

## **ANNEX I TO PSUR**

### **CORE SAFETY PROFILE (EU SPC Sections 4.2-4.9)**

**Dormicum ampoules**  
Midazolam

**Approved Trade names:**

Hypnovel/Dormicum

**Active substance:** Midazolam

**Route of Administration**

IV-IM

#### **4.2 Posology and method of administration**

**Use in Special Populations:**

*Renal Impairment:*

In patients with renal impairment (creatinine clearance <10ml/min) the pharmacokinetics of unbound midazolam following a single IV dose is similar to that reported in healthy volunteers. However, after prolonged infusion in intensive care unit (ICU) patients, the mean duration of the sedative effect in the renal failure population was considerably increased most likely due to accumulation of  $\alpha$ -hydroxymidazolam glucuronide.

There is no specific data in patients with severe renal impairment (creatinine clearance below 30 ml/min) receiving midazolam for induction of anaesthesia.

*Hepatic Impairment*

Hepatic impairment reduces the clearance of i.v. midazolam with a subsequent increase in terminal half-life. Therefore the clinical effects may be stronger and prolonged. The required dose of midazolam may be reduced and proper monitoring of vital signs should be established. (See section 4.4).

*Paediatric population*

See above and section 4.4.

#### **4.3 Contraindications**

Use of this drug in patients with known hypersensitivity to benzodiazepines or to any excipient of the product.

Use of this drug for conscious sedation in patients with severe respiratory failure or acute respiratory depression.

#### **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. Severe cardiorespiratory adverse events have been reported. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest. Such life-threatening incidents are more likely to occur when the injection is given too rapidly or when a high dosage is administered (see section 4.8).

Special caution is required for the indication of conscious sedation in patients with impaired respiratory function.

Paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful respiratory rate and oxygen saturation monitoring are essential.

When midazolam is used for premedication, adequate observation of the patient after administration is mandatory as interindividual sensitivity varies and symptoms of overdose may occur.

Special caution should be exercised when administering midazolam to high-risk patients:

- adults over 60 years of age
- chronically ill or debilitated patients, e.g.
- patients with chronic respiratory insufficiency
- patients with chronic renal failure, impaired hepatic function or with impaired cardiac function
- paediatric patients specially those with cardiovascular instability.

These high-risk patients require lower dosages (see section 4.2) and should be continuously monitored for early signs of alterations of vital functions.

As with any substance with CNS depressant and/or muscle-relaxant properties, particular care should be taken when administering midazolam to a patient with myasthenia gravis.

##### *Tolerance*

Some loss of efficacy has been reported when midazolam was used as long-term sedation in intensive care units (ICU).

### *Dependence*

When midazolam is used in long-term sedation in ICU, it should be borne in mind that physical dependence on midazolam may develop. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse (cf section 4.8).

### *Withdrawal symptoms*

During prolonged treatment with midazolam in ICU, physical dependence may develop. Therefore, abrupt termination of the treatment will be accompanied by withdrawal symptoms. The following symptoms may occur: headaches, muscle pain, anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood changes, hallucinations and convulsions. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, it is recommended to decrease doses gradually.

### *Amnesia*

Midazolam causes anterograde amnesia (frequently 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. Prolonged amnesia can present problems in outpatients, who are scheduled for discharge following intervention. After receiving midazolam parenterally, patients should be discharged from hospital or consulting room only if accompanied by an attendant.

### *Paradoxical reactions*

Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, have been reported to occur with midazolam. These reactions may occur with high doses and/or when the injection is given rapidly. The highest incidence to such reactions has been reported among children and the elderly.

### *Altered elimination of midazolam*

Midazolam elimination may be altered in patients receiving compounds that inhibit or induce CYP3A4 *and the dose of midazolam may need to be adjusted accordingly* (see section 4.5).

Midazolam elimination may also be delayed in patients with liver dysfunction, low cardiac output and in neonates (see section 5.2).

### *Preterm infants and neonates*

Due to an increased risk of apnoea, extreme caution is advised when sedating preterm and former preterm non intubated patients. Careful monitoring of respiratory rate and oxygen saturation is required.

Rapid injection should be avoided in the neonatal population.

Neonates have reduced and/or immature organ function and are also vulnerable to profound and/or prolonged respiratory effects of midazolam.

Adverse haemodynamic events have been reported in paediatric patients with cardiovascular instability; rapid intravenous administration should be avoided in this population.

*Paediatric patients less than 6 months:*

In this population, midazolam is indicated for sedation in ICU only.

Paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful respiratory rate and oxygen saturation monitoring are essential (see also section 'Preterm infants' above).

*Concomitant use of alcohol / CNS depressants:*

The concomitant use of midazolam with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of midazolam possibly including severe sedation or clinically relevant respiratory depression (see section 4.5).

*Medical history of alcohol or drug abuse:*

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

Discharging criteria

After receiving midazolam, patients should be discharged from hospital or consulting room only when recommended by treating physician and if accompanied by an attendant. It is recommended that the patient is accompanied when returning home after discharge.

This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially 'sodium- free'

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

*Pharmacokinetic Interactions*

Midazolam is metabolized by CYP3A4.

Inhibitors and inducers of CYP3A 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 i.v. midazolam, in particular since CYP3A4 also exists in the upper gastro-intestinal tract. This is because for the oral route both systemic clearance and availability will be altered while for the parenteral route only the change in the systemic clearance becomes effective.

After a single dose of IV midazolam, the consequence on the maximal clinical effect due to CYP3A4 inhibition will be minor while the duration of effect may be prolonged. However, after prolonged dosing of midazolam, both the magnitude and duration of effect will be increased in the presence of CYP3A4 inhibition.

There are no available studies on CYP3A4 modulation on the pharmacokinetics of midazolam after rectal and intramuscular administration. It is expected that these interactions will be less pronounced for the rectal than for the oral route because the gastro-intestinal tract is by-passed whereas after IM administration the effects of CYP3A4 modulation should not substantially differ from those seen with IV midazolam.

It is therefore recommended to carefully monitor the clinical effects and vital signs during the use of midazolam, taking into account that they may be stronger and last longer after co-administration of a CYP3A4 inhibitor, be it given only once. Notably, administration of high doses or long-term infusions of midazolam to patients receiving strong CYP3A4 inhibitors, e.g. during intensive care, may result in long-lasting hypnotic effects, delayed recovery and respiratory depression, thus requiring dose adjustments.

With respect to induction, it should be considered that the inducing process needs several days to reach its maximum effect and also several days to dissipate. Contrary to a treatment of several days with an inducer, a short term-treatment is expected to result in less apparent DDI with midazolam. However, for strong inducers a relevant induction even after short-term treatment cannot be excluded.

Midazolam is not known to change the pharmacokinetics of other drugs.

#### *Drugs that inhibit CYP3A:*

##### *Azole antifungals:*

- Ketoconazole increased the plasma concentrations of intravenous midazolam by 5-fold while the terminal half-life increased by about 3-fold. If parenteral midazolam is co-administered with the strong CYP3A inhibitor ketoconazole, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Staggered dosing and dosage adjustment should be considered, especially if more than a single i.v. dose of midazolam is administered. The same recommendation may apply also for other azole antifungals (see further), since increased sedative effects of IV midazolam, although lesser, are reported.
- 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 – 3-fold associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole, respectively.
- Posaconazole increased the plasma concentrations of intravenous midazolam by about 2-fold.

It should be kept in mind that if midazolam is given orally, its exposure will drastically be higher than the above-mentioned ones, notably with ketoconazole, itraconazole, voriconazole.

Midazolam ampoules are not indicated for oral administration.

#### *Macrolide antibiotics*

- Erythromycin resulted in an increase in the plasma concentrations of intravenous midazolam by about 1.6 – 2-fold associated with an increase of the terminal half-life of midazolam by 1.5–1.8-fold.
- Clarithromycin increased the plasma concentrations of midazolam by up to 2.5-fold associated with an increase in terminal half-life by 1.5–2-fold.

#### *Additional information from oral midazolam*

- Roxithromycin: While no information on roxithromycin with IV midazolam is available, the mild effect on the terminal half-life of oral midazolam tablet, increasing by 30%, indicates that the effects of roxithromycin on intravenous midazolam may be minor.

#### *HIV Protease inhibitors*

- Saquinavir and other HIV protease inhibitors: Co-administration with protease inhibitors may cause a large increase in the concentration of midazolam. Upon co-administration with ritonavir-booster lopinavir, the plasma concentrations of intravenous midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life. If parenteral midazolam is coadministered with HIV protease inhibitors, treatment setting should follow the description in the above section for azole antifungals, ketoconazole.

#### *Additional information from oral midazolam*

- Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore protease inhibitors should not be co-administered with orally administered midazolam.

#### *Calcium-channel blockers*

- Diltiazem: A single dose of diltiazem increased the plasma concentrations of intravenous midazolam by about 25% and the terminal half-life was prolonged by 43%.

#### *Additional information from oral midazolam*

- Verapamil / diltiazem increased the plasma concentrations of oral midazolam by 3- and 4-fold, respectively. The terminal- half-life of midazolam was increased by 41% and 49%, respectively.

#### *Various drugs/Herbs*

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

#### *Additional information from oral midazolam*

- Nefazodone increased the plasma concentrations of oral midazolam by 4.6-fold with an increase of its terminal half-life by 1.6-fold.
- Aprepitant dose-dependently increased the plasma concentrations of oral midazolam by 3.3-fold after 80 mg/day associated with an increase in terminal half-life by ca. 2-fold.

#### *Drugs that induce CYP3A*

- Rifampicin decreased the plasma concentrations of intravenous midazolam by about 60% after 7 days of rifampicin 600 mg o.d. The terminal half-life decreased by about 50-60%.

Additional information from oral midazolam

- Rifampicin decreased the plasma concentrations of oral midazolam by 96% in healthy subjects and its psychomotor effects were almost totally lost.
- Carbamazepine / phenytoin: Repeated dosages of carbamazepine or phenytoin resulted in a decrease in plasma concentrations of oral midazolam by up to 90% and a shortening of the terminal half-life by 60%.
- Efavirenz: The 5-fold increase in the ratio of the CYP3A4 generated metabolite  $\alpha$ -hydroxymidazolam to midazolam confirms its CYP3A4-inducing effect.

#### *Herbs and food*

- 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.

#### Pharmacodynamic:

#### Drug-Drug Interactions (DDI):

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

Examples include opiates derivatives (be they used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; sedative antidepressants, non recent H1-antihistamines and centrally acting antihypertensive drugs.

Alcohol 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 inhalational anaesthetics.

## **4.6 Pregnancy and lactation**

Insufficient data are available on midazolam to assess its safety during pregnancy.

Animal studies do not indicate a teratogenic effect, but foetotoxicity was observed as with other benzodiazepines. No data on exposed pregnancies are available for the first two trimesters of pregnancy.

The administration of high doses of midazolam in the last trimester of pregnancy, during labour or when used as an induction agent of anaesthesia for caesarean section has been reported to produce maternal or foetal adverse effects (inhalation risk in mother, irregularities in the fetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the neonate).

Moreover, infants born from mothers who received benzodiazepines chronically during the latter stage of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Consequently, midazolam may be used during pregnancy if clearly necessary but it is preferable to avoid using it for caesarean.

The risk for neonate should be taken into account in case of administration of midazolam for any surgery near the term.

Midazolam passes in low quantities into breast milk. Nursing mothers should be advised to discontinue breast-feeding for 24 hours following administration of midazolam.

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

Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive or use machines. Prior to receiving midazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered. The physician should decide when these activities may be resumed. It is recommended that the patient is accompanied when returning home after discharge.



#### 4.8 Undesirable effects

The following undesirable effects have been reported (*frequency not known, cannot be estimated from the available data*) to occur when midazolam is injected:

Frequency categories are 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 ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

|                                 |  |
|---------------------------------|--|
| <i>Immune System Disorders</i>  |  |
| frequency not known             | Hypersensitivity, <a href="#">angioedema</a> ,<br>anaphylactic shock   |
| <i>Psychiatric Disorders</i>    |  |
| frequency not known             | Confusional state, euphoric mood,<br>hallucinations<br><br>Agitation*, hostility*, rage*,<br>aggressiveness*, excitement*<br><br>Physical drug dependence and<br>withdrawal syndrome<br><br><a href="#">Abuse</a>  |
| <i>Nervous System Disorders</i> |  |
| frequency not known             | Involuntary movements (including<br>tonic/clonic movements and muscle<br>tremor)*, hyperactivity*<br><br>Sedation (prolonged and<br>postoperative), alertness decreased,<br>somnolence, headache, dizziness,<br>ataxia, anterograde amnesia**, the<br>duration of which is directly related to<br>the administered dose<br><br>Convulsions have been reported in<br>premature infants and neonates |

|   |  |
|---|--|
|   | Drug withdrawal convulsions  |
| <i>Cardiac Disorders</i>                                    |  |
| frequency not known   | Cardiac arrest, bradycardia  |
| <i>Vascular Disorders</i>                                   |  |
| frequency not known   | Hypotension, vasodilation, thrombophlebitis, thrombosis                            |
| <i>Respiratory Disorders</i>                                |  |
| frequency not known   | Respiratory depression, apnoea, respiratory arrest, dyspnea, laryngospasm, hiccups |
| <i>Gastrointestinal Disorders</i>                           |  |
| frequency not known   | Nausea, vomiting, constipation, dry mouth  |
| <i>Skin and Subcutaneous Tissue Disorders</i>               |  |
| frequency not known   | Rash, urticaria, pruritus  |
| <i>General Disorders and Administration Site Conditions</i> |  |
| frequency not known   | Fatigue, injection site erythema, injection site pain                              |
| <i>Injury, Poisoning and Procedural Complications</i>       |  |
| frequency not known   | Falls, fractures***  |
| <i>Social Circumstances</i>                                 |  |
| frequency not known   | Assault*   |

\* Such paradoxical drug reactions have been reported particularly among children and the elderly (see section 4.4).

\*\* Anterograde amnesia may still be present at the end of the procedure and in few cases prolonged amnesia has been reported (see section 4.4).

\*\*\* The risk of falls and fractures is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Dependence: Use of midazolam even in therapeutic doses may lead to the development of physical dependence. After prolonged IV administration, discontinuation, especially abrupt discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions (see section 4.4). Cases of abuse have been reported.

Severe cardio-respiratory adverse events have occurred. Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered (see section 4.4).

## **4.9 Overdose**

### **Symptoms:**

Like other benzodiazepines, midazolam commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of midazolam is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnoea, hypotension, cardiorespiratory depression and in rare cases to coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.

### **Treatment:**

Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.

If taken orally further absorption should be prevented using an appropriate method e.g. treatment within 1-2 hours with activated charcoal. If activated charcoal is used airway protection is imperative for drowsy patients. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.

If CNS depression is severe consider the use of flumazenil, a benzodiazepine antagonist.

This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of this drug.