COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Miprosed 5 mg/ml oral solution

(midazolam)

NL/H/4682/001/DC

Date: 14 October 2020

This module reflects the scientific discussion for the approval of Miprosed 5 mg/ml oral solution. The procedure was finalised at 28 April 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CNS	Central Nervous System
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Miprosed 5 mg/ml oral solution, from Syri Pharma Limited.

The product is indicated in children aged 6 months to 14 years for:

- Sedation and anxiolysis prior to diagnostic, surgical, therapeutic or endoscopic procedures.
- Premedication before induction of general anaesthesia.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of midazolam. For this type of application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature.

The concerned member states (CMS) involved in this procedure were Denmark, Malta and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, a well-established application.

II. QUALITY ASPECTS

II.1 Introduction

Miprosed is a clear, colourless to pale yellow coloured oral solution. Each 1 ml of oral solution contains 5 mg midazolam.

The oral solution is packed in amber glass bottles with tamper evident, child resistant, white plastic cap with polypropylene inner, polyethylene outer and an expanded polyethylene (EPE) liner with a 1 ml oral syringe with 0.01 ml graduations and a 5 ml oral syringe with 0.1 ml graduations supplied with a syringe adaptor.

The excipients are: sodium benzoate (E211), sucralose, glycerol (E422), dilute hydrochloric acid, orange flavour (contains propylene glycol (E1520)), sodium hydroxide (for pH adjustment) and purified water.

II.2 Drug Substance

The active substance is midazolam, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Midazolam is a white or almost white crystalline powder and is practically insoluble in water, freely soluble in acetone and in ethanol (96%) and soluble in methanol. The polymorphic form and particle size of the active substance are not of relevance, as the product is a solution.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional tests for appearance, residual catalyst and microbial purity. Batch analytical data demonstrating compliance with this specification have been provided for one batch.

Stability of drug substance
The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Results provided for the compatibility studies between the drug and the excipients used in the formulation are acceptable. Overall, the pharmaceutical development is adequate.

Manufacturing process
The manufacturing process consists of mixing and solubilisation, filtration, filling and capping of the bulk solution, labelling and packaging and finally release testing as per specifications proposed and has been validated according to relevant European guidelines. Process

validation data on the product have been presented for three commercial scaled batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. and/or British Pharmacopoeia requirements, except for the orange flavouring. The orange flavouring used in the formulation has in-house specifications. A test for identification by chromatographic technique is included.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, odour, pH, fill volume, assay, identification, related substances, density, uniformity of dosage unit, microbial limits and preservative efficacy testing. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three commercial scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three commercial scaled batches at 2°C-8°C (6 months), 25°C/60% RH (6 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in amber coloured Type III glass bottles. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable in the proposed packaging when exposed to light. On basis of the data submitted, a shelf life was granted of 6 months. The labelled storage conditions are: 'This medicinal product does not require any special storage conditions. Do not refrigerate or freeze.' As the proposed product is a single unit dose product, no in-use stability data are considered necessary.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Miprosed 5 mg/ml oral solution has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacodynamics

Primary pharmacodynamics

Several *in vitro* assays using neuronal tissue of juvenile and adult rats and mice (of different strains) are described, which show the midazolam-induced changes in electrolyte currents through channels, resulting in reduced cell membrane excitability and signal transmission.

The *in vivo* binding of several benzodiazepines (including midazolam) in mice or rats after oral or intravenous administration was shown with data from seven different studies. Midazolam resulted in rapid occupancy of the BZR (starting within minutes after systemic administration) in both juveniles and adults, but with a shorter duration of action than e.g. diazepam.

Midazolam reduces locomotor activity and induces muscle relaxation when administrated via various routes, which are signs of sedation. Anaesthetic effects (i.e. loss of activity/mobility, reflexes and consciousness) can be rapidly induced by parenteral administration of midazolam. Recovery is rapid as well, both in juveniles and adults (approximately 20-30 min. after administration or withdrawal of continuous infusion). Oral administration also considerably decreased locomotor activity in rodents. Next to sedation/anaesthesia, midazolam leads to reduced anxiety when administered prior to a stress response, by attenuating fear-related responses in the amygdala. Midazolam-mediated anxiolysis was observed in rodents as well as in larger animals.

The MAH has provided sufficient data to show the central nervous system (CNS) effects of midazolam. Although the majority of the studies was performed using parenteral routes the pharmacodynamic effects found in studies using midazolam per os were not markedly different from the results in studies using parenteral routes.

Secondary pharmacodynamics

Apart from sedative/anaesthetic and anxiolytic effects, midazolam also exerts secondary pharmacodynamic effects. Midazolam (orally or systemically administrated) has anti-convulsant effects in seizures induced with drugs or chemical substances or with electroshock. In comparison with other benzodiazepines (such as diazepam), the anti-convulsant potency is similar, but the duration of effect is considerably shorter. Midazolam also exerts an analgesic effect which is, like the primary pharmacodynamic effects, a result of attenuation of the BZR-GABA complex.

Studies in mice and rats show that midazolam administration to juveniles did not have long-term effects on learning and memory behaviour, although short-term anterograde amnesia could be induced (both in juveniles and adults), which may partly explain anxiolytic effects found in studies with adult rats.

The studies described by the MAH provide sufficient insight in the secondary pharmacological effects of midazolam, although most effects described have only been tested after parenteral administration. However, based on the primary pharmacology, oral administration of midazolam is not expected to result in other effects.

Safety pharmacology

The safety pharmacology is described by means of studies already mentioned in primary or secondary pharmacodynamics and studies not described before. Midazolam intravenous resulted in depression of cerebral metabolism and vascular responses, which were milder in young rats compared to older animals. Midazolam may also indirectly attenuate autonomic functions (e.g. gastric acid secretion) because of its depressive actions on central regulatory mechanisms.
In *in vivo* and *ex vivo* experiments, midazolam did not substantially impair central sympathetic outflow (nerves), cardiac rhythm or haematological and respiratory parameters in rats and dogs. Continuous intrathecal midazolam infusion for several weeks (as performed in sheep and pigs) did not result in any remarkable change in behaviour and neurologic function or vital signs, except for some inflammation around the catheter.
These studies show that midazolam results in depression of central mechanisms, but without severe side-effects on vital signs. It was noted that all described studies have been performed systemically or intrathecally. However, it is expected that oral administration will not induce more severe or other safety effects when the systemic or local central nervous system CNS concentration does not become higher than the described doses.

Pharmacodynamic drug interactions
The MAH has provided several examples of sedative/anaesthetic agents and CNS depressants that will enhance the CNS effects of midazolam. In the clinic, midazolam is used as premedication for general anaesthesia or as sedative component in anaesthesia. The pharmacodynamic interactions with some of the mentioned agents are therefore used to induce the desired CNS effect. Overall, the MAH has provided a substantial number of *in vitro* and *in vivo* studies, which show the pharmacodynamic properties of midazolam when used in different species/strains, doses or administration routes. The MAH has properly cited the reference per described study.

III.2 Pharmacokinetics

The MAH has provided an overview of studies related to absorption, distribution, metabolism and excretion of midazolam. Midazolam is rapidly absorbed after oral administration. Independent of the species studied, bioavailability is considered low in most studies, which is most likely caused by high hepatic metabolism (first-pass). Values for the other pharmacokinetic parameters such as AUC, C_{max} and T_{max} have been provided, but they differ between studies because of the dose or animal species used.
Midazolam has a large distribution volume and distributes to tissues (accumulation in fat > brain > muscles) within minutes, although one study in rats reported a slower distribution specially into the brain.
This benzodiazepine agonist is rapidly metabolised in the liver (via cytochrome P450 enzymes), resulting in at least- 3 metabolites, which do not account to a significant extent for the pharmacological effects of midazolam. Subsequent glucuronidation of these metabolites by uridine 5'-diphospho-glucuronosyltransferase leads to inactivation and elimination by the kidneys ($t_{1/2}$ is around 30 min). Within 24 hours, >90% of the glucuronised metabolites are excreted. Values for PK parameters for midazolam metabolites have been provided (rats and mice, data from two studies). Also excretion parameters are presented

for various animal species. The MAH has provided sufficient data from pharmacokinetic studies in different animal species.

III.3 Toxicology

General toxicity

The MAH has provided single-dose toxicity data from mice and rats administered intravenous or intraperitoneal injection or orally with midazolam. The anticipated clinical dose is approximately 267 times smaller than the maximum tolerated dose in juvenile animals. Further, the described studies for adults show high but distinct values for the lowest lethal dose value and median lethal dose, most likely because of differences in study design (e.g. route of administration used). General depressed activity, respiratory depression and memory-impairing effects are most frequently mentioned as effects of a high midazolam dose. Repeat-dose toxicity studies using oral midazolam in juveniles did not result in general and neuronal toxicity. In adults, toxic effects included increased liver weight and serum enzymes (related to liver toxicity) after oral administration and decreased numbers of acini in parotid glands after intramuscular injection.

Genotoxicity

In vivo, no signs for genotoxicity were observed. In vitro, midazolam could be potentially regarded genotoxic based on low levels of chromosome aberrations in a Chinese hamster cell line (when using ≥5 µg/ml). In addition, gene expression changes were caused by midazolam use (100 µM).

When comparing the *in vitro* genotoxic dose with the *in vivo* C_{max} values (after oral administration of ~1 to 5 mg/kg), the maximum concentrations reached *in vivo* are considerably less than those leading to chromosome aberrations or gene expression changes in vitro. Therefore, based on the provided data, no mutagenic toxicity is expected in animals using the proposed oral dose of midazolam.

Carcinogenicity

In immunocompromised juvenile mice, midazolam inhibited the growth of tumour xenografts, among others via induction of apoptosis pathways. Also *in vitro*, midazolam-related proliferation inhibition and apoptosis of tumour cells was found. However, midazolam could induce tumours *in vivo*, but this was after long-term exposure to a high dose (i.e. > human dose).

Reproduction and developmental toxicity

In the described studies of midazolam use in young animals and *in vitro*, moderate to high midazolam doses adversely affected development of the CNS in some studies, while in other studies a neuroprotective effect or no effect on neuronal development was found. No juvenile studies using midazolam orally were available. Based on these data, no indication for reproduction toxicity after oral midazolam use appears to be present.

Other toxicity

Based on literature, administration of midazolam (either locally in the CNS or (par)enterally) can induce neurotoxicity. Midazolam also has a suppressive effect on inflammatory (immune) responses. Midazolam use may also result in physical dependence.

It can be concluded that based upon the reviewed literature in the majority of studies midazolam showed cytotoxicity only to cancerous cells with abnormal growth. The studies showed that midazolam had least effect on normal cells or demonstrated a cytoprotective effect.

Impurities and excipients

The MAH has provided a short table with release and shelf-life specifications of the impurities. For the excipients with an acceptable daily intake limit, levels of excipients in children and adults at a dose of 0.5 mg/kg (midazolam 5 mg/ml) and at the maximum proposed dose of 20 mg are calculated and do not exceed the limit as proposed by World Health Organization. For the excipients without a specified limit (glycerol, dilute hydrochloric acid and sodium hydroxide), the MAH has sufficiently explained the expected levels and their safety consequences. Thus, no safety concerns are expected when using midazolam at clinically relevant doses.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Miprosed 5 mg/ml oral solution is intended for substitution of comparable products currently on the market, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.5 Discussion on the non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The pharmacodynamic, pharmacokinetic and toxicological properties of the active substance midazolam are well known. The MAH has not provided additional studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The MAH demonstrated that glycerol in amounts higher than that in Miprosed (5 g vs 2.52 g) does not affect other BSC Class I drugs, like amlodipine and fluoxetine. Furthermore, after oral administration, glycerol is readily absorbed from the gastro-intestinal tract, and unlike sorbitol for instance, not available to have a sustained osmotic effect. It is therefore expected that at the maximal dose given at one occasion, 2.52 g of glycerol, the absorption of the BCS Class I drug midazolam will not be affected clinically relevant.

IV.2 Pharmacodynamics

The known primary pharmacology of midazolam is anticonvulsive, sedation and sleep inducing, anxiolytic and muscle relaxant effect. The evidence for both primary and secondary efficacy came from a total of 11 papers dating from 1981 up to 2002. No evidence was submitted in support of the known anticonvulsive effect. However, given the active substance and proposed indication, this is considered acceptable.

IV.3 Clinical efficacy

The MAH has assessed and made an overview of studies to establish the most appropriate dose for sedation and premedication. The dose for sedation also included anxiolysis and amnesia prior to diagnostic, therapeutic or endoscopic procedures.
Comparative literature, in which the efficacy of midazolam was compared to other products showed that Midazolam has a rapid onset of sedation, a fast recovery compared to other products, such as ketamine or nitrous oxide. In addition, midazolam also has an amnesic effect, which makes it more favourable for use during traumatic procedures, indicating a need for oral midazolam.
Originally the MAH proposed a fix dose of 0.5 mg/kg. However, the literature showed that oral midazolam may be effective for sedation in a concentration as low as 0.25 mg/kg. Although in general the 0.5 mg/kg dose was safe, also in the youngest age group relative lower doses per kg body weight may be appropriate for older, more cooperative children. Moreover doses ranging from 0.25 mg/kg up to 0.5 mg/kg are clinical practice within the EU. Therefore, the MAH changed original fixed dose to a dose range of 0.25-0.5 mg/kg.
A maximum dose of 20 mg is proposed by the MAH. The 25 mg dose was well tolerated in the study; however, the maximum dose of 20 mg is well established and sufficient.

IV.4 Clinical safety

The MAH has provided an elaborate overview of oral midazolam used for sedation and as premedication. The safety of 0.25-0.5 mg/kg midazolam from oral administration was no different than that known for intravenous, intrabuccal, or intranasal.

The single patient pack proposed by the MAH contains a volume of 7.5 ml, corresponding to 37.5 mg. However, the maximum volume that can be drawn from the bottle is 5.5 ml. This decreases the risk for overdosing.

Moreover, the SmPC includes a warning on monitoring the respiratory function and that midazolam should only be administered by professionals in a setting where apparatus is available to initiate reanimation when needed.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Miprosed 5 mg/ml oral solution.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	- Pharmacokinetic interactions with CYP3A4 inhibitors or inducers - Pharmacodynamic interactions with other central nervous system depressants - Use in patients with hepatic impairment, renal impairment, respiratory/cardiac insufficiency or in chronically ill or debilitated patients - Impaired ability to perform activities requiring mental alertness or physical coordination - Overdose - Hypersensitivity/allergic reactions - Anterograde amnesia - Paradoxical reactions
Important potential risks	- Abuse/misuse for illegal purposes - Potential for IV or IM administration - Potential/risk of medication error
Missing information	- Use during pregnancy and breast-feeding - Use in children less than 6 months old

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

Benefit of the product

There is a need for a midazolam oral solution, indicated by current practice where the intravenous formulation of midazolam is used off-label, which has to be mixed with juices to mask the bitter flavour when administered orally. Midazolam has a rapid onset of sedation, a fast recovery compared to other products. In addition midazolam also has an amnesic effect, which makes it more favourable for use during traumatic procedures, indicating a need for oral midazolam. Other products currently available such nitrous oxide gas, propofol or ketamine. However, nitrous oxide may not be feasible for all procedures. In addition, propofol or ketamine may also not be appropriate for all procedures as a deeper sedation is achieved than clinically warranted.

Uncertainties of beneficial effect

The benefits for oral midazolam for sedation and premedication in paediatric population is well described. The proposed dosing range from 0.25-0.5 mg/kg is in line with clinical practice in the EU for the proposed indication, and other European products.
Information has been provided to demonstrate that similar bioavailability of midazolam can be expected between formulations used in the literature, which do not contain glycerol, and Miprosed formulation containing 2.52 g of glycerol at maximal single dose.

Risks related to the product
The fill volume of 7.5 ml exceeds the maximum acceptable (daily) dose of midazolam of 20 mg (= 4 ml), however the maximum volume that can be drawn from the bottle is 5.5 ml. This decreases the risk of overdosing. In addition, the risks related to midazolam are well documented and well known. In general, the medicinal product is well tolerated, and hypoxia rarely occurs in this setting. There is a risk of respiration defects, therefor the SmPC includes adequate warnings on use of the product. Paradoxal reactions may occur. These are sufficiently addressed by the MAH, with appropriate actions in place in the SmPC.

Uncertainties related to the risk
The single patient unit leads to waste and environmental risks, this has been increased as there is now dose range introduced.

Overall, the benefit/risk assessment of Miprosed is considered positive.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Miprosed 5 mg/ml oral solution has a proven chemical-pharmaceutical quality. Miprosed is an effective drug, which is considered widely established. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated for Miprosed 5 mg/ml oral solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 April 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse