PACK INSERT FOR MALAYSIA

Dormicum®-Ampoules

Midazolam

1. DESCRIPTION

1.1 Therapeutic/ Pharmacologic Class of Drug

Pharmacotherapeutic group: Hypnotics and sedatives: Benzodiazepine derivative
ATC code: N05CD08

1.2 Type of Dosage Form

Solution for injection

1.3 Route of Administration

Ampoules for intravenous infusion, intravenous injection, intramuscular and rectal administration

1.4 Sterile/ Radioactive Statement

Sterile product

1.5 Qualitative and Quantitative Composition

Active ingredient: midazolam (as midazolam hydrochloride formed *in situ*).
Dormicum ampoules 5 mg/1 ml, 15 mg/3 ml and 5 mg/5 ml for i.v., i.m. and rectal administration.
Excipients: sodium chloride, hydrochloric acid, sodium hydroxide, water for injection.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication~~(s)~~

Dormicum is a short-acting sleep-inducing drug that is indicated as follows:
In adults

- Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia
- Anaesthesia
  - Premedication before induction of anaesthesia
  - Induction of anaesthesia
  - As a sedative component in combined anaesthesia
- Sedation in intensive care units

In paediatrics

- Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia
- Anaesthesia
  - Premedication before induction of anaesthesia
- Sedation in intensive care units

For dosage recommendation in specific age range see section 2.2~~ Dosage and Administration~~, table 1.

2.2 Dosage and Administration

Midazolam is a potent sedative agent that requires slow administration and individualization of dosage.
The dose should be individualised and titration is strongly recommended to safely obtain the desired state of sedation according to the clinical need, physical status, age and concomitant medication.
In adults over 60 years of age, critically ill patients, high risk patients and paediatric patients, the dose should be determined with caution and risk factors related to each patient should be taken into account.
The drug takes effect in about 2 minutes after intravenous injection. Maximum effect is obtained in about 5 to 10 minutes.

Standard dosages are provided in the table below. Additional details are given in the text following the table.

Table 1 Standard dosage

Indication	**Adults < 60 y**	**Adults ≥ 60 y/ critically ill, high-risk patients**	**Paediatrics**
Conscious sedation	***i.v.*** Initial dose: 2–2.5 mg Titration doses: 1 mg Total dose: 3.5-7.5 mg	***i.v.*** Initial dose: 0.5–1 mg Titration dose: 0.5-1 mg Total dose: < 3.5 mg	***i.v. 6 months–5 years:*** Initial dose: 0.05-1 mg/kg Total dose: < 6 mg ***i.v. 6-12 years:*** Initial dose: 0.025-0.05 mg/kg Total dose: < 10 mg ***13-16 years:*** As adult ***Rectal > 6 months:*** 0.3-0.5 mg/kg ***i.m. 1-15 years:*** 0.05-0.15 mg/kg
Anaesthesia premedication	***i.v.*** 1-2 mg repeated ***i.m.*** 0.07-0.1 mg/kg	***i.v.*** Initial dose: 0.5 mg Slow uptitration as needed ***i.m.*** 0.025-0.05 mg/kg	***Rectal > 6 months:*** 0.3-0.5 mg/kg ***i.m. 1-15 years:*** 0.08-0.2 mg/kg
Anaesthesia induction	***i.v.*** 0.2 mg/kg (0.2-0.35 mg/kg without premedication)	***i.v.*** 0.05-0.15 mg/kg (0.15-0.2 mg/kg without premedication)	Not indicated in paediatrics
Sedative component in combined anaesthesia	***i.v.*** Intermittent doses of 0.03-0.1 mg/kg or continuous infusion of 0.03-0.1 mg/kg/h	***i.v.*** Lower doses than recommended for adults < 60 years	Not indicated in paediatrics
Sedation in ICU	***i.v.*** Loading dose: 0.03-0.3 mg/kg in increments of 1-2.5 mg Maintenance dose: 0.03-0.2 mg/kg/h		***i.v. ≤ 32 weeks gestational age:*** 0.03 mg/kg/h ***i.v. > 32 weeks gestational age up to 6 months:*** 0.06 mg/kg/h ***i.v. > 6 months of age:*** Loading dose: 0.05-0.2 mg/kg Maintenance dose: 0.06-0.12 mg/kg/h

Conscious sedation

For basal (conscious) sedation prior to diagnostic or surgical intervention, Dormicum is administered i.v. The dose must be individualised and titrated and should not be administered by rapid or single bolus injection. The onset of sedation may vary individually depending on the physical status of the patient and the detailed circumstances of dosing (e.g. speed of administration, amount of dose). If necessary, subsequent doses may be administered according to the individual need. Special caution is required for the indication of conscious sedation in patients with impaired respiratory function, see section 2.4 ~~Warnings and Precautions~~.

Adults

The i.v. injection of Dormicum should be given slowly at a rate of approximately ~~1~~ 1 mg in 30 seconds.
In adults below the age of 60, the initial dose is 2 to 2.5 mg given 5-10 minutes before the beginning of the procedure. Further doses of 1 mg may be given as necessary. Mean total doses have been found to range from 3.5-7.5 mg. A total dose greater than 5.0 mg is usually not necessary.
In adults over 60 years of age, critically ill patients, and/or high-risk patients, the initial dose must be reduced to 0.5–1.0 mg and given 5-10 minutes before the beginning of the procedure. Further doses of 0.5-1 mg may be given as necessary. Since in these patients the peak effect may be reached less rapidly, additional Dormicum should be titrated very slowly and carefully.
A total dose greater than 3.5 mg is not usually necessary.

Paediatrics

I.V. administration:
Dormicum should be titrated slowly to the desired clinical effect. The initial dose of Dormicum should be administered over 2 to 3 minutes and, it is recommended to wait an additional 2 to 5 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments until the appropriate level of sedation is achieved. Infants and young children less than 5 years of age may require substantially higher doses than older children and adolescents.

- *Paediatric patients less than 6 months of age:* Paediatric patients less than ~~6~~ 6 months of age are particularly vulnerable to airway obstruction and hypoventilation. For this reason, the use in conscious sedation in children less than 6 months of age is not recommended unless the benefits outweigh the risks. In such cases titration with small increments to clinical effect and careful monitoring are essential.
- *Paediatric patients > 6 months to 5 years of age:* initial dose 0.05 to ~~0.1~~ 1 mg/kg. A total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint but the total dose should not exceed 6 mg. Prolonged sedation and risk of hyperventilation may be associated with the higher doses (see section 2.4 Warnings and Precautions).
- *Paediatric patients 6 to 12 years of age:* initial dose 0.025 to 0.05 mg/kg. A total dose up to 0.4 mg/kg to a maximum of 10 mg may be necessary. Prolonged sedation and risk of hyperventilation may be associated with the higher doses (see section 2.4 ~~Warnings and Precautions~~).
- *Paediatric patients 13 to 16 years of age:* should be dosed as adults.

Rectal administration (paediatrics > 6 months):
The total dose of Dormicum, ranges from 0.3-0.5 mg/kg.
Total dose should be administered at once and repeated rectal administration avoided. The use in paediatrics less than 6 months of age is not recommended, as available data in this population are limited.

For rectal administration of Dormicum see section 4.2 Special Instruction for Use, Handling and Disposal.

I.M. administration (paediatrics 1-16 years):

The recommended dose range is 0.05 to 0.15 mg/kg given 5-10 minutes before the beginning of the procedure. A total dose greater than 10.0 mg is not usually necessary. This route should only be used in exceptional cases. Rectal administration should be preferred as i.m. injection may be painful.

In paediatrics less than 15 kg of body weight, midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

***Anaesthesia - premedication*:**

Premedication with Dormicum given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of apprehension) and preoperative impairment of memory. Dormicum can also be administered in combination with anticholinergics. For this indication, Dormicum should be administered i.v. or i.m. (deep into a large muscle mass 20-60 minutes before induction of anaesthesia), or preferably via the rectal route in paediatrics (see below). Adequate observation of the patient after administration is mandatory as interindividual sensitivity varies and symptoms of overdose may occur.

Adults

For preoperative sedation and to impair memory of preoperative events, the recommended dose for adults of ASA Physical Status I & II and patients below 60 60 years is 1-2 mg i.v. repeated as needed, or 0.07-0.1 mg/kg i.m.

The dose must be reduced and individualised when Dormicum is administered to adult over 60 years of age, critically ill, high-risk patients. The recommended initial i.v. dose is 0.5 mg and should be slowly uptitrated as needed. Allow 2-3 3 minutes to fully evaluate the effect between doses. An i.m. dose of 0.025-0.05 mg/kg is recommended if there is no concomitant administration of narcotics.

Paediatrics

Rectal administration (> 6 months):

The total dose of Dormicum, usually 0.4 mg/kg, ranging from 0.3-0.5 mg/kg, should be administered 20-30 minutes before induction of anaesthesia.

For rectal administration of Dormicum see section 4.2 Special Instructions for Use, Handling and Disposal.

The use in paediatrics less than 6 months of age is not recommended as available data are limited.

I.M. administration (1-15 years)

As i.m. injection may be painful, this route should only be used in exceptional cases. Rectal administration should be preferred. However, a dose range from 0.08-0.2 mg/kg of Dormicum administered i.m. has been shown to be effective and safe.

In children between ages 1 and 15, proportionally higher doses are required than in adults in relation to body weight. It is recommended that Dormicum should be administered deep into a large muscle mass 30-60 minutes prior to the induction of anaesthesia.

In paediatrics less than 15 kg of body weight, midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

Induction of anaesthesia

Adults

If Dormicum is used for induction of anaesthesia before other anaesthetic agents have been administered, the individual response is variable. The dose should be titrated to the desired effect according to the patient's age and clinical status. When Dormicum is used before or in combination with other i.v. or inhalation agents for induction of anaesthesia, the initial dose of each agent may be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents. The desired level of anaesthesia is reached by stepwise titration. The i.v. induction dose of Dormicum should be given slowly in increments. Each increment of not more than 5 mg should be injected over 20 - 30 seconds allowing 2 minutes between successive increments.

Adults below the age of 60 years

- A dose of 0.15-0.2 mg/kg, administered i.v. over 20-30 seconds and allowing 2 minutes for effect, will usually suffice.
- In non-premedicated patients the dose may be higher (0.3-0.35 mg/kg), administered i.v. over 20-30 seconds and allowing about 2 minutes for effect. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used. Induction may instead be completed with volatile liquid inhalational anaesthetics. In resistant cases, a total dose of up to 0.6 mg/kg may be used for induction, but such larger doses may prolong recovery.

Adults above the age of 60 years and/or critically ill and/or high-risk patients

- In non-premedicated patients, the lowest initial dose of 0.15-0.2 mg/kg is recommended.
- In premedicated patients, a dose of 0.05-0.15 mg/kg administered i.v. over 20-30 seconds and allowing 2 minutes for effect, will usually suffice.

Paediatrics

The use of Dormicum for the induction of anesthesia is limited to adults only as there is very limited experience in children.

Sedative component in combined anaesthesia

Adults

Dormicum can be given as a sedative component in combined anaesthesia by either further intermittent small i.v. doses (range between 0.03 and 0.1 mg/kg) or continuous infusion of i.v. Dormicum (range between 0.03 and 0.1 mg/kg/h) typically in combination with analgesics. The dose and the intervals between doses vary according to the patient's individual reaction.

In adults over 60 years of age, critically ill and/or high-risk patients, lower maintenance doses will be required.

Paediatrics

The use of Dormicum as sedative component in combined anesthesia is limited to adults only as there is very limited experience in children.

Sedation in the intensive care unit

The desired level of sedation is reached by stepwise titration of Dormicum followed by either continuous infusion or intermittent bolus, according to the clinical need, physical status, age and concomitant medication (see section 2.4.4 Interactions with other Medicinal Products and other Forms of Interaction).

Adults

I.V. loading dose: 0.03-0.3 mg/kg should be given slowly in increments. Each increment of 1-2.5 mg should be injected over 20-30 seconds allowing 2 minutes between successive increments.

In hypovolemic, vasoconstricted or hypothermic patients, the loading dose should be reduced or omitted.

When Dormicum is given with potent analgesics, the latter should be administered first so that the sedative effects of Dormicum can be safely titrated on top of any sedation caused by the analgesic.

I.V. maintenance dose: doses can range from 0.03-0.2 mg/kg/h. In hypovolemic, vasoconstricted or hypothermic patients, the maintenance dose should be reduced. The level of sedation should be assessed regularly if the patient's condition permits. With long-term sedation, tolerance may develop and the dose may have to be increased.

Paediatrics

In preterm new-born infants, term newborn infants, and paediatrics less than 15 kg of body-weight, midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1mg/ml.

Paediatrics up to 6 months of age

Dormicum should be given as a continuous i.v. infusion:

- Paediatrics ≤ 32 weeks of gestational age: starting dose at 0.03 mg/kg/h (0.5 µg/kg/min)
- Paediatrics > 32 weeks of gestational age up to 6 months of age: starting dose 0.06 mg/kg/h (1 µg/kg/min)

Intravenous loading doses should not be used rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. The rate of infusion should be carefully and frequently reassessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation.

Careful monitoring of respiratory rate and oxygen saturation is required.

Paediatrics over 6 months of age

In intubated and ventilated patients, a loading dose of 0.05 to 0.2 mg/kg i.v. should be administered slowly over at least 2 to 3 minutes to establish the desired clinical effect. Dormicum should not be administered as a rapid intravenous dose. The loading dose is followed by a continuous i.v. infusion at 0.06 to 0.12 mg/kg/h (1 to 2 µg/kg/min). The rate of infusion can be increased or decreased (generally by 25% of the initial or subsequent infusion rate) as required, or supplemental i.v. doses of Dormicum can be administered to increase or maintain the desired effect.

When initiating an infusion with Dormicum in haemodynamically compromised patients, the usual loading dose should be titrated in small increments and the patient monitored for haemodynamic instability, e.g. hypotension. These patients are also vulnerable to the respiratory depressant effects of Dormicum and require careful monitoring of respiratory rate and oxygen saturation.

2.2.1 Special Dosage Instructions

Patients with renal Impairment

In patients with severe renal impairment Dormicum may be accompanied by more pronounced and prolonged sedation possibly including clinically relevant respiratory and cardiovascular depression. Dormicum should therefore be dosed carefully in this patient population and titrated for the desired effect. (See sections 2.2 Dosage and Administration and 2.5 Use in Special Populations).

Hepatic Impairment

The clinical effects in patients with hepatic impairment may be stronger and prolonged. The dose of midazolam may have to be reduced and vital signs should be monitored (see sections 2.4 Warnings and Precautions and 3.2.5 Pharmacokinetics in Special Populations).

2.3 Contraindications

Dormicum must not be used in patients with known hypersensitivity to benzodiazepines or any of their formulation excipients.

2.4 Warnings and Precautions

2.4.1 General

Benzodiazepines are not recommended for the primary treatment of psychotic illness. I.V. midazolam has been associated with severe respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognised promptly and treated effectively, death or hypoxic encephalopathy resulted. I.V. midazolam should be used only in hospital or ambulatory care setting that provide for continuous monitoring of respiratory and cardiac functions. Assure immediate availability of resuscitative drugs, equipment, appropriate antidote and personnel training in their use.

Dosage of i.v. IV midazolam must be individualised for each patient. Lower doses are usually required for elderly, debilitated or higher risk surgical patients.

When midazolam is administered intravenously for conscious sedation, it should be injected slowly (over at least 2 minutes); it should not be administered by rapid or single bolus i.v. IV injection because of respiratory depression and/or arrest, especially elderly or debilitated patients. The initial dose may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult; administer over at least 2 minutes and allow additional 2 or more minutes to fully evaluate sedative effects. If further titration is necessary, use small increments to appropriate level of sedation, allowing an additional 2 or more minutes for each increment to fully

evaluate sedative effects. (See section 2.2 Dosage and Administration for complete dosing information).
Midazolam should be used only when age- and size-appropriate resuscitation facilities are available, as i.v. administration of midazolam may depress myocardial contractility and cause apnoea. Severe cardiorespiratory adverse events have occurred on rare occasions. 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 2.6 Undesirable effects).
In case of conscious sedation provided by non-anaesthesiologist review of the latest practice guideline is strongly advised.
Premedication
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.
High-risk patients
Special caution should be exercised when administrating midazolam to high-risk patients:
- Adults over 60 years of age
- Critically ill
- Patients with impaired organ function:
- impaired respiratory function
- impaired kidney function
- impaired hepatic function (benzodiazepines may precipitate or exacerbate encephalopathy in patients with severe hepatic impairment)
- impaired cardiac function

These high-risk patients require lower dosages (see section 2.2 Dosage and Administration) and should be continuously monitored for early signs of alterations of vital functions.
Discharging criteria
After receiving Dormicum, 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 discharged.
Tolerance
Some loss of efficacy has been reported when Dormicum has been used as long-term sedation in intensive care units (ICU).
Withdrawal symptoms
Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, especially after long-term sedation i.e. ≥ 2-3 days, it is recommended that the dose is decreased gradually. The following withdrawal symptoms may occur: headaches, diarrhoea, muscle pain, extreme anxiety, tension, restlessness, confusion, irritability, sleep disturbance, mood changes, hallucinations and convulsions. In severe cases, the following symptoms may occur: depersonalisation, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact.
Amnesia
Anterograde amnesia may occur with therapeutic doses, with the risk increasing at higher dosages. Prolonged amnesia can present problems in outpatients, who are scheduled for discharge following intervention.
"Paradoxical" reactions
Paradoxical reactions such as restlessness, agitation, irritability, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, delusion, anger, aggressiveness, anxiety, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, paroxysmal excitement and assault, have been reported to occur with midazolam. Should this be so, discontinuation of the drug should be considered. These reactions may occur with higher doses and/or when the injection is given rapidly. The rare incidence of susceptibility to such reactions has been reported among children and at higher i.v. doses in 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 2.4.4 Interactions with other Medicinal Products and other Forms of Interaction).
Midazolam elimination may also be delayed, in patients with liver dysfunction, low cardiac output and in newborns (see section 2.5 Use in Special Populations).
Sleep Apnoea
Midazolam ampoules should be used with extreme caution in patients with sleep apnoea syndrome and patients should be regularly monitored.
Preterm infants
Due to an increased risk of apnoea, extreme caution is advised when sedating preterm infants less than 36 weeks of gestational age whose trachea is not intubated. Rapid injection should be avoided in the preterm infants less than 36 weeks of gestational age. Careful monitoring of respiratory rate and oxygen saturation is required.
Paediatric patients less than 6 months
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 Dormicum with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of Dormicum possibly including severe sedation that could result in coma or death, clinically relevant respiratory and/or cardio-vascular depression (see section 2.4.4 Interactions with other Medicinal Products and other Forms of Interactions).
Medical history of alcohol or drug abuse
Dormicum should be avoided in patients with a medical history of alcohol or drug abuse.
Others
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.
Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling) which can occur as early as the first time the product is taken.
Complex sleep - Related behaviours which may include sleep driving, making phone calls, preparing and eating food (while asleep).
Risks from Concomitant Use with Opioids
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Dormicum with opioids. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.
If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.
If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.
Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Dormicum is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of opioids (see section 2.4.4 Interactions with other Medicinal Products and other Forms of Interaction).

2.4.2 Drug Abuse and Dependence

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.

2.4.3 Ability to Drive or Use Machines

Sedation, amnesia, impaired concentration and impaired muscular function adversely affect the ability to drive or use machines. Prior to receiving Dormicum, 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.
If sleep duration is insufficient or alcohol is consumed, the likelihood of impaired alertness may be increased (see section 2.4.4 Interactions with other Medicinal Products and other Forms of Interaction).

2.4.4 Interactions with other Medicinal Products and other Forms of Interaction

Pharmacokinetic Drug-Drug Interactions (DDI)
Midazolam is almost exclusively metabolised by cytochrome P450 3A4 (CYP3A4, CYP3A5). Inhibitors and inducers of CYP3A have the potential to increase and decrease the plasma concentrations and, subsequently, the pharmacodynamic effects of midazolam. No other mechanism than modulation of CYP3A activity has been proven as a source for a clinically relevant pharmacokinetic drug-drug interaction with midazolam. Midazolam is not known to change the pharmacokinetics of other drugs.
When co-administration with a CYP3A inhibitor, the clinical effects of midazolam may be stronger and also longer lasting and a lower dose may be required. Conversely, the effect of midazolam may be weaker and last shorter when co-administered with a CYP3A inducer and a higher dose may be required.
In case of CYP3A induction and irreversible inhibition (so-called mechanism-based inhibition), the effect on the pharmacokinetics of midazolam may persist for several days up to several weeks after administration of the CYP3A modulator. Examples of mechanism-based CYP3A inhibitors include antibacterials (e.g. clarithromycin, erythromycin, isoniazid); anti-retroviral agents (e.g. HIV protease inhibitors such as ritonavir (including ritonavir-boosted protease inhibitors), delavirdine); calcium channel blockers (e.g. verapamil, diltiazem); tyrosine kinase inhibitors (e.g. imatinib, lapatinib, idelalisib); or the oestrogen receptor modulator raloxifene, and several herbal constituents (e.g. bergamottin),). In contrast to other mechanism-based inhibitors, ethinyloestradiol combined with norgestrel or gestodene, used for oral contraception and grapefruit juice (200 ml) did not modify exposure to midazolam to a clinically significant degree.
The range of the inhibiting/inducing potency of drugs is wide. The antifungal ketoconazole, a very potent CYP 3A inhibitor, increased the plasma concentrations of i.v. midazolam by about 5-fold. The tuberculostatic drug rifampicin belongs to the strongest inducers of CYP3A and its co-administration resulted in decreased in the plasma concentrations of intravenous midazolam by about 60%.
The administration route of midazolam also determines the magnitude of change in its pharmacokinetic due to CYP3A modulation: (i) The change in plasma concentrations is expected to be less for intravenous compared to oral administration of midazolam because CYP3A modulation is not confined to the liver but also occurs in the intestinal wall and hence not only affects the systemic clearance, but also bioavailability of oral midazolam. (ii) There are no studies investigating the effect of CYP3A modulation on the pharmacokinetics of midazolam after rectal and intramuscular administration, respectively. As after rectal administration the drug partly bypasses the liver and the expression of CYP3A in the colon is less compared to the upper gastro-intestinal tract, it is expected that the change in midazolam plasma concentrations due to CYP3A modulation will be less for the rectal than for the oral route of administration. As after intramuscular administration the drug directly enters systemic circulation, it is expected that the effects of CYP3A modulation will be

similar to those for intravenous midazolam. (iii) In line with pharmacokinetics principles, clinical studies have shown that after i.v. single dose of midazolam the change in the maximum clinical effect due to CYP3A modulation will be minor while the duration of effect may be prolonged. However, after prolonged dosing of midazolam, both magnitude and duration of effect will be increased in the presence of CYP3A inhibition.
The following listing gives examples of clinical pharmacokinetic drug-drug interactions with midazolam after intravenous administration. Importantly, any drug shown to possess CYP3A modulating effects *in vitro* and *in vivo*, respectively, has the potential to change the plasma concentrations of midazolam and therefore its effects. The listing includes information from clinical drug-drug interaction studies for oral midazolam in case that for the co-administered drug in question no information on intravenous midazolam is available. However, as outlined above the change in plasma concentrations is expected to be less for intravenous compared to oral midazolam.

Drugs that inhibit CYP3A

Azole antifungals

- Ketoconazole and voriconazole increased the plasma concentrations of intravenous midazolam by 5-fold and by 3-4-fold respectively, while the terminal half-life increased by about 3-fold. If parenteral midazolam is co-administered with these strong CYP3A inhibitors, 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 iv dose of midazolam is administered.
- Fluconazole and itraconazole both increased the plasma concentrations of intravenous midazolam by 2-3 folds associated with an increased 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.

Macrolide antibiotics

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

Additional information from oral midazolam

- Telithromycin increased the plasma levels of oral midazolam 6-fold.
- Roxithromycin: The roxithromycin effects on midazolam's pharmacokinetics are less compared to erythromycin and clarithromycin. After oral administration, the plasma concentrations of midazolam were increased by about 50% compared to 4.4- and 2.6-fold increase caused by erythromycin and clarithromycin, respectively. The mild effect on the terminal half-life of midazolam by about 30% indicates that the effects of roxithromycin on intravenous midazolam may be minor.

Intravenous anesthetics

- Disposition of intravenous midazolam was also changed by intravenous propofol (AUC and half-life increased by 1.6-fold).

Protease inhibitors

- Saquinavir and other HIV protease inhibitors: 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. If parenteral midazolam is co-administered with HIV protease inhibitors, treatment setting should follow the description in the section above for ketoconazole within azole antifungals.
- HCV protease inhibitors: Boceprevir and telaprevir reduce midazolam clearance. This effect resulted in a 3.4-fold increase of midazolam AUC after i.v. administration and prolonged its elimination half-life 4-fold.

Histamine receptor 2 antagonists

- Cimetidine increased the steady state plasma concentration of midazolam by 26%.

Calcium-channel blockers

- Diltiazem: A single dose of diltiazem given to patients undergoing coronary artery bypass grafting increased the plasma concentrations of intravenous midazolam by about 25% and the terminal half-life was prolonged by about 43%. This was less than the 4-fold increase seen after oral administration of midazolam.

Additional information from oral midazolam

- Verapamil increased the plasma concentrations of oral midazolam by 3 fold. The terminal-half-life of midazolam was increased by 41%.

Various drugs/Herbs

- Atorvastatin resulted in a 1.4 fold increase in plasma concentrations of i.v. midazolam compared to control group.
- Intravenous fentanyl is a weak inhibitor of midazolam's elimination: AUC and half-life of i.v. midazolam were increased by 1.5-fold in presence of fentanyl.

Additional information from oral midazolam

- Fluvoxamine resulted in a mild increase in plasma concentration of oral midazolam (28%) while the terminal half-life doubled.
- Nefazodone increased the plasma concentrations of oral midazolam by 4.6-fold with an increase in terminal half-life by 1.6-fold.
- Tyrosine kinase inhibitors have been shown either *in vitro* (imatinib, lapatinib) or after oral administration of *in vivo* (idelalisib) to be potent inhibitors of CYP3A4. After concomitant administration of idelalisib, oral midazolam exposure was increased on average 5.4-fold.
- NK1 receptor antagonist (aprepitant, netupitant, casoprepitant) dose dependently increased the plasma concentrations of oral midazolam up to about 2.5-3.5-fold and increased terminal half-life by approximately 1.5–2-fold.
- Chlorzoxazone decreased the ratio of the CYP3A generated metabolite 1'-hydroxymidazolam (also known as α-hydroxymidazolam) to midazolam indicating a CYP3A inhibiting effect.
- For a number of drugs or herbal medicines, a weak interaction with midazolam's elimination was observed with concomitant changes in its exposure (< 2-fold change in AUC) (bicalutamide, everolimus, cyclosporine, simeprevir, propiverine, berberine as also contained in goldenseal). These weak interactions are expected to be further attenuated after i.v. administration.

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%.
- Ticagrelor is a weak CYP3A inducer but has only small effects on intravenously administered midazolam (-12%) and 4-hydoxy-midazolam (-23%) exposures.

Additional information from oral midazolam

- Carbamezapine/ phenytoin: Repeat 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 about 60%.
- The very strong CYP3A4 induction seen after mitotane or enzalutamide resulted in a profound and long-lasting decrease of midazolam levels in cancer patients. AUC of orally administered midazolam was reduced to 5% and 14% of normal values respectively.
- Clobazam and Efavirenz are weak inducers of midazolam metabolism and reduce the AUC of the parent compound by approximately 30%. There is a resulting 4-5-fold increase in the ratio of the active metabolite (α-hydroxy-midazolam) to the parent compound but the clinical significance of this is unknown.
- Vemurafenib modulates CYP isozymes and inhibits CYP3A4 mildly: Repeat-dose administration resulted in a mean decrease of oral midazolam exposure of 32% (up to 80% in individuals).

Herbs and food

- *Echinacea purpurea* root extract decreased plasma concentrations (AUC) of i.v. midazolam by 20% associated with a decrease in half-life of about 42%.
- 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%.

Additional information from oral midazolam

- Quercetin (also contained in *Gingko biloba*) and *Panax ginseng* both have weak enzyme inducing effects and reduced exposure to midazolam after its oral administration to the extent of 20-30%.

Acute protein displacement

- Valproic acid: Increased concentrations of free midazolam due to displacement from plasma protein binding sites by valproic acid cannot be excluded although the clinical relevance of such an interaction is not known.

Pharmacodynamic Drug-Drug Interactions (DDI)

The co-administration of midazolam with other sedative/hypnotic agents, including alcohol, is likely to result in increased sedative/hypnotic effects. Examples include opiates/opioids (when they are used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate, sedative antidepressants, antihistaminics and centrally acting antihypertensive drugs. Midazolam decreases the minimum alveolar concentration (MAC) of inhalation anaesthetics
Enhanced side effects such as sedation and cardio-respiratory depression may also occur when midazolam is co-administered with any centrally acting depressants including alcohol, therefore adequate monitoring of vital signs has to be established. Alcohol should be avoided in patients receiving midazolam (see sections 2.4.1 General (Warnings and Precautions)and).
See section 2.7 Overdose for warning of other central nervous system depressants, including alcohol).
It has been shown that spinal anaesthesia can increase the sedative effect of i.v. midazolam. The midazolam dose may therefore have to be reduced. When lidocaine or bupivacaine, were administered intramuscularly, the dose of i.v. midazolam required for sedation was reduced.
Drugs increasing alertness/memory, e.g. physostigmine, reversed the hypnotic effects of midazolam. Similarly, 250 mg of caffeine partly reversed the sedative effects of midazolam.
Opioids
Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.
The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see section 2.4 Warnings and

Precautions). Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

2.5 Use in Special Populations

2.5.1 Pregnancy

An increased risk of congenital malformation associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested.

Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. The administration of midazolam in the last trimester of pregnancy or at high doses during labor has been reported to produce irregularities in the foetal heart rate, hypotonia, poor sucking and hypothermia and moderate respiratory depression in the neonate. Moreover, infants born to 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.

2.5.2 Nursing Mother

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

2.5.3 Paediatric Use

See sections 2.2 Dosage and Administration and 2.4 Warnings and Precautions.

- In preterm newborn infants, term newborn infants, and paediatrics less than 15 kg of body weight, midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml
- I.V. and rectal administration in paediatric patients less than 6 months of age is not recommended with exception in ICU as they are vulnerable to airway obstruction and hyperventilation
- Dormicum is not indicated in children in induction of anaesthesia and as sedative component in combined anaesthesia as limited data is available.

2.5.4 Geriatric Use

Geriatric patients, ≥ 60 years, require lower dosages and should be continuously monitored for early signs of alterations of vital functions (see sections 2.2 Dosage and Administration and 2.4 Warnings and Precautions).

2.5.5 Renal Impairment

There is a greater likelihood of adverse drug reactions in patients with severe renal impairment (see sections 2.2.1 Special Dosing Instructions and 3.2.5 Pharmacokinetics in Special Populations).

Table 2 Time to awaken (h) following cessation of the midazolam infusion

		Time to awaken (min)	
	Number of patients	Mean ± SD	range
All patients	37	27.8 ± 37.2	0-140
Patients without renal of hepatic dysfunction	24	13.6 ± 16.4	0-58
Patients with renal dysfunction without liver dysfunction	9	44.6 ± 42.5	2-120
Patients with renal failure and liver disease	2	-	124-140

2.5.6 Hepatic Impairment

Hepatic impairment reduces the clearance of i.v. midazolam with subsequent increase in terminal half-life. Therefore, the clinical effects may be stronger and prolonged. The required dose of midazolam may have to be reduced and proper monitoring of vital signs should be established. (see sections 2.2 Dosage and Administration, and 2.4 Warnings and Precautions).

2.6 Undesirable Effects

2.6.1 Post Marketing

The following undesirable effects have been reported to occur when Dormicum is injected:

Immune System Disorders: Generalized hypersensitivity reactions (skin reactions, cardiovascular reactions, bronchospasm), angioedema, anaphylactic shock.

Psychiatric Disorders: Confusional state, disorientation, emotional and mood disturbance. Changes in libido have been reported occasionally.

Paradoxical reactions such as restlessness, agitation, irritability, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, nervousness, hostility, anger, aggressiveness, anxiety, nightmares, abnormal dreams, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, paroxysmal excitement and assault, have been reported, particularly among children and the elderly.

Dependence

Use of Dormicum - even in therapeutic doses - may lead to the development of physical dependence. After prolonged i.v. administration, discontinuation, especially abrupt discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions. Abuse has been reported in poly-drug abusers.

Nervous System Disorders: Prolonged sedation, decreased alertness, headache, dizziness, ataxia, postoperative sedation, anterograde amnesia, the duration of which is directly related to the administered dose. Anterograde amnesia may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported.

Convulsions have been reported in premature infants and neonates.

Cardiac Disorders: Severe cardiorespiratory adverse events have occurred on rare occasions. These have included cardiac arrest, hypotension, bradycardia, vasodilating effects. 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 2.4 Warnings and Precautions).

Respiratory Disorders: Severe cardiorespiratory adverse events have occurred on rare occasions. These have included respiratory depression, apnoea, respiratory arrest, dyspnoea, laryngospasm. 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 2.4 Warnings and Precautions). Hiccup.

Gastrointestinal System Disorders: Nausea, vomiting, constipation, dry mouth.

Skin and Appendages Disorders: Skin rash, urticaria, pruritus.

General and Application Site Disorders: Erythema and pain on injection site, thrombophlebitis, thrombosis.

Injury, Poisoning and Procedural Complications: There have been reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

2.7 Overdose

Symptoms

Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of Dormicum 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 (Anexate®), 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 (Anexate®), for further information on the correct use of this drug.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Dormicum has hypnotic and sedative effects characterized by a rapid onset and short duration. It also exerts anxiolytic, anticonvulsant and muscle-relaxant effects. Dormicum impairs psychomotor function after single and/or multiple doses, but causes minimal haemodynamic changes.

The central actions of benzodiazepines are mediated through an enhancement of the GABAergic neurotransmission at inhibitory synapses. In the presence of benzodiazepines the affinity of the GABA receptor for the neurotransmitter is enhanced through positive allosteric modulation resulting in an increased action of released GABA on the postsynaptic transmembrane chloride ion flux.

Chemically, midazolam is a derivative of the imidazobenzodiazepine group. Although the free base is a lipophilic substance with low solubility in water, the basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables the active ingredient of Dormicum to form water-soluble salts with acids. This together with rapid metabolic transformation are the reasons for rapid onset and, short duration of effects. Because of its low toxicity, midazolam has a wide therapeutic range.

After i.m. or i.v. administration anterograde amnesia of short duration occurs (the patient does not recall events that occurred during the peak of activity of the compound).

3.2 Pharmacokinetics Properties

3.2.1 Absorption

Absorption after i.m. injection

Absorption of midazolam from the muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. The absolute bioavailability after i.m. injection is over 90%.

Absorption after rectal administration

After rectal administration midazolam is absorbed quickly. Maximum plasma concentration is reached in about 30 minutes. The absolute bioavailability is about 50%.

3.2.2 Distribution

When midazolam is injected i.v., the plasma concentration-time curve shows one or two distinct disposition phases. The volume of distribution at steady state is 0.7-1.2 l/kg. 96-98% of midazolam is bound to plasma proteins. The major binding protein is albumin. 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. Midazolam is not a substrate for drug transporters.

3.2.3 Metabolism

Midazolam is almost entirely eliminated by biotransformation. Midazolam is hydroxylated by the cytochrome P450 CYP3A4 and CYP3A5 isozymes and the major urinary and plasma metabolite is 1'-hydroxymidazolam (also known as α-hydroxymidazolam). Plasma concentrations of 1'-hydroxymidazolam are 12% of those of the parent compound. 1'-hydroxymidazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous midazolam.

3.2.4 Elimination

In young healthy volunteers, the elimination half-life of midazolam ranges from 1.5 to ~~–~~2.5 hours. The elimination half-life of the metabolite is shorter than 1 hour; therefore, after midazolam administration the concentration of the parent compound and the main metabolite decline in parallel. Plasma clearance of midazolam is in the range of 300-500 ml/min. Midazolam's metabolites are excreted mainly by the renal route: 60-80% of the dose is excreted in the urine as glucuro~~-~~conjugated 1'-hydroxymidazolam. Less than 1% of the dose is recovered in urine as unchanged drug.

When midazolam is given by i.v. infusion, its elimination kinetics do not differ from those, following bolus injection. Repeated administrations of midazolam do not induce drug-metabolis~~z~~ing enzymes.

3.2.5 Pharmacokinetics in Special Populations

Elderly

In adults over 60 years of age, the elimination half-life may be prolonged up to four times~~.~~ (S~~s~~ee section~~s~~ 2.4.1 ~~General (Warnings and Precautions)~~ and ~~section~~ 2.5.4 ~~Geriatric Use~~).

Children

The rate of rectal absorption in children is similar to that in adults but the bioavailability is lower (5-18%). However, the elimination half-life (t½) after i.v. and rectal administration is shorter in children 3-10 years as compared with that in adults (1-1.5 h~~r~~). The difference is consistent with an increased metabolic clearance in children~~.~~ (S~~s~~ee section~~s~~ 2.4.1 ~~General (Warnings and Precautions)~~ and ~~section~~ 2.5.3 ~~Paediatric Use~~).

Newborn

In preterm and term new~~-~~born infants, the elimination half-life is on average 6-12 hours, probably due to liver immaturity and the clearance is reduced. Neonates with asphyxia-related hepatic and renal impairment are at risk of generating unexpectedly high serum midazolam concentrations due to a significantly decreased and variable clearance~~.~~ (S~~s~~ee section 2.4.1~~ General (Warnings and Precautions~~).

Obese

The mean half-life is greater in obese than in non-obese patients (8.4 vs 2.7 hours). This is due to an~~d~~ increase of approximately 50% in the volume of distribution corrected for total body~~-~~weight. The clearance is not significantly different in obese and non-obese patients.

Patients with hepatic impairment

The clearance in cirrhotic patients may be reduced and the elimination half-life may be longer when compared to those in healthy volunteers~~.~~ (S~~s~~ee section 2.4.1~~ General (Warnings and Precautions)~~).

Patients with renal impairment

The pharmacokinetics of unbound midazolam are not altered in patients with severe renal impairment. The pharmacologically mildly active major midazolam metabolite, 1'-hydroxymidazolam glucuronide, which is excreted through the kidney, accumulates in patients with severe renal impairment. This accumulation produces a prolonged sedation. Midazolam should therefore be administered carefully and titrated to the desired effect~~.~~ (s~~S~~ee section~~s~~ 2.4.1~~ General (Warnings and Precautions)~~ and ~~section~~ 2.5.5~~ Use in Special populations - Renal impairment~~).

Critically ill patients

The elimination half-life of midazolam is prolonged in the critically ill~~.~~ (S~~s~~ee section 2.4.1~~ General (Warnings and Precautions)~~).

Patients with cardiac insufficiency

The elimination half-life is longer in patients with congestive heart failure compared with that in healthy subjects~~ .(~~ s~~S~~ee section 2.4.1~~ General (Warnings and Precautions)~~).

3.3 Preclinical Safety

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the CDS.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Do not store above 30ºC.

This medicine should not be used after the expiry date (EXP) shown on the pack.

Keep the ampoules in the outer carton in order to protect from light.

Precipitation may occur after freezing which dissolves completely after warming to room temperature and mixing well.

4.2 Special Instructions for Use, Handling and Disposal

Do not dilute Dormicum ampoule solutions with 6% Dextran 70 in dextrose.

Do not mix Dormicum ampoule solutions in alkaline injections. Midazolam precipitates in sodium bicarbonate.

The Dormicum ampoule solution can be diluted with sodium chloride 0.9%, dextrose 5% and 10%, levulose 5%, Ringer's solution and Hartmann's solution in a mixing ratio of 15 mg midazolam per 100-1000 ml infusion solution. These solutions remain physically and chemically stable for 24 hours at room temperature, or 3 days at 5-°C.

To avoid potential incompatibility with other solutions, Dormicum ampoule solution must not be mixed with other solutions except those mentioned above.

From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 h at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Dormicum ampoules are for single use only. Discard any unused solution.

The solution should be visually inspected prior to use. Only clear solutions without particles should be used.

Rectal administration

Rectal administration of the ampoule solution is performed by means of a plastic applicator fixed on the end of the syringe. If the volume to be administered is too small, water may be added up to a total volume of 10 ml.

4.3 Packs

Ampoules 5 mg in 1 ml	... 10
Ampoules 15 mg in 3 ml	... 5
Ampoules 5 mg in 5 ml	... 10

Medicine: Keep out of reach of children

~~MYDormicumInj1117/CDS7.1~~

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Revision Date: November 2020

Made for
CHEPLAPHARM Arzneimittel GmbH,~~F. Hoffmann-La Roche Ltd,~~

Greifswald, Germany~~Basel, Switzerland~~

by CENEXI ~~SAS~~, Fontenay-sous-Bois, France