

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Miprosed 5mg/ml Oral Solution

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is midazolam.

Each ml of oral solution contains 5mg midazolam.

Each ml of oral solution contains 1.94mg propylene glycol (E1520) and 630mg glycerol (E422).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Oral solution

Clear colourless to pale yellow coloured oral solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Miprosed 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.

## 4.2 Posology and method of administration

*Sedation and anxiolysis prior to diagnostic, surgical, therapeutic or endoscopic procedures:*

Children (6 months to 14 years): 0.25mg/kg to 0.5mg/kg administered 15-30 minutes before the intervention. Maximum per dose: 20mg.

*Premedication before induction of general anaesthesia:*

Children (6 months to 14 years): 0.25mg/kg to 0.5mg/kg administered 15-30 minutes before the induction of anaesthesia. Maximum per dose: 20mg.

The dose should be adapted to the patient's weight and administered rounded to the nearest syringe graduation in millilitres. The maximum dose should not exceed 20mg of midazolam even for children weighing more than 80kg (0.25mg/kg) or 40kg (0.5mg/kg). In obese children the dose should be given according to the actual body weight up to the maximum limit of 20mg. General fasting guidelines should be respected before sedation with Miprosed.

### Special populations

#### *Renal impairment*

No dose adjustment is required; however, midazolam should be used with caution in patients with chronic renal failure as elimination of midazolam may be delayed and the effects prolonged (see section 4.4).

#### *Hepatic impairment*

Hepatic impairment reduces the clearance of midazolam with a subsequent increase in terminal half-life. Therefore, the clinical effects may be stronger and prolonged, hence careful monitoring of the clinical effects and vital signs is recommended following administration of midazolam in patients with hepatic impairment (see section 4.4).

Miprosed is contraindicated in patients with severe hepatic impairment (see section 4.3).

#### *Children under 6 months*

The safety and efficacy of midazolam in children aged 0 to 6 months for the indications listed above has not been established. Miprosed should not be used in children under 6 months of age.

### Method of administration

For oral administration only.

The oral solution should be administered using the oral syringes provided.

Miprosed may be mixed with and administered in apple juice and diluted blackcurrant cordial.

Please refer to section 6.6 for any special precautions related to the manipulation or administration of the product.

### **4.3 Contraindications**

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Severe hepatic impairment
- Severe respiratory failure or acute respiratory depression
- Myasthenia gravis
- Sleep apnea
- Anatomical respiratory impairment or lung diseases

### **4.4 Special warnings and precautions for use**

Midazolam should be administered only by experienced physicians in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function and by persons specifically trained in the recognition and management of expected adverse events including respiratory and cardiac resuscitation.

Midazolam should be used with caution in patients with mild or moderate hepatic impairment, heart failure or chronic renal failure. Midazolam or its metabolite may accumulate in patients with chronic renal failure or with liver failure, and the clearance of midazolam may be decreased in patients with heart failure.

Oral midazolam should be used with caution in patients in poor general health as they are more sensitive to the effects of benzodiazepines on the central nervous system.

#### Risk from concomitant use of opioids:

Concomitant use of midazolam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as midazolam with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe midazolam concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

#### Respiratory insufficiency

Midazolam should be used with caution in patients with chronic respiratory insufficiency because midazolam may further depress respiration.

#### Paediatric patients aged less than 6 months

Given the higher metabolite to parent drug ratio in younger children, a delayed respiratory depression as a result of high active metabolite concentrations in the children under 6 months age group cannot be excluded. Therefore, Midazolam Oral solution should not be used in children under 6 months of age.

#### Altered elimination of midazolam

Midazolam should be used with caution in patients with chronic renal failure, impaired hepatic or cardiac function. Midazolam may accumulate in patients with chronic renal failure or impaired hepatic function whilst in patients with impaired cardiac function it may cause decreased clearance of midazolam.

#### Concomitant use with other benzodiazepines

Debilitated patients are more prone to the central nervous system (CNS) effects of benzodiazepines and, therefore, lower doses may be required.

#### Medical history of alcohol or drug abuse

Midazolam should be avoided in patients with a medical history of alcohol or drug abuse.

#### Concomitant use of alcohol/central nervous system depressants

Combined use of midazolam and alcohol and/or central nervous system depressants should be avoided. Such a combination is likely to increase the clinical effects of midazolam, which may cause deep sedation or clinically significant respiratory depression (see section 4.5).

#### Amnesia

Midazolam may cause anterograde amnesia. This effect is very desirable in situations such as before and during surgical and diagnostic procedures, the duration of which is directly related to the administered dose (see discharge below).

#### Paradoxical reactions

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, hostility, rage reaction, aggression, paroxysmal excitement have been reported. Should such reactions occur, the response to midazolam and all other drugs including local anaesthetics should be evaluated before proceeding.

#### Discharge

It is recommended that children receiving oral midazolam are discharged post-surgery accompanied by a parent or guardian.

#### Excipients warning:

This medicine contains less than 1 mmol sodium (23 mg) in each ml of solution, that is to say essentially 'sodium-free'.

## 4.5 Interaction with other medicinal products and other forms of interaction

### Pharmacokinetic Drug Interactions

Midazolam is metabolized by CYP3A4. Inhibitors and inducers of CYP3A4 have the potential to respectively increase and decrease the plasma concentrations and, subsequently, the effects of midazolam thus requiring dose adjustments accordingly. Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral as compared to oromucosal or parenteral midazolam as CYP3A4 enzymes are also present in the upper gastro-intestinal tract. Hence, a careful monitoring of the clinical effects and vital signs is recommended during the use of midazolam with a CYP3A4 inhibitor even after a single dose.

#### *Rifampicin*

7 days of 600 mg once daily decreased the plasma concentrations of intravenous midazolam by about 60%. The terminal half-life decreased by about 50-60%.

#### *Herbs*

St John's Wort decreased plasma concentrations of midazolam by about 20-40% associated with a decrease in terminal half-life of about 15-17%. Depending on the specific St John's Wort extract, the CYP3A4-inducing effect may vary.

The effect of CYP3A4 inhibitors may be larger in infants.

#### *Anaesthetics and narcotic analgesics*

Fentanyl may reduce midazolam clearance.

#### *Antiepileptics*

After repeated administration of carbamazepine or phenytoin, the plasma concentration of oral midazolam is reduced by a whopping 90% and the terminal half-life is reduced by 60%.

#### *Calcium-channel blockers*

Diltiazem and verapamil have been shown to reduce the clearance of midazolam and other benzodiazepines and may potentiate their actions. A single dose of diltiazem increased the plasma concentrations of intravenous midazolam by about 25% and the terminal half-life was prolonged by 43%.

#### *H<sub>2</sub>-receptor antagonists and ulcer-healing medicinal products*

Cimetidine, ranitidine and omeprazole have been shown to reduce the clearance of midazolam and other benzodiazepines and may potentiate their actions. Cimetidine has been shown to increase the diazepam and metabolite plasma concentration by 57%.

### *Substance P antagonists*

Aprepitant causes a dose dependent increase in the plasma concentrations of oral Midazolam. The plasma concentration of oral Midazolam increased by 3.3-fold after 80mg/day dose of aprepitant on day 5 and the terminal half-life increased by approximately 2-fold.

### *Xanthines*

Metabolism of midazolam and other benzodiazepines is accelerated by xanthines.

### *Dopaminergic medicinal products*

Midazolam may cause inhibition of levodopa.

### *Muscle relaxants*

Midazolam may cause potentiation of muscle relaxants, with increased CNS depressant effects, e.g., baclofen.

### *Nabilone*

Co-administration with midazolam may cause enhanced sedation or respiratory and cardiovascular depression.

### *Food*

Grapefruit juice and caffeine reduces the clearance of midazolam and potentiates its action.

### *Azole antifungals*

Ketoconazole increased the plasma concentrations of intravenous midazolam by 5-fold while the terminal half-life increased by about 3-fold.

Voriconazole increased the exposure of intravenous midazolam by 3-fold whereas its elimination half-life increased by about 3-fold.

Fluconazole and itraconazole both increased the plasma concentrations of intravenous midazolam by 2 to 3-fold associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole.

Posaconazole increased the plasma concentrations of intravenous midazolam by about 2-fold.

When bolus doses of midazolam (given for short term sedation) were administered to patients receiving itraconazole or fluconazole the effect of midazolam was not enhanced to a clinically significant degree and dosage reduction is not required. High doses of midazolam may require dosage adjustments.

### *Macrolide antibiotics*

Erythromycin resulted in an increase in the plasma concentrations of intravenous midazolam by about 1.6 to 2 -fold associated with an increase of the terminal half-life of midazolam by 1.5 to 1.8-fold.

Clarithromycin increased the plasma concentrations of intravenous midazolam by up to 2.5-fold associated with an increase in terminal half-life by 1.5 to 2-fold.

### *Anticholinergics*

Propiverine reduce the hepatic and intestinal CYP3A4 activity by 0.89-fold and to 0.80-fold, respectively, and with the combined effect resulting in a 1.46-fold increase in AUC of oral midazolam.

### *Selective serotonin reuptake inhibitors*

Fluvoxamine has been shown to possess CYP3A4 inhibitory properties, therefore increase the midazolam AUC and C<sub>max</sub> by approximately 60% and decrease clearance by 30%.

### *Nefazodone*

Treatment with nefazodone increased the AUC<sub>0-∞</sub> of midazolam by about four times and doubled the C<sub>max</sub>.

### *Glucocorticoids (GCs)*

Use of GCs decreased the mean AUC of Midazolam (63.9%), whereas total clearance of midazolam was increased to a mean of 125.7%. Terminal t<sub>1/2</sub> and AUC<sub>0-∞</sub> of the metabolite 1'-OH midazolam significantly declined in the patients taking GCs.

### *HIV Protease inhibitors*

Co-administration with protease inhibitors (e.g. Saquinavir and other HIV protease inhibitors) may cause a large increase in the concentration of midazolam. Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of intravenous midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life.

### *Reverse transcriptase inhibitors:*

Efavirenz: the ratio of  $\alpha$ -hydroxymidazolam (metabolite that is generated by CYP3A4) increases by a factor of five compared to midazolam, confirming the induction effect of efavirenz on CYP3A4.

### *Various medicinal products*

Atorvastatin showed a 1.4-fold increase in plasma concentrations of intravenous midazolam compared to control group.

### Pharmacodynamic Drug Interactions

The co-administration of midazolam with other sedative/hypnotic medicinal products and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression.

Examples include opiate derivatives (used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; sedative antidepressants, non-recent H<sub>1</sub>-antihistamines and centrally acting antihypertensive medicinal products.

Alcohol (including alcohol-containing medicinal products) may markedly enhance the sedative effect of midazolam. Alcohol intake should be strongly avoided in case of midazolam administration (see section 4.4).

Midazolam decreases the minimum alveolar concentration (MAC) of inhalation anaesthetics.

Midazolam may cause potentiation of muscle relaxants, with increased CNS depressant effects, e.g., baclofen.

Co-administration with midazolam may cause enhanced sedation or respiratory and cardiovascular depression.

### Opioids

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as midazolam with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

No data on the use of midazolam in women during the first two trimesters of pregnancy are available.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Midazolam may be used during pregnancy if clearly necessary. The risk for new-born infants should be taken into account in the event of administration of midazolam in the third trimester of pregnancy.

### Breast-feeding

Midazolam is excreted in low quantities in human milk. As a result, it may not be necessary to stop breast feeding following a single dose of midazolam.

## Fertility

Animal studies did not show an impairment of fertility (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

Midazolam has a major influence on the ability to drive and use machines.

Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive, ride a bicycle or use machines. After receiving midazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered.

## **4.8 Undesirable effects**

The safety of orally administered Midazolam Oral Solution in conscious sedation in children has been evaluated from the results of 32 clinical studies in which 4148 patients participated. The frequency of adverse reactions is classified as follows:

Very common ( $\geq 1/10$ );

Common ( $\geq 1/100$  to  $< 1/10$ );

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ );

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ );

Very rare ( $< 1/10,000$ ) and

Not known (cannot be estimated from the available data).

System Organ Class	Frequency			Not known
	Common	Uncommon	Rare	
Cardiac disorders				Kounis syndrome*
Eye disorders		Diplopia		
Gastrointestinal disorders		Nausea Vomiting		
Injury, poisoning, procedural complication		Sedation complication		
Nervous system disorders	Agitation Somnolence	Dyskinesia Ataxia Dizziness Headache Compulsive lip biting Excessive/prolonged sedation	Aphasia	
Psychiatric disorders	Paradoxical reactions	Crying Gait disorders	Anger Hallucination Mood swings Aggression Screaming Irritability	
Respiratory		Hiccups	Oxygen	

		Respiratory disorder	saturation decreased	
Surgical and medical procedures		Endotracheal intubation		
Vascular disorders			Hypotension	

\*particularly after parenteral administration

From the available clinical studies reporting the use of oral midazolam as a premedicant before induction of anaesthesia, it has not been possible to estimate the frequency of adverse events. The adverse events that have been reported in these clinical studies in patients receiving oral midazolam include: nausea, vomiting, salivation, hypoxia, hypertension, tachycardia, agitation, vertigo, euphoria, excitation, restlessness and nocturnal enuresis.

#### Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

### Symptoms

Midazolam overdose can present a threat to life if the patient has pre-existing respiratory or cardiac insufficiency, or when combined with other CNS depressants (including alcohol).

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

### Management

In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

In most cases, monitoring of vital signs is necessary. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Following overdose with oral midazolam, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Flumazenil may be useful as an antidote.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, benzodiazepine derivatives

ATC code: N05CD08

Midazolam is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water. The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables midazolam to form the hydrochloride salt with acids. These produce a stable solution suitable for oral administration.

#### Mechanism of action

Midazolam is a derivative of the imidazobenzodiazepine group. The pharmacological effects of benzodiazepines are the consequence of reversible interactions with the gamma-aminobutyric acid (GABA) receptor in the central nervous system (CNS). Benzodiazepines intensify the physiological mechanisms of GABA, the most common inhibitory neurotransmitter within the CNS.

#### Pharmacodynamic effects

The pharmacological action of midazolam is characterized by short duration because of rapid metabolic transformation. Midazolam has an anticonvulsant effect. It also exerts a sedative and sleep-inducing effect of pronounced intensity, and an anxiolytic and a muscle-relaxant effect.

#### Clinical efficacy and safety

##### *Paediatric use*

In a randomized, double-blind, placebo-controlled study, the safety, efficacy and feasibility of oral midazolam premedication in children were evaluated in an ambulatory surgery unit. Eighty unmedicated children (ASA PS Class I or II, ages 1-6 yr) were randomly assigned to one of four groups receiving midazolam 0.5, 0.75, or 1.0 mg/kg or a placebo 30 min before separation from parents. Heart rate, systolic blood pressure, arterial oxygen saturation, respiratory rate, sedation and anxiolysis scores were recorded before premedication, every five minutes for 30 min and then during induction of anaesthesia and recovery. It was found that heart rate, systolic blood pressure, arterial oxygen saturation and respiratory rate were unchanged during the study. Sedation and anxiolysis scores in the midazolam-treated groups were greater than those in the placebo group and that anxiolysis at the time of separation from the parents was judged excellent in 80-90% of the children who received midazolam. However, sedation and anxiolysis did not differ among the three midazolam groups. Mean times to discharge from hospital were similar for all four groups. The side effects, loss of balance and head control, blurred vision and dysphoric reactions were observed only in the 0.75 and 1.0 mg/kg midazolam groups. The study concluded that oral midazolam 0.5 mg/kg is a safe and effective premedication and that 0.75 and 1 mg/kg while offering no additional benefit, may cause more side effects.

In a prospective clinical trial aimed to determine the effectiveness of oral midazolam in co-operation of the subjects before general anaesthesia for dental treatment and in recalling the pre-anaesthetic phases, 62 healthy non-cooperative children, were randomly divided into study

and control groups. The children received 20ml orange juice, 20 minutes before starting the anaesthesia. The juice of the test group contained 0.5mg/kg of midazolam and that of the control group included no medication. The induction and the maintenance process of anaesthesia were similar in both groups. The manner of subjects when separated from parents, their cooperation during intravenous catheterization, and recalling the pre-anaesthetic events were recorded. Data were analysed by adopting chi-square and Mann-Whitney tests. Most of the children in the test group had a comfortable separation from parents, restful IV catheterization and 90% of the subjects did not recall the pre-anaesthetic events. The authors concluded that 0.5mg/kg oral midazolam premedication is effective for comfortable separation of children from parents and restful IV catheterisation and also forgetting the pre-anaesthetic events.

## 5.2 Pharmacokinetic properties

### *Absorption*

Midazolam is rapidly absorbed after oral administration and is subject to substantial intestinal and hepatic first-pass metabolism. The pharmacokinetics of midazolam and its major metabolite,  $\alpha$ -hydroxymidazolam, and the absolute bioavailability of midazolam hydrochloride syrup were studied in paediatric patients of different ages (6 months to <16 years old) over a 0.25 to 1 mg/kg dose range. The mean  $T_{max}$  values across dose groups (0.25, 0.5, and 1 mg/kg) range from 0.17 to 2.65 hours. The absolute bioavailability of the Midazolam Oral Solution in paediatric patients is between 36% and 50%, which is not affected by paediatric age or weight. The  $AUC_{0-\infty}$  ratio of  $\alpha$ -hydroxymidazolam to midazolam for the oral dose in paediatric patients is higher than for an IV dose (0.38 to 0.75 versus 0.21 to 0.39 across the age group of 6 months to <16 years), and the  $AUC_{0-\infty}$  ratio of  $\alpha$ -hydroxymidazolam to midazolam for the oral dose is higher in paediatric patients than in adults (0.38 to 0.75 versus 0.40 to 0.56).

Food effect has not been tested using Midazolam Oral Solution. When a 15 mg oral tablet of midazolam was administered with food to adults, the absorption and disposition of midazolam was not affected. Feeding is generally contraindicated prior to sedation of patients for procedures.

### *Distribution*

Midazolam is highly lipophilic and distributes extensively. The extent of plasma protein binding of midazolam is moderately high and concentration independent. In adults and paediatric patients older than 1 year, midazolam is approximately 97% bound to plasma protein, principally albumin. In healthy volunteers,  $\alpha$ -hydroxymidazolam is bound to the extent of 89%. In paediatric patients (6 months to <16 years) receiving 0.15 mg/kg IV midazolam, the mean steady-state volume of distribution ranged from 1.24 to 2.02 L/kg.

There is a slow and insignificant passage of midazolam into the cerebrospinal fluid. In humans, midazolam has been shown to cross the placenta slowly and to enter foetal circulation. Small quantities of midazolam are found in human milk.

### *Biotransformation*

Midazolam is primarily metabolized in the liver and gut by human cytochrome P450 IIIA4 (CYP3A4) to its pharmacologic active metabolite,  $\alpha$ -hydroxymidazolam, followed by

glucuronidation of the  $\alpha$ -hydroxyl metabolite which is present in unconjugated and conjugated forms in human plasma. The  $\alpha$ -hydroxymidazolam glucuronide is then excreted in urine.  $\alpha$ -hydroxymidazolam is equipotent and equally effective as unchanged midazolam. After oral or intravenous administration, 63% to 80% of midazolam is recovered in urine as  $\alpha$ -hydroxymidazolam glucuronide. No significant amount of parent drug or metabolites is extractable from urine before beta-glucuronidase and sulfatase deconjugation, indicating that the urinary metabolites are excreted mainly as conjugates.

Midazolam is also metabolized to two other minor metabolites: 4-hydroxy metabolite (about 3% of the dose) and 1,4-dihydroxy metabolite (about 1% of the dose) are excreted in small amounts in the urine as conjugates.

#### *Elimination*

The mean elimination half-life of midazolam ranged from 2.2 to 6.8 hours following single oral doses of 0.25, 0.5, and 1 mg/kg of midazolam (Midazolam Hydrochloride Oral Solution). Similar results (ranged from 2.9 to 4.5 hours) for the mean elimination half-life were observed following IV administration of 0.15 mg/kg of midazolam to paediatric patients (6 months to <16 years old). In the same group of patients receiving the 0.15 mg/kg IV dose, the mean total clearance ranged from 9.3 to 11 mL/min/kg.

#### *Linearity/non-linearity*

Midazolam exhibits linear pharmacokinetics between oral doses of 0.25 to 1 mg/kg (up to a maximum dose of 40 mg) across the age groups ranging from 6 months to <16 years.

#### Special Populations:

##### *Renal Impairment:*

Although the pharmacokinetics of intravenous midazolam in adult patients with chronic renal failure differed from those of subjects with normal renal function, there were no alterations in the distribution, elimination, or clearance of unbound drug in the renal failure patients. However, the effects of renal impairment on the active metabolite  $\alpha$ -hydroxymidazolam are unknown.

##### *Hepatic Dysfunction:*

Chronic hepatic disease alters the pharmacokinetics of midazolam. Following oral administration of 15 mg of midazolam,  $C_{max}$  and bioavailability values were 43% and 100% higher, respectively, in adult patients with hepatic cirrhosis than adult subjects with normal liver function. In the same patients with hepatic cirrhosis, following IV administration of 7.5 mg of midazolam, the clearance of midazolam was reduced by about 40% and the elimination half-life was increased by about 90% compared with subjects with normal liver function. Midazolam should be titrated for the desired effect in patients with chronic hepatic disease.

##### *Congestive Heart Failure:*

Following oral administration of 7.5 mg of midazolam, elimination half-life values were 43% higher in adult patients with congestive heart failure than in control subjects.

##### *Neonates:*

Miprosed has not been studied in paediatric patients less than 6 months of age.

### Pharmacokinetic/pharmacodynamic relationship(s)

The relationship between plasma concentration and sedation and anxiolysis scores of an oral Midazolam Syrup (single oral doses of 0.25, 0.5, or 1 mg/kg) was investigated in three age groups of paediatric patients (6 months to <2 years, 2 to <12 years, and 12 to <16 years old). In this study, the patient's sedation scores were recorded at baseline and at 10-minute intervals up to 30 minutes after oral dosing until satisfactory sedation ("drowsy" or "asleep but responsive to mild shaking" or "asleep and not responsive to mild shaking") was achieved. Anxiolysis scores were measured at the time when the patient was separated from his/her parents and at mask induction. The results of the analyses showed that the mean midazolam plasma concentration as well as the mean of midazolam plus  $\alpha$ -hydroxymidazolam for those patients with a sedation score of 4 (asleep but responsive to mild shaking) is significantly different than the mean concentrations for those patients with a sedation score of 3 (drowsy), which is significantly different than the mean concentrations for patients with a sedation score of 2 (awake/calm). The statistical analysis indicates that the greater the midazolam, or midazolam plus  $\alpha$ -hydroxymidazolam concentration, the greater the maximum sedation score for paediatric patients. No such trend was observed between anxiolysis scores and the mean midazolam concentration or mean of midazolam plus  $\alpha$ -hydroxymidazolam concentration; however, anxiolysis is a more variable surrogate measurement of clinical response.

### **5.3 Preclinical safety data**

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sucralose

Glycerol (E422)

Hydrochloric acid, dilute

Orange flavour (contains propylene glycol (E1520))

Sodium hydroxide (for pH adjustment)

Purified water

### **6.2 Incompatibilities**

Miprosed is incompatible with cranberry juice.

### **6.3 Shelf life**

12 months

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

Do not refrigerate or freeze.

### **6.5 Nature and contents of container**

Amber glass bottle with tamper evident, child resistant, white plastic cap with polypropylene inner, polyethylene outer and an expanded polyethylene (EPE) liner with 1ml oral syringe with 0.01ml graduations and a 5ml oral syringe with 0.1ml graduations supplied with a syringe adaptor.

Pack size: Each carton contains one 15 ml amber glass bottle containing 7.5ml oral solution.

### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Do not use if the solution is not clear (e.g. particles are present).

Each bottle is intended for single patient use. Discard the bottle and dosing syringe immediately after use.

## **7      MARKETING AUTHORISATION HOLDER**

Syri limited,  
Unit 4, Bradfield Road,  
Ruislip, Middlesex,  
HA4 0NU, UK

Trading as:  
Thame Laboratories,  
Unit 4, Bradfield Road,  
Ruislip, Middlesex,  
HA4 0NU, UK

OR

SyriMed,  
Unit 4, Bradfield Road,  
Ruislip, Middlesex,  
HA4 0NU, UK

## **8      MARKETING AUTHORISATION NUMBER(S)**

PL 39307/0096

## **9      DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

04/10/2024

## **10     DATE OF REVISION OF THE TEXT**

04/10/2024