale of the medicinal product for recreational purposes nor the use of the medicinal product to facilitate assault. There have been no identified reports of abuse or addiction to methylthioninium chloride presentations.

Part II: Module SVII - Identified and potential risks

Not applicable.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

In the initial RMP all the identified risks have been included in the list of safety concerns.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Extract from the section 1.5.2 Details of important identified and potential risks of the Initial RMP:

Although the use of Methylthioninium chloride formulations as registered medicinal products is well-established; access to the established safety database is limited to existing Marketing Authorisation holders and the Member State regulatory authorities. Therefore, the safety database is at present limited and the frequency of identified and potential AEs for Methylthioninium chloride has been based on safety data from handbooks of medicines, published clinical studies and case reports. The safety data presented here includes data from the diverse uses of Methylthioninium chloride and the different routes of administration.

The AEs for Methylthioninium chloride Proveblue® are presented by frequency in section 4.8 of the proposed SmPC. All the undesirable effects reported in the Reference Medicinal Product SmPC have been reported (nausea, abdominal and chest pain, dizziness, headache, hyperhirosis, confusional state, hypertension and the formation of methaemoglobin). Additional AEs identified from the literature have also been included in the Provepharm SmPC. The AEs for Methylthioninium chloride Proveblue® are detailed in the table below; any AEs not mentioned in the Reference Medicinal Product have been highlighted.

Table SVII.1.1: Adverse events associated with Methylthioninium chloride Proveblue®

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION

Blood and the lymphatic system disorders	Common	Methaemoglobinaemia, hyperbilirubinaemia in infants
	Common in: - Severe overdose - Infants - Adults with aniline-induced methaemoglobinaemia	Haemolytic anaemia
Psychiatric disorders	Common	Confusional state
Nervous system disorders	Common	Dizziness, headache, anxiety, tremor
	Rare	Fever
Eye disorders	Rare	Mydriasis
Cardiac disorders	Not known	Cardiac arrhythmia
	Not known	Tachycardia
Vascular disorders	Common	Hypertension
	Not known	Hypotension
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Rare	Tachypnoea
Gastrointestinal disorders	Common	Nausea, vomiting, abdominal pain, faeces discolouration (blue-green)
Skin and subcutaneous tissue disorders	Common	Skin discolouration, sweating
Renal and urinary disorders	Common	Chromaturia (blue-green)
General disorders and administration site conditions	Common	Chest pain
	Very rare	Death (2 case reports in infants, Methylthioninium chloride only partially responsible)
Investigations	Common	Haemoglobin decreased

Frequencies are as follows: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000) , Very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Common Adverse Effects

The most common AEs from intravenous administration of Methylthioninium chloride include abdominal pain, headache, dizziness, tremors, apprehension, confusion, chest pain, dyspnea, tachycardia, hypertension, and profuse sweating. However, several of these are also symptoms of methaemoglobinaemia (especially acquired methaemoglobinaemia) and therefore it is difficult to determine the proportion of these effects which are a direct result of the administration of Methylthioninium chloride (Therapeutic Drugs 1999; Martindale 2007; Clifton 2003; Bradberry 2001). Nausea, vomiting, dysuria and mild diarrhoea have also been reported in patients treated with oral Methylthioninium chloride (Therapeutic Drugs 1999; Martindale 2007; Deutsch 1997).

Methylthioninium chloride may impart a blue colouration to the skin, urine, faeces, saliva, oral mucosa and teeth. As a result of its discolouration of the skin, it can hinder the diagnosis of cyanosis (Therapeutic Drugs 1999; Martindale 2007). A warning to this effect has been inserted in section 4.4 of the SmPC 'Special warning and precautions'.

The proposed dose range of Methylthioninium chloride Proveblue® is 1 to 2 mg (0.2-0.4 mL) per kg body weight over a period of 5 minutes. Higher doses increase the risk of toxic effects; of particular note is the risk of symptomatic haemolysis after high doses as a result of the oxidation of ferrous iron to ferric ions which converts haemoglobin to MetHb (Therapeutic Drugs 1999; Martindale 2007). At large doses, Methylthioninium chloride can itself produce methaemoglobinaemia and so methaemoglobin concentration should be closely monitored during treatment. A warning is written in section 4.4 of the SmPC to ensure that this is avoided; 'Methylthioninium chloride Proveblue® must be injected very slowly over a period of several minutes to prevent high local concentrations of the compound from producing additional methaemoglobin. Do not exceed the recommended dose'. Furthermore, outer carton have been updated to include the cautionary statement 'For slow intravenous infusion'.

Literature suggests that photosensitisation (photoallergy or phototoxicity) may occur after administration of Methylthioninium chloride in patients exposed to ultraviolet light or sunlight (Drug facts and comparisons 2004). The occurrence of this effect is unknown and a causal relationship cannot be proven. Therefore, in accordance with the Reference Medicinal Product, no warnings are included in the SmPC at this time.

Serious Adverse Effects

No cases of death following IV administration of Methylthioninium chloride to treat methaemoglobinaemia have been reported in the literature. One case of death was reported to the Medicines and Healthcare products Regulatory Agency (MHRA) after administration of Methylthioninium chloride but unfortunately, no information has been available concerning this case report and so the role of Methylthioninium chloride cannot be determined (MHRA 2008). The literature suggests that methaemoglobin levels of 70% or more can result in death, so it is possible that the condition itself resulted in the fatality (Hersh 2004).

Intravenous injection of Methylthioninium chloride has occasionally caused hypotension and cardiac arrhythmias however and such disorders could prove fatal on rare occasions (Therapeutic Drugs 1999). Both hypotension and cardiac arrhythmia are therefore addressed in the Provepharm SmPC.

Tissue necrosis and necrotic ulcers have been reported at the site of injection when Methylthioninium chloride was injected rapidly or subcutaneously (Perry 1974, Bradberry 2001). A warning advising that Methylthioninium chloride Proveblue® should be injected very slowly is included in both section 4.2 and 4.4 of the SmPC to ensure that this does not occur. Furthermore, outer carton have been updated to include the cautionary statement 'For slow intravenous infusion'.

Spinal cord necrosis causing paraplegia occurred in a patient in whom Methylthioninium chloride was administered intrathecally (Sharr 1978). Intrathecal administration of Methylthioninium chloride Proveblue® is contraindicated to eliminate this risk.

Two case reports of anaphylactic reaction to Methylthioninium chloride infusion are described in the literature when Methylthioninium chloride was used as a marker in surgical procedures (Rzymski 2003; Dewachter 2005). Since Methylthioninium chloride Proveblue® is not indicated for use as a marker in the Provepharm SmPC, no warnings are considered necessary.

Cumulative doses of Methylthioninium chloride have also been reported to lead to dyspnoea, chest pain, tremor, cyanosis, and haemolytic anaemia (E-medicine); see Section 1.9.1 Overdose of this document, for further information.

Drug Analysis Prints

Drug Analysis Prints (DAPs), obtained from the UK regulatory agency the MHRA (registered authority for the Reference Medicinal Product), give a full list of suspected ADRs reported from Marketing Authorisation Holders and spontaneously by healthcare professionals. DAPs for Methylthioninium chloride for various different routes of administration and uses have been reported.

ADRs of Methylthioninium chloride have been collected by the MHRA since 1963 (MHRA 2008). The DAPs indicate that 180 adverse reactions, included in 40 ADR reports, were reported to the MHRA, during the period July 1963 to October 2009. During the period covered, one fatal ADR report was reported but unfortunately, no information has been available concerning this case report and so no causal relationship to the administration of Methylthioninium chloride can be determined.

It is important to note that healthcare professionals are asked to report even if they only have a suspicion that the medicine may have caused the ADR. The fact that a report has been submitted does not necessarily mean that the medicine has been proven to cause a reaction.

ADRs reported by system organ class from the MHRA DAPs (July 1963 to October 2009) are reported in the table below:

Table SVII.1.2: ADRs reported from MHRA DAPs associated with Methylthioninium chloride (July 1963 to October 2009)

System Organ Class	Single active constituent		Multiple active constituent		Total unique reports*	
	All	Fatal	All	Fatal	All	Fatal
Cardiac disorders	6	0	0	0	6	0
Ear disorders	1	0	0	0	1	0
Endocrine disorders	2	0	0	0	2	0
Eye disorders	13	0	0	0	13	0
Gastrointestinal disorders	5	0	0	0	5	0
General disorders	21	1	0	0	21	1
Immune system disorders	3	0	0	0	3	0
Infections	1	0	0	0	1	0
Injuries	5	0	0	0	5	0
Investigations	10	0	0	0	10	0
Metabolic disorders	2	0	0	0	2	0
Muscle & tissue disorders	1	0	0	0	1	0
Nervous system disorders	55	0	0	0	55	0
Psychiatric disorders	29	0	0	0	29	0
Renal & urinary disorders	1	0	0	0	1	0
Respiratory disorders	7	0	0	0	7	0
Skin disorders	11	0	0	0	11	0
Surgical & medical procedures	1	0	0	0	1	0
Vascular disorders	6	0	0	0	6	0
TOTAL NUMBER OF REACTIONS	180	1	0	0	180	1
TOTAL NUMBER OF FATAL ADR REPORTS*		1		0		1*
TOTAL NUMBER OF ADR REPORTS*	40		0		40*	

*This provides the number of individual reports and may be less than the sum of the single-active constituent and multi-active constituent columns. For example, if both a single- and multi-active constituent product is considered by the reporter to have a suspected causal relationship with the suspected reaction, then the same report will appear in both columns.

Of particular note from these data is the number of nervous system disorders reported. The number of reactions almost doubled between September 2008 and October 2009. A Drug Safety Alert was issued by the MHRA in relation to CNS toxicity upon co-administration of Methylthioninium chloride and serotonergic drugs, especially when Methylthioninium chloride is used as a visualising agent in surgical procedures (MHRA 2009). Therefore, this rise in reports is thought to be due to an increase in awareness of these reactions (and subsequent increased reporting), rather than an increase in incidence of such AEs. Warnings regarding potential CNS toxicity are included in the proposed SmPC.

Many of the psychiatric and eye disorders reported (42 reactions in total) are most likely a result of the use of Methylthioninium chloride as a stain in corneal examinations and surgery. They are therefore unlikely to be indicative of the AEs likely to be experienced by patients being treated with Methylthioninium chloride for methaemoglobinaemia and so do not warrant inclusion in the Provepharm SmPC.

Adverse effects in special populations

Glucose-6-phosphate dehydrogenase deficiency (G6PD):

Methylthioninium chloride Proveblue® is contraindicated for the treatment of methaemoglobinaemia in patients with glucose-6-phosphate dehydrogenase deficiency (G6PD). These patients have a diminished capacity to reduce Methylthioninium chloride to leucomethylene blue and therefore the administration of

Methylthioninium chloride is not effective. It is also potentially harmful as patients with G6PD deficiency are particularly susceptible to the haemolytic anaemia induced by Methylthioninium chloride (Liao 2002).

Renal Impairment:

In patients with severe renal impairment, conventional doses of Methylthioninium chloride can result in toxic blood concentrations accumulating. AEs in these patients, in particular haemolytic anaemia, can therefore be much worse and so Methylthioninium chloride should be used with caution in these patients.

Patients with hepatic impairment:

There is no experience in patients with severe hepatic impairment. Lower doses may be needed.

Patients who are hypersensitive to Methylthioninium chloride:

Methylthioninium chloride Proveblue® is contraindicated for the treatment of methaemoglobinaemia in patients with a hypersensitivity to Methylthioninium chloride. Methylthioninium chloride belongs to a group of drugs known as thiazine dyes and therefore patients with hypersensitivity to such dyes should also avoid the use of Methylthioninium chloride Proveblue®. Administration to such patients can result in anaphylactic reactions which can be fatal.

Children:

Infants younger than 3 months of age have higher levels of foetal haemoglobin, which has a structure that is easily oxidised into MetHb. Moreover, they have lower concentrations of NADPH-MetHb reductase necessary for reducing MetHb to haemoglobin (levels at birth of this enzyme are only 50% to 60% of adults levels) (Groeper 2003; Savino 2006; Wilburn-Goo 1999). This makes these infants more susceptible to methaemoglobinaemia produced by high doses of Methylthioninium chloride, haemolytic anaemia and hyperbilirubinaemia. As a result Methylthioninium chloride Proveblue® is not recommended for use in newborns and infants below the age of three months. A warning is included in section 4.4 of the SmPC and in the PIL.

Elderly:

In elderly patients with reasonable renal function, no specific toxic effects have been reported and the AEs experienced are the same as for adult patients.

Pregnant and lactating women:

There is no published data on IV injection of Methylthioninium chloride during pregnancy or on whether or not the drug crosses into breast milk. Therefore no AEs in pregnant women have been recorded.

Provepharm would recommend that the product is not used during pregnancy unless there is a clear clinical need, e.g. in life-threatening methaemoglobinaemia. If the intravenous use of Methylthioninium chloride cannot be avoided in pregnant women, the lowest possible dose should be chosen and the patient observed closely after administration and for the duration of treatment.

In several cases of intra-amniotic administration of Methylthioninium chloride, when used as a diagnostic aid in pregnant women, teratogenicity of Methylthioninium chloride has been demonstrated. Further details of this can be found in 1.9.4. 'Potential for off-label use'.

It is unknown whether methylthioninium chloride is excreted in human breast milk and the excretion of methylthioninium chloride in milk has not been studied in animals. A risk to the suckling child cannot be excluded. Therefore breast-feeding should be discontinued during and after treatment with Methylthioninium chloride Proveblue.

Summary of important identified and potential risks:

Table SVII.1.3: *Haemolytic anaemia*

Identified Risk	Haemolytic anaemia
Seriousness/outcomes	Unquantifiable from the available data.
Severity and nature of risk	Unquantifiable from the available data.
Frequency	Not known. Reported in: • Neonates and infants • Adults with aniline-induced methaemoglobinaemia and G6PD-deficiency.
Background incidence/prevalence	Not known
Risks group or risk factors	At risk populations: • Glucose-6-phosphate dehydrogenase deficiency (G6PD) • Severe renal impairment • Neonates and infants younger than 3 months of age • Adults with aniline-induced methaemoglobinaemia • Severe overdose.
Potential mechanisms	Several potential mechanisms exist (see section 1.3 and 1.5).
Preventability	Methylthioninium chloride should be injected very slowly over several minutes to prevent high local concentrations of the compound from producing additional methaemoglobin. The recommended dose should not be exceeded and in infants and sufferers of renal impairment, the dose should be administered with caution. In G6DP patients, the use of Methylthioninium chloride is contraindicated.
Potential public health impact of safety concern	Unquantifiable from the available data.
Evidence source	Module 2.5 Clinical Overview
Regulatory action taken	Haemolytic anaemia has been listed as an undesirable effect in section 4.8 of the SmPC. Patients with G6DP are contra-indicated in the proposed Provepharm SmPC (section 4.3) and caution is advised in patients with severe renal impairment and/or aniline-induced methaemoglobinaemia (section 4.4).

	The posology and administration information in the SmPC (section 4.2) recommends that Methylthioninium chloride should not be administered to infants below 3 months and advises that smaller doses may be required in patients with renal impairment. It is proposed to cross-reference section 4.2 in section 4.4 and vice versa to ensure that the warning regarding smaller doses to be administered to patients suffering from renal impairment is reinforced

Identified and potential interactions with other medicinal products, food and other substances

In the literature, no potential interactions with extrinsic factors such as use of tobacco, use of alcohol or food habits associated with the use of Methylthioninium chloride have been reported.

Methylthioninium chloride and drugs inducing methaemoglobinaemia

Methylthioninium chloride should be used with caution in the treatment of aniline-induced methaemoglobinaemia since it may precipitate Heinz body formation and haemolytic anaemia. Methylthioninium chloride may reduce MetHb concentrations, but repeated doses could aggravate haemolysis without further reducing methaemoglobinaemia (Martindale 2007; Liao 2002; Harvey 1983).

Many of the cases of acquired methaemoglobinaemia reported in the adult population are related to the use of the antibiotic dapsone. Dapsone has a long half-life and the effects of Methylthioninium chloride are short, therefore it is not unusual to observe recurrence of methaemoglobinaemia in such patients. This can require the use of additional Methylthioninium chloride doses, but doses of Methylthioninium chloride higher than 7 mg/kg may worsen methaemoglobinaemia and haemolysis because of the Methylthioninium chloride oxidising effect. Methylthioninium chloride can also exacerbate dapsone-induced haemolytic anaemia because of the formation of the dapsone reactive metabolite hydroxylamine, which oxidises haemoglobin (Goldstein 1974). As a result Methylthioninium chloride Proveblue® should be used with caution in patients presenting with dapsone-induced haemolytic anaemia.

Methylthioninium chloride should not be used to treat methaemoglobinaemia induced by sodium nitrite during the treatment of cyanide poisoning, since Methylthioninium chloride increases the release of cyanide from methemoglobin (as it reduces cyanide binding) resulting in a greater concentration of cyanide in the blood and resultant increased toxicity. It is therefore contraindicated.

Methylthioninium chloride is also contraindicated in methaemoglobinaemia due to chlorate poisoning as the more toxic hypochlorite may be formed (Martindale 2007; Mokhlesi 2003).

Methylthioninium chloride in high intravenous doses should be avoided for patients being treated with selective serotonin reuptake inhibitors (SSRIs) such as clomipramine, bupropion, buspirone and venlafaxine. Co-administration of Methylthioninium chloride with SSRIs has been shown to result in potentially fatal serotonin toxicity as a result of the inhibition of monoamine oxidase (Ramsay 2007).

The MHRA published a warning in their April 2009 Drug Safety Update following several case reports of central nervous system (CNS) toxicity when Methylthioninium chloride was used as a visualising agent in surgical procedures in patients that also received serotonergic drugs (MHRA 2008; MHRA 2009). Features of toxicity include confusion, disorientation, agitation, expressive aphasia, altered muscle tone in limbs, hypoxia, ocular symptoms, and depressed level of consciousness. All the cases reviewed in the MHRA Drug Safety Update described CNS toxicity after the use of methylthioninium as a visualising agent

in parathyroid or thyroid surgery and since the review was published, further cases of CNS toxicity in association with Methylthioninium chloride have come to light. In all new cases, the patients were being treated with either an SSRI antidepressant or clomipramine, and the features of toxicity were similar to those reported previously.

Whilst the use of Methylthioninium chloride for localisation in parathyroid surgery and the management of intractable hypotension fall outside the proposed indications for Methylthioninium chloride, the MHRA strengthened the advice for healthcare professionals. The following wording has subsequently been included in section 4.5 of the Methylthioninium chloride Proveblue® SmPC as per the Reference Medicinal Product and in full accordance with the MHRA's advice:

"Methylthioninium chloride should preferably be avoided in patients receiving drugs that enhance serotonergic transmission including SSRIs, bupropion, buspirone, clomipramine, mirtazapine, and venlafaxine. If the intravenous use of Methylthioninium chloride cannot be avoided in patients treated with serotonergic drugs, the lowest possible dose should be chosen and the patient observed closely for CNS effects for up to 4 hours after administration."

The warning and precaution in relation to medicinal products that may have serotonergic activity is also emphasised within section 4.4 of the SmPC.

Summary of important interactions:

Table SVII.1.4: *Serotonergic drugs*

Interacting substance	Serotonergic drugs
Effect of interaction (including MedDRA terms if appropriate)	Confusion, disorientation, agitation, expressive aphasia, altered limb muscle tone, hypoxia, ocular symptoms, depressed consciousness level.
Evidence source	MHRA Drug Safety Update Volume 2, Issue 9, April 2009 (MHRA 2009)
Possible mechanisms	Not known
Potential health risk	The cases reported have occurred in patients being treated with Methylthioninium chloride for localisation in parathyroid surgery and the management of intractable hypotension. Neither of these uses is indicated in the proposed Methylthioninium chloride Proveblue® SmPC. The doses used in these treatments are also much higher than those used for the management of methaemoglinaemia. Consequently, the potential risk of CNS toxicity resulting from co-administration of Methylthioninium chloride and serotonergic drugs for the indication is minimal.
Discussion	Intravenous Methylthioninium chloride should preferably be avoided in patients who have been treated recently with drugs that have serotonergic activity.

	If use of intravenous Methylthioninium chloride cannot be avoided, the minimum possible dose should be used and the patient observed closely for CNS effects for up to 4 hours after administration. These warnings are included in sections 4.4 and 4.5 of the Methylthioninium chloride Proveblue® SmPC.

Off label use

Methylthioninium chloride is currently approved for the management of drug-induced methaemoglobinaemia in adults. It is also used for other purposes however, but these uses are not covered by the Marketing Authorisation.

Diagnostic and surgical procedures

Methylthioninium chloride is often used as a dye in diagnostic procedures, such as fistula detection and for the selective staining of certain body tissues during surgery as it is a bacteriological stain (Martindale 2007). Methylthioninium chloride falls within ATC code V04CG05 when used for this purpose.

Urinary tract antibacterial agent

Methylthioninium chloride has mild antiseptic activity that may inhibit bacterial proliferation and has therefore been used as a urinary tract antibacterial agent; however, this medication has since been replaced by more effective agents (Drugs.com, Methylene Blue).

Off-label paediatric use

Intra-amniotic injection

Methylthioninium chloride has been used off -label as a dye to diagnose premature rupture of foetal membrane in neonates via transabdominal intra-amniotic injection since 1970 (Vincer 1987).

Neonatal complications of intra-amniotic Methylthioninium chloride in doses ranging from 3.2 to 58.8 mg/kg have been reported in the literature since 1973 (Plunkett 1973; Serota 1979; Cowett 1976; Crooks 1982; McEnerney 1983; Spahr 1980). A number of toxic side effects as a direct result of the Methylthioninium chloride dye injection have been described in newborns, including skin discolouration, haemolytic anaemia, hyperbilirubinaemia and methaemoglobinaemia and the authors suggest discontinuation of intra-amniotic injection of Methylthioninium chloride dye as a diagnostic aid (McEnerney 1983; Vincer 1987; Fish 1992).

Nicolini 1990 and Van der Pol 1992, also report complications associated with intra-amniotic Methylthioninium chloride and conclude that intra-amniotic injection of Methylthioninium chloride appears hazardous in the second trimester. They too recommend that no dyes should be injected into the amniotic sac (Nicolini 1990; Van der Pol 1992).

Photoxicity has been reported as an adverse effect of Methylthioninium chloride in neonates after prenatal exposure to Methylthioninium chloride (Clifton 2003; Porat 1996). After exposure to a toxic amount of Methylthioninium chloride (10 mL of a 10 mg/mL solution injected into the amniotic cavity), redness developed on all exposed areas of the patient's skin (which was initially deep blue), followed by bullae and desquamation of about 35% of the total skin surface area within hours of exposure to phototherapy. The authors concluded that Methylthioninium chloride phototoxicity is a previously unrecognised complication associated with high prenatal exposure to Methylthioninium chloride and

treatment with phototherapy. Methylthioninium chloride phototoxicity may be related to the high prenatal dose (10 mL of 10 mg/mL solution) of the dye relative to patient's small size and young gestational age (Porat 1996).

Provepharm, whilst aware that Methylthioninium chloride is used off-label for this purpose, do not condone it and will not be proposing Methylthioninium chloride Proveblue® 5 mg/mL Solution for Injection be used for this purpose.

Intra-uterine injection

There have also been reports of Methylthioninium chloride being administered to pregnant women via intra-uterine injection for the diagnosis of premature rupture of foetal membrane in neonates. One report, of 18 mL of 0.2% solution of Methylthioninium chloride being administered at 5½ weeks gestation, suggests that Methylthioninium chloride administered in this way does not necessarily affect the embryo and the author of the study suggests that its use for diagnosis of premature rupture of membranes should not be condemned (Katz 1981).

Another case report also suggests that Methylthioninium chloride exposure does not affect the embryo. A diagnostic laparoscopy with Methylthioninium chloride intra-uterine injection (the injected dose was not mentioned) was performed approximately 7 days after conception in a 39-year old woman with infertility and chronic pelvic pain. No effects were reported on pregnancy and neonatal outcome (Gerli 2004).

Again, Provepharm do not condone the use of Methylthioninium chloride Proveblue® 5 mg/mL Solution for Injection for this purpose.

Table SVII.1.5: Summary of on-going safety concerns (in RMP version 2.0)

Important identified risks	• Rapid injection of Methylthioninium chloride • Dilution with sodium chloride (NaCl) • Neonates and infants below 3 months of age • Hypersensitivity to methylthioninium chloride, or any other thiazine dyes • Sodium[1] nitrite-induced methaemoglobinaemia during the treatment of cyanide poisoning • Methaemoglobinaemia resulting from chlorate poisoning • Patients with Glucose-6-phosphate dehydrogenase deficiency (G6PD) • Deficiency in NADPH reductase • Subcutaneous and intrathecal injection • Patients with aniline-induced methaemoglobinaemia • Patients with dapsone-induced haemolytic anaemia • Patients with moderate or severe renal impairment • Diagnosis of cyanosis • Interaction with serotonergic drugs resulting in CNS toxicity • Pregnancy and breast-feeding

[1] 'Sodium' was added in error. It has been deleted in the product information and in the initial RMP through a variation.

	• Haemolytic anaemia • Overdose
Important potential risks	• AEs with an unknown frequency • Photosensitivity • Patients with congenital methaemoglobinaemia • Methaemoglobinaemia rebound
Important missing information	• Relevant co-morbidities • Ethnicity • Long term exposure

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risk: Interaction with serotonergic drugs (including opioids) resulting in CNS toxicity. MedDRA Preferred Terms; Drug interaction (PT), Serotonin syndrome (PT), Neurotoxicity (PT)

Potential mechanisms:

Methylthioninium chloride is a potent monoamine oxidase inhibitor (MAOI) that interacts with all serotonin reuptake inhibitors of all sorts (selective and non-selective, SRI/SSRI) to induce severe potentially fatal serotonin toxicity serotonin syndrome, a severe reaction is likely with therapeutic doses of such MAOI/SRI combinations and can frequently be fatal.

Evidence source(s) and strength of evidence:

Eleven cases of serotonin syndrome have been reported, including cases described in literature. Methylthioninium chloride is recognised to be associated with severe central nervous system toxicity and has been shown to act as a monoamine oxidase inhibitor that can give rise to serotonin toxicity. The available evidence supports the possibility of a causal relationship (Haacker 2018, Gillman 2006).

Interaction of methylthioninium chloride with serotonergic drugs can induce severe and potentially fatal serotonin toxicity. A severe reaction is likely with therapeutic doses of monoamine oxidase inhibitor (MAOI)/serotonin reuptake inhibitor (SRI) combinations and can be fatal (WHO 2008, MHRA 2008).

Characterisation of the risk:

Frequency with 95% confidence interval: As this risk has not been observed during Provepharm's clinical trials nor from observational/epidemiological studies, the frequency of the risk cannot be calculated from available data. Absolute and relative risks cannot be estimated from the available data.

Serotonin syndrome is potentially fatal but can be preventable upon accurate diagnosis and appropriate treatment.

Risk factors and risk groups:

Patients receiving medicinal products that enhance serotonergic transmission.

Preventability:

Although not entirely preventable, this risk is considered preventable by providing clear warning of potential interaction between Methylene Blue and medicinal products that enhance serotonergic transmission in the product information.

Impact on the risk-benefit balance of the product:

Risk of CNS reaction including potentially fatal serotonin syndrome

Public health impact:

Given that the maximum incidence of acquired methaemoglobinaemia within Europe is estimated to be 75 cases per year, the public health impact of this safety concern is considered to be minimal. It is conceivable that this safety concern may prolong the hospitalisation however the expected number of patients affected, hospitalisations and fatalities cannot be predicted from Provepharm's available data.

The existing warning of the potential for interaction with serotonergic drugs previously detailed in the label was extended and strengthened in a variation submitted to EMA in December 2017. The wording was approved on 08 February 2018. The increased risk minimisation messages in the product information are now considered sufficient.

Routine pharmacovigilance is considered adequate to monitor serotonin syndrome with concomitant use of serotonergic drugs.

Important identified risk: Photosensitivity, MedDRA preferred terms; Photosensitivity reaction (PT)

Potential mechanisms:

Methylene blue is a chromophore and strongly absorbs light between 550-700nm3. optimal light absorption occurs at 664nm. After absorption of photons from light sources, methylene blue is elevated from its ground state to its excited, unstable energy state. When returning to its ground state, the absorbed light energy is released in the form of reactive oxygen species resulting in local tissue damage. Due to a cycle of excitement and energy release in the presence of light sources, phototoxic reactions occur at sites exposed to light of relevant wavelengths.

Evidence source(s) and strength of evidence:

Two cases of phototoxicity have occurred in patients after systemic administration of methylene blue. The patients were exposed to light from 2 different sources; surgical lights (ALM PRX) and through oxygen saturation probe (Nellcor Covidien with Oximax technology). An additional 4 cases of photosensitisation have been described in the literature occurring in the context of parathyroid surgery.

Characterisation of the risk:

Frequency with 95% confidence interval: As this risk has not been observed during Provepharm's clinical trials nor from observational/epidemiological studies, the frequency of the risk cannot be calculated from available data. Absolute and relative risks cannot be estimated from the available data.

Photosensitivity can be preventable upon patient's advise to take protective measures against exposure to light after administration of methylthioninium chloride.

Risk factors and risk groups:

Patients exposed to light.

Preventability:

This risk is considered preventable by providing clear warning of cutaneous photosensitivity reaction after methylthioninium chloride administration and when exposed to strong light sources in the product information. Taking protective measures against exposure to light such as indicated in the product information are considered are preventive measures.

Impact on the risk-benefit balance of the product:

Unquantifiable from the available data.

Public health impact:

Two cases of phototoxicity have occurred in patients after systemic administration of methylene blue. The patients were exposed to light from 2 different sources; surgical lights (ALM PRX) and through oxygen saturation probe (Nellcor Covidien with Oximax technology). An additional 4 cases of photosensitisation have been described in the literature occurring in the context of parathyroid surgery.

SVII.3.2. Presentation of the missing information

There is no information missing that presents a safety concern.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns	
Important identified risks	• Interaction with serotonergic drugs (including opioids) resulting in CNS toxicity • Photosensitivity reaction
Important potential risks	• None presently identified
Missing information	• None that presents a safety concern

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Interaction with serotonergic drugs (including opioids) resulting in CNS toxicity and photosensitivity, do not present safety concerns. Routine pharmacovigilance activities will continue to monitor both risks.

Specific adverse reaction follow-up questionnaires for safety concerns:

Not applicable.

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2 Additional pharmacovigilance activities

Not Applicable

III.3 Summary Table of additional Pharmacovigilance activities

Not Applicable

Part IV: Plans for post-authorisation efficacy studies

The MA in Europe was granted without conditions. However, as a condition of license grant in the United States, FDA have requested a Phase IV study to confirm the safety and efficacy of the product.

This is an open label clinical study to evaluate the safety and efficacy of ProyayBlue® (methylene blue) for the treatment of acquired methaemoglobinemia.

Patients recruited are those who present in hospital/urgent care setting diagnosed with acquired methemoglobinemia. The population may include pediatric and adult patients (males and females of all ages are included).

FDA have also requested that a further three Phase I PK studies are conducted. These are as follows:

Drug Interactions Study:

A clinical study of various drug interactions had been conducted in healthy volunteers. This was an open-label, randomized, two-period, crossover study to assess the effect of a single dose of methylene blue 5 mg/mL on the pharmacokinetics of the probe drugs midazolam, caffeine, warfarin, omeprazole and dextromethorphan. Twenty volunteers had been recruited.

Use in patients with renal impairment:

A clinical study in renally impaired patients had been conducted. A total of 34 subjects with renal impairment had been included: both male and female patients with mild, moderate or severe renal impairment.

Use in patients with hepatic impairment:

A clinical study in hepatic impaired patients had been conducted. A total of 78 patients had been enrolled and treated (30 healthy subjects comprised the control group, 16 patients each comprised the 3 groups of mild, moderate, and severe hepatic-impaired function) in the Safety Population and 37 patients in the PK Population (13 healthy subjects and 8 patients each in the 3 hepatic impairment groups).

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

Not applicable

V.1. Routine Risk Minimisation Measures

The safety information in the current label is considered sufficient.

V.2. Additional Risk Minimisation Measures

No additional risk minimisation measures are required.

V.3 Summary of risk minimisation measures

Safety concern	Routine risk minimisation activities
Interaction with serotonergic drugs resulting in CNS toxicity	Routine risk communication: SmPC section 4.4, 4.5 and 4.8 Product leaflet section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to avoid concomitant use of methylene blue with medicinal products that enhance serotonergic transmission. In the case, methylene blue administration cannot be avoided with serotoninergic medicinal products, the lowest possible dose should be chosen and the patient observed closely for central nervous system effects for up to 4 hours after administration.
Photosensitivity reaction	Routine risk communication: SmPC section 4.4 and 4.8 Package leaflet section 2 and section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to take protective measures against exposure to light after administration of methylene blue.

Part VI: Summary of the risk management plan

Summary of risk management plan for Methylthioninium chloride Proveblue (methylthioninium chloride)

This is a summary of the risk management plan (RMP) for Methylthioninium chloride Proveblue. The RMP details important risks of Methylthioninum chloride Proveblue, how these risks can be minimised, and how more information will be obtained about Methylthioninum chloride Proveblue's risks and uncertainties (missing information).

Methylthioninum chloride Proveblue's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Methylthioninum chloride Proveblue should be used.

This summary of the RMP for Methylthioninum chloride Proveblue should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Methylthioninum chloride Proveblue's RMP.

I. The medicine and what it is used for

Methylthioninum chloride Proveblue is authorised for acute symptomatic treatment of medicinal and chemical products-induced methaemoglobinaemia (see SmPC for the full indication). It contains methylthioninium chloride as the active substance and it is given by intravenous injection.

Further information about the evaluation of Methylthioninum chloride Proveblue's benefits can be found in Methylthioninum chloride Proveblue's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002108/WC500107131.pdf

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Methylthioninium chloride Proveblue, together with measures to minimise such risks and the proposed studies for learning more about Methylthioninium chloride Proveblue 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

II.A List of important risks and missing information

Important risks of Methylthioninium chloride Proveblue are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Methylthioninium chloride Proveblue. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Interaction with serotonergic drugs (including opioids) resulting in CNS toxicity • Photosensitivity reaction
Important potential risks	• None presently identified
Missing information	• None that presents a safety concern

II.B Summary of important risks

Important Identified Risk: Interaction with serotonergic drugs (including opioids) resulting in CNS toxicity	
Evidence for linking the risk to the medicine	Methylthioninium chloride is a potent monoamine oxidase inhibitor (MAOI) that interacts with all serotonin reuptake inhibitors of all sorts (selective and non-selective, SRI/SSRI) to induce severe potentially fatal serotonin toxicity serotonin syndrome, a severe reaction is likely with therapeutic doses of such MAOI/SRI combinations and can frequently be fatal.
Risk factors and risk groups	Patients receiving medicinal products that enhance serotonergic transmission.
Risk minimisation measures	SmPC: Section 4.4 Special Warnings & Precautions for use; Section 4.5 Interaction with other medicinal products and other forms of interaction; Section 4.8 Undesirable Effects. Package leaflet: Section 2 and Section 4.

Important Identified Risk: Photosensitivity reaction	
Evidence for linking the risk to the medicine	Two cases of phototoxicity have occurred in patients after systemic administration of methylene blue. The patients were exposed to light from 2 different sources; surgical lights (ALM PRX) and through oxygen saturation probe (Nellcor Covidien with Oximax technology). An additional 4 cases of

	photosensitisation have been described in the literature occurring in the context of parathyroid surgery.
Risk factors and risk groups	Patients exposed to light.
Risk minimisation measures	SmPC: Section 4.4 Special Warnings & Precautions for use; Section 4.8 Undesirable Effects. Package leaflet: Section 2 and Section 4.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Methylthioninium Chloride Proveblue.

II.C.2 Other studies in post-authorisation development plan

In response to the FDA's request of post-marketing requirements for NDA 20-4630, four clinical studies had been conducted.

Part VII: Annexes

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Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1 Annex II: Planned and on-going studies

No planned or on-going studies.

Table 2 Annex II: Completed studies

Study	**Summary of objectives**	**Safety concerns addressed**	**Date of Final Study Report submission Link to report**
PVP-2016005: Hepatic Impairment	To compare the concentration-time profile and pharmacokinetics of methylene blue and azure B after administration of a single 1 mg/kg intravenous dose of ProvayBlue® to patients with mild, moderate or severe hepatic impairment with that of the healthy matched (race, age, gender and weight) control subjects.	PK Data – no safety concern	CSR submitted in EU on March 2025 CSR submitted in US on 23/06/2023 NDA 204630 SeqNo 0224
PVP-2016003 MEBIPAM - **ME**thylene **B**lue **I**n **P**atients with **A**cquired **M**ethemoglobinemia	Open label clinical study to evaluate the safety and efficacy of ProyeBlue™ (methylene blue) for the treatment of acquired methaemoglobinemia	Confirmation of efficacy and safety	Link to protocol CSR submitted in EU on 16/12/2022 CSR submitted in US on 15/12/2021 NDA SeqNo 0190

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
PVP-2016004: Cocktail study	A study to assess the effect of ProvayBlue® on the pharmacokinetics of midazolam (CYP3A4), caffeine (CYP1A2), warfarin (CYP2C9), omeprazole (CYP2C19) and dextromethorphan (CYP2D6) following single-dose intravenous administration in healthy subjects.	PK Data – no safety concern	CSR submitted in US on 21/12/2018 NDA SeqNo 0134 CSR submitted in EU on 27/08/2021 Seq No 0092
PVP-2016006: Renal Impairment	To compare the values of primary pharmacokinetic (PK) parameters after administration of a single 1 mg/kg dose of ProvayBlue® to patients with varying degrees of renal impairment (mild, moderate, and severe) to those of matched (age, gender and weight) control subjects with normal renal function.	PK Data – no safety concern.	CSR submitted in US on 24/10/2019 NDA Seq No 0154 CSR submitted in EU on 27/08/2021 Seq No 0092

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

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Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority

Not applicable

Annex 4 - Specific adverse drug reaction follow-up forms

Not Applicable

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not Applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not Applicable

Annex 7 - Other supporting data (including referenced material)

Not Applicable

Annex 8 – Summary of changes to the risk management plan over time

Version	**Approval date** **Procedure**	**Change**
1.0	SN 0000: At the time of the submission	N/A
1.0	SN 0003: Responses to D120 questions, September 2010	Safety concerns - Anaphylaxis added as an identified or potential risk Important potential risk added: - 'List of the AE with unknown frequency'
2.0	SN 0066: October 2016	Reclassification from Important potential risk to missing information added: - Misdiagnosis as a result of underlying cardiac, pulmonary, or haematologic diseases
3.0	September 2018 (Following discussion during PSUR 9 assessment. Not submitted to EMA)	Re-Evaluation of Safety Concerns and Important/Identified Risks Reclassification: Photosensitivity has been re-classified from a potential risk to an identified risk.
3.1	July 2020	Update of the completed, on-going clinical studies Change of the reporting period and update od post-marketing experience

3.2	July 2023	Update safety concerns: - Important Identified Risk: Interaction with opioids increasing risk of developing serotonin syndrome - Important Potential risk: Potent reversible inhibitor of monoamine oxidase Update of the completed, on-going clinical studies Change of the reporting period and update od post-marketing experience
3.3	December 2023 (Following receipt PRAC Rapporteur's preliminary assessment under the procedure PSUSA/00002029/202305)	As suggested by the PRAC Rapporteur's preliminary assessment the MAH proposes: - To delete the new proposed important identified risk "*Interaction with opioids increasing risk of developing serotonin syndrome*" in the RMP v3.2 submitted in July 2023*,* - To delete the new proposed potential risk "*Potent reversible inhibitor of monoamine oxidase" in the RMP v3.2 submitted in July 2023*, - To add a minor edit ("including opioids") for additional clarity regarding the Interaction with serotonergic drugs resulting in CNS toxicity.
3.4	March 2025	Update of the completed, on-going clinical studies: - PVP-2016005 from on-going to complete Change of the reporting period and update of post-authorisation exposure data