Provepharm is a Provepharm Life Solutions company

Swiss Summary of the Risk Management Plan (RMP) for

Methylthioninium Chloride Proveblue 5 mg/ml, solution for injection

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RMP Summary: Version 1.0, October 2020

EU RMP: Version 3.0, 2018

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of Methylthioninium Chloride Proveblue 5 mg/ml, solution for injection, is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the ”Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Methylthioninium Chloride Proveblue 5 mg/ml, solution for injection in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic.

Grosse Apotheke Dr. G. Bichsel AG, Bahnhofstrasse 5a, 3800 Interlaken, as Swiss MAH, is fully responsible for the accuracy and correctness of the content of the here published summary RMP of Methylthioninium Chloride Proveblue 5 mg/ml, solution for injection.

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

This is a summary of the risk management plan (RMP) for Methylthioninum chloride Proveblue in Switzerland. 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.

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 swiss SmPC.,

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 Methylthioninum 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 Methylthioninum 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 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 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: Special Warnings & Precautions for use; Interaction with other medicinal products and other forms of interactionUndesirable Effects. .

The following risk was upgraded to an identified risk:

- **Photosensitivity, MedDRA preferred terms; Photosensitivity reaction (PT)**

The risk of photosensitivity with the use of methylthioninium chloride is upgraded from a potential risk to an identified risk on the basis of additional case reports identified from the literature.

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.

Important Identified Risk: Photosensitivity reaction	
Evidence for linking the risk to the medicine	Methylene blue is a chromophore and strongly absorbs light between 550-700nm[3]. 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.
Risk factors and risk groups	Patients exposed to light.
Risk minimisation measures	SmPC: Special Warnings & Precautions for use; Undesirable Effects.

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. One of them are on-going:

PVP-2016005: Hepatic Impairment

Purpose of the study: A study to compare the whole blood 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.