Dormicum®

Midazolam

Ampoules for intravenous, intramuscular and rectal administration

COMPOSITION

Active substance: midazolam

Excipients: 5 mg sodium chloride per ml (5 mg / 1 ml; 15 mg / 3 ml; 50 mg / 10 ml); 9 mg sodium chloride per ml (5 mg / 5 ml); water for solution.

PHARMACEUTICAL FORM AND QUANTITY OF ACTIVE SUBSTANCE PER UNIT DOSE

1 ml ampoules containing 5 mg midazolam, 3 ml ampoules containing 15 mg midazolam, 5 ml ampoules containing 5 mg midazolam and 10 ml ampoules containing 50 mg midazolam as a clear and sterile injectable solution (free of organic solvents, and ready to use) for intravenous, intramuscular and rectal administration.

INDICATIONS AND USES

Adults

Conscious sedation before diagnostic or surgical interventions with or without local anesthesia (intravenous administration).

Premedication before the induction of anesthesia (intramuscular).

Induction and maintenance of anesthesia. As an induction agent in inhalation anesthesia or as a sedative component in balanced anesthesia, including intravenous general anesthesia (intravenous injection, intravenous infusion).

Long-term sedation in intensive care units (i.v. administration as bolus injection or continuous infusion).

Children

Conscious sedation before diagnostic or surgical interventions with or without local anesthesia (i.v., i.m. or rectal administration).

Premedication before induction of anesthesia (i.m. or mainly rectal administration).

Ataralgesia in combination with ketamine in children (intramuscular administration).

Long-term sedation in intensive care units (intravenous injection as a bolus or continuous infusion).

(Dosage recommendations for specific age groups: see *Posology and method of administration.*)

POSOLOGY AND METHOD OF ADMINISTRATION

Standard dosage

Midazolam is a potent sedative that requires slow administration and an individualised dosage.

The dose must be adapted to each case. Dose titration is a mandatory recommendation to ensure the safe induction of the desired degree of sedation according to clinical need, physical status, age and comedication.

In patients over 60 years of age, critically ill patients, or patients belonging to a high-risk group, and in pediatric patients, the dosage must be determined with caution and careful regard for the specific characteristics of each patient. Intravenous injection must be given slowly (approximately 2.5 mg in 10 seconds for the induction of anesthesia and 1 mg in 30 seconds for conscious sedation). Onset of effect is approximately 2 minutes after the start of injection. Peak effect is achieved after approximately 5 to 10 minutes.

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

Table 1. Standard dosages (BW: body weight; i.m.: intramuscular; i.v.: intravenous)

Indication	**Adults <60 years**	**Adults ≥60 years / critically ill patients or those at high risk**	**Children and adolescents**
Conscious sedation	i.v. Initial dose: 2–2.5 mg Titration dose: 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: 0.05–0.1 mg/kg BW Total dose: ≤6 mg i.v. 6–12 years: Initial dose: 0.025–0.05 mg/kg BW Total dose: ≤10 mg i.v. 13–16 years: as for adults Rectal administration >6 months: 0.3–0.5 mg/kg BW i.m. 1–15 years: 0.05–0.15 mg/kg BW

Indication	Adults <60 years	Adults ≥60 years / critically ill patients or those at high risk	Children and adolescents
Premedication before induction of anesthesia	i.v. 1–2 mg, repeated i.m. 0.07–0.1 mg/kg BW	i.v. Initial dose: 0.5 mg Slow uptitration as needed i.m. 0.025–0.05 mg/kg BW	Rectal administration >6 months: 0.3–0.5 mg/kg BW i.m. 1–15 years: 0.08–0.2 mg/kg BW
Induction of anesthesia	i.v. 0.2 mg/kg BW (0.2–0.35 mg/kg BW without premedication)	i.v. 0.05–0.15 mg/kg BW (0.2 mg/kg BW without premedication)	Not indicated in children
Sedative component in combined anesthesia	i.v. intermittent doses of 0.03–0.1 mg/kg BW or continuous infusion of 0.03–0.1 mg/kg BW/h	i.v. Lower doses than recommended for adults <60 years	Not indicated in children
Sedation in intensive care units	i.v. Initial dose: 0.03–0.3 mg/kg BW increasing by 1–2.5 mg increments Maintenance dose: 0.03–0.2 mg/kg BW/h		i.v. Gestational age <32 weeks: 0.03 mg/kg BW/h i.v. Gestational age >32 weeks up to 6 months: 0.06 mg/kg BW/h i.v. Age >6 months: Initial dose: 0.05–0.2 mg/kg BW Maintenance dose: 0.06–0.12 mg/kg BW/h

Conscious sedation

Dormicum is administered intravenously for conscious sedation before a diagnostic or surgical procedure. The dose must be individualised and titrated; the drug must not be administered by rapid or single bolus injection. The onset of sedation may vary between individuals depending on the patient's physical status and the exact administration conditions (e.g. rate of administration, amount of dose). If necessary, subsequent doses may be administered according to individual need.

Special care is mandatory in conscious sedation in patients with respiratory disorders: see *Special warnings and precautions for use*.

Adults

Intravenous Dormicum injection must be given slowly – at a rate of approximately 1 mg in 30 seconds.

In adults below the age of 60 years, the initial dose is 2 to 2.5 mg; this is administered 5 to 10 minutes before the beginning of the procedure. Further doses of 1 mg may be given as necessary. Mean total doses of 3.5 to 7.5 mg are generally administered. A total dose exceeding 5.0 mg is not generally necessary.

In adults over the age of 60 years, critically ill patients or high-risk patients, the initial dose must be reduced to 0.5–1.0 mg and administered 5–10 minutes before the start of the procedure. Further doses of 0.5–1 mg may be given as needed. Since maximum effect may be reached less rapidly in these patients, additional doses of Dormicum should be titrated very slowly and carefully.

A total dose exceeding 3.5 mg is not generally necessary.

Children

Intravenous administration

Dormicum should be administered with slow dose titration until the desired clinical effect is achieved. The initial dose of Dormicum should be administered over 2 to 3 minutes. Waiting a further 2–5 minutes is then recommended to allow careful assessment of the sedative effect before beginning the procedure or administering a new dose. If further sedation appears necessary, continue to titrate the dose with small increments until the desired level of sedation is achieved. Under certain conditions, infants and children under 5 years of age require markedly higher doses than older children or adolescents.

- Infants *under 6 months of age:* In infants under 6 months of age, the risk of upper respiratory tract obstruction and hypoventilation is particularly high. For this reason, the use of Dormicum is not recommended for conscious sedation in infants under 6 months of age, except if the benefit outweighs the risks. In such cases, dose titration in small increments and close supervision are essential until clinical effect is achieved.

- Children *aged 6 months to 5 years:* Initial dose: 0.05 to 0.1 mg/kg. A total dose up to 0.6 mg/kg may prove necessary to achieve the desired effect; however, the total dose should not exceed 6 mg. Prolonged sedation and a risk of hypoventilation may occur with the administration of higher doses (see *Special warnings and precautions for use*).

- Children *aged 6 to 12 years:* Initial dose: 0.025 to 0.05 mg/kg. A total dose of up to 0.4 mg/kg (to a maximum of 10 mg) may prove necessary. Prolonged sedation and a risk of hypoventilation may occur with the administration of higher doses (see *Special warnings and precautions for use*).

- Adolescents *aged 13 to 16 years:* The dose is identical to that in adults.

Rectal administration (in children >6 months)

The total dose of Dormicum ranges from 0.3 to 0.5 mg/kg.

The total dose should be administered at once; repeated rectal administration should be avoided. Use in infants under 6 months of age is not recommended, as only limited data are available in this group of patients.

Rectal administration of Dormicum: see *Pharmaceutical particulars* and *Special precautions for preparation and handling*.

Intramuscular administration (children aged 1 to 15 years)

The recommended dose ranges from 0.05 to 0.15 mg/kg and administration should be performed 5–10 minutes before the start of the procedure. A total dose exceeding 10.0 mg is not generally necessary. This route of administration should only be used in exceptional cases. Rectal administration should be preferred as intramuscular injection can be painful.

Administration of midazolam solutions at concentrations exceeding 1 mg/ml in children whose body weight is under 15 kg is not recommended. Higher concentrations should be diluted to 1 mg/ml.

Premedication before induction of anesthesia

Premedication with Dormicum administered just before a procedure produces sedation (with drowsiness and anxiolysis) and decreases preoperative memory capacity. Dormicum can also be administered in combination with anticholinergics. For this indication, Dormicum should be administered intravenously or intramuscularly (by deep injection into a large muscle mass 20 to 60 minutes before induction of anesthesia) or in children preferably via the rectal route (see below). Close patient monitoring is mandatory after administration as response varies between individuals and symptoms of overdose may occur.

Adults

For preoperative sedation and to decrease memory of preoperative events, the recommended dose for ASA I/II adults under 60 years of age is 1–2 mg intravenously (repeat administration as required) or 0.07–0.1 mg/kg intramuscularly.

The dose must be reduced and individually adjusted when Dormicum is administered to adults over 60 years of age, critically ill patients or those at high risk. The recommended initial intravenous dose is 0.5 mg, which should be increased as required by slow dose titration. This should be followed by 2–3 minutes' wait to allow careful assessment of the effect of dose augmentation. A dose of 0.025–0.05 mg/kg i.m. is recommended in the absence of narcotic coadministration. The usual dose is 2–3 mg.

Children

Rectal administration (children >6 months):

The total dose of Dormicum is generally 0.4 mg/kg (range: 0.3–0.5 mg/kg), which should be administered 20 to 30 minutes before induction of anesthesia**.**

Rectal administration of Dormicum: see *Pharmaceutical particulars* and *Special precautions for preparation and handling*.

Use in infants under 6 months of age is not recommended, as only limited data are available in this group of patients.

Intramuscular administration (children aged 1 to 15 years):

Since intramuscular injections can be painful, this route of administration should only be used in exceptional cases. Rectal administration should be preferred. However, Dormicum doses ranging from 0.08 to 0.2 mg/kg have proved effective and safe.

Children aged 1 to 15 years require proportionally higher doses relative to body weight than adults. It is recommended that Dormicum be administered by deep injection into a large muscle mass 30 to 60 minutes before induction of anesthesia.

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

Induction of anesthesia

Adults

When Dormicum is used to induce anesthesia before the administration of other anesthetics, 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 intravenous or inhalational agents for inducing anesthesia, the initial dose of the various drugs can be set much lower (25% of their initial dose may suffice).

The desired level of anesthesia is reached by stepwise titration. The initial intravenous dose of Dormicum must be administered slowly and in increments. Each dose increment, which must not exceed 5 mg, must be injected over 20 to 30 seconds. A 2-minute pause should be observed between injections to titrate the dose.

Adults under 60 years of age

- A dose of 0.2 mg/kg, administered intravenously over 20 to 30 seconds and followed by a 2-minute pause to evaluate the effect, generally suffices.
- In non-premedicated patients, higher doses (0.3–0.35 mg/kg) may prove necessary; these are administered intravenously over 20 to 30 seconds and are followed by a 2-minute pause to evaluate the effect. If necessary, to complete the induction of anesthesia, the patients concerned can be given increments of approximately 25% of the initial dose. To complete the induction of anesthesia, inhalation of volatile liquid anesthetics can also be used as an alternative. In the event of inadequate patient response, a total dose of up to 0.6 mg/kg can be used to induce anesthesia; however, doses as high as this may delay recovery.

Adults over 60 years of age and/or critically ill patients or those at high risk

- 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 intravenously over 20–30 seconds and followed by a 2-minute pause to evaluate the effect, generally suffices.

Children

The use of Dormicum to induce anesthesia is reserved for adults, as experience is very limited in children.

Sedative component in combined anesthesia

Adults

When used as a sedative component in combined anesthesia, Dormicum can be administered as a series of intermittent low doses (ranging from 0.03 to 0.1 mg/kg) or as a continuous intravenous infusion (range: 0.03–0.1 mg/kg/h), generally in combination with analgesics. Dose and dose range depend on individual patient response.

Adults over 60 years of age, critically ill patients or those at high risk require lower maintenance doses.

Children

The use of Dormicum as a sedative component in combined anesthesia is reserved for adults as experience in children is very limited.

Sedation in intensive care units

The desired level of sedation is reached by increasing the dose of Dormicum stepwise (dose titration). Continuous infusion or intermittent bolus injection are then performed depending on clinical need, physical status, age and comedication (see *Interaction with other medicinal products and other forms of interaction*).

Adults

Administration of the initial intravenous dose (0.03–0.3 mg/kg) should be given slow and incremental. Each increment of 1–2.5 mg should be injected over 20 to 30 seconds. A 2-minute pause for dose titration should be observed between injections.

The initial dose should be reduced or even withdrawn in patients with hypovolemia, vasoconstriction or hypothermia.

When Dormicum is combined with very potent analgesics, these should be administered first in order to evaluate their sedative effect. The patient’s level of sedation can then be increased without risk by titrating the dose of Dormicum.

Intravenous maintenance dose: The intravenous maintenance dose may range between 0.03 and 0.2 mg/kg/h. The maintenance dose should be reduced in patients with hypovolemia, vasoconstriction or hypothermia. If the patient’s condition allows, the level of sedation should be regularly checked. In long-term sedation loss of effect may occur, requiring an increase in dose.

Children

Administration of midazolam solutions in concentrations exceeding 1 mg/ml is not recommended in neonates (whether pre- or full-term) or in children weighing less than 15 kg. Higher concentrations should be diluted to 1 mg/ml.

Infants under 6 months of age

Dormicum should be administered as a continuous intravenous infusion.

- Preterm infants of gestational age <32 weeks: initial dose: 0.03 mg/kg/h (0.5 µg/kg/min).
- Infants of gestational age >32 weeks to 6 months: initial dose: 0.06 mg/kg/h (1 µg/kg/min).

Intravenous initial doses should not be administered. Instead the infusion rate can be increased for the first few hours until therapeutic plasma concentrations are reached. The infusion rate should be carefully monitored, in particular after the first 24 hours, to ensure that the lowest possible effective dose is administered and that the risk of accumulation is kept as low as possible.

Respiratory rate and oxygen saturation should be closely monitored.

Children aged >6 months

In intubated and ventilated patients, an initial dose of 0.05–0.2 mg/kg should be administered slowly i.v. over at least 2–3 minutes to achieve the desired effect. Dormicum should not be given by rapid intravenous administration. The initial dose is followed by a continuous intravenous infusion of 0.06–0.12 mg/kg/h (1–2 µg/kg/min) Dormicum. The rate of infusion can be increased or decreased (generally by 25% of the initial infusion rate or the rate chosen immediately afterwards); supplemental doses of Dormicum can be administered intravenously to augment or maintain the effect.

When initiating treatment with Dormicum infusion in patients with hemodynamic disorders, the usual initial dose should be initiated by titrating the dose in small increments and the patient should be monitored for hemodynamic instability (e.g. the development of hypotension). These patients are also at risk of Dormicum-induced respiratory depression; their respiratory rate and oxygen saturation must be closely monitored for that reason.

Special dosage instructions

Renal impairment

Patients with renal impairment are similar to healthy volunteers in the pharmacokinetics of free midazolam**.**

However, α-hydroxymidazolam accumulation has been observed in patients with chronic renal disease. The clinical effect of midazolam may therefore be augmented and lead to prolonged sedation.

Table 2. Time to recovery (h) after the end of midazolam infusion*

		Time to recovery (min)	
	Patients (n)	**Mean ± standard deviation**	**Range**
All patients	37	27.8 ± 37.2	0–140
Patients without renal or hepatic impairment	24	13.6 ± 16.4	0–58
Patients with renal but not hepatic impairment	9	44.6 ± 42.5	2–120
Patients with renal and hepatic impairment	2	–	124–140

*Ref.: M.P. Shelly, M.A. Sultan, .A. Bodenham and G.R. Park. Intensive Care Unit, Addenbrooke's Hospital, Cambridge CB2 2QQ, United Kingdom

Hepatic impairment

Hepatic impairment delays the elimination of intravenously administered midazolam, leading to an increase in terminal half-life. This may enhance and prolong the clinical effect. The dose of midazolam required to achieve the desired effect may be lower and vital functions need to be closely monitored (see *Posology and method of administration*, and *Special warnings and precautions for use*).

CONTRAINDICATIONS

Dormicum should not be administered to patients hypersensitive to benzodiazepines or to any of the excipients listed under *Composition*.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Dormicum ampoules should only be used when the availability of resuscitation facilities appropriate to the patient's age and size can be guaranteed, as intravenous Dormicum administration may depress myocardial contractility and cause apnea. Severe cardiorespiratory adverse events, such as respiratory depression, apnea, and respiratory and/or cardiac arrest, have been observed in rare cases. The probability of such life-threatening events occurring is increased if the product is injected too rapidly or at too high a dose.

When conscious sedation is to be performed by a physician who is not an anesthetist, the mandatory recommendation is to check current guidelines concerning practice in this regard.

Premedication

When using midazolam for premedication, intensive patient monitoring is mandatory after administration since response may vary between individuals and symptoms of overdosage may occur.

High-risk patients

Caution is especially mandatory when administering Dormicum to patients in high-risk groups:

- patients over 60 years of age
- critically ill patients
- patients with organ dysfunction:
    - respiratory impairment
    - renal impairment
    - hepatic impairment
    - cardiac impairment.

These high-risk patients require lower dosages (see *Posology and method of administration*) and should be continuously monitored for early signs of alterations in vital functions.

Criteria for discharging patients from hospital

Patients who have received parenteral Dormicum should not leave hospital until at least 3 hours after the last injection and must be accompanied. Their attention should be drawn to the fact that they must not drive or operate machinery for at least 12 hours.

Tolerance

Some loss of efficacy has been observed when Dormicum has been used for long-term sedation in intensive care units (ICU).

Withdrawal symptoms

Since abrupt treatment discontinuation increases the risk of withdrawal symptoms, in particular after long-term sedation lasting ≥2–3 days, gradual dose reduction is recommended. The following withdrawal symptoms may occur: headaches, muscle pains, anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood swings, hallucinations and convulsions.

Amnesia

Midazolam causes anterograde amnesia. Prolonged amnesia can present problems in outpatients who are due to go home after their procedure.

Paradoxical reactions

Paradoxical reactions such as agitation, involuntary movements (e.g. 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 after the administration of high doses and/or rapid injection. Low susceptibility to such reactions has been reported in children and after high intravenous doses in the elderly.

Altered elimination of midazolam

Midazolam elimination may be altered in patients receiving drugs that inhibit or induce CYP3A4. The dose of midazolam may need to be adjusted accordingly (see *Interactions with other medicinal products and other forms of interaction*).

Midazolam elimination may also be delayed in patients with hepatic impairment, low cardiac output, and in neonates (see *Pharmacokinetics* and *Pharmacokinetics in certain patient groups*).

Preterm infants

Due to the increased risk of apnea, extreme caution is mandatory when sedating preterm infants of gestational age <36 weeks without an endotracheal tube *in situ*. Rapid injection must always be avoided in preterm infants of gestational age <36 weeks. Respiratory rate and oxygen saturation must be closely monitored.

Infants under 6 months of age

In infants under 6 months of age, the risks of airway obstruction and hypoventilation are particularly high. Dose titration in small increments until clinical effect is achieved and careful monitoring of respiratory rate and oxygen saturation are therefore essential (see also the *Preterm infants* section above).

Concomitant use of alcohol/CNS depressants

The concomitant use of Dormicum and alcohol and/or CNS depressants should be avoided due to the risk of potentiation of the clinical effect of Dormicum, possibly severe sedation and clinically significant respiratory and/or cardiovascular depression (see *Interactions with other medicinal products and other forms of interaction*).

History of alcohol, drug or prescription drug abuse

Dormicum should not be used in patients with a history of alcohol or prescription drug abuse.

Miscellaneous

As with all substances having a central depressant and/or muscle relaxant effect, particular caution is mandatory when administering Dormicum to patients with myasthenia gravis.

Dependence

Physical dependence on midazolam may develop when Dormicum is used for long-term sedation. The risk of dependence increases with dose and treatment duration and is also increased in patients with a history of alcohol or prescription drug abuse.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Pharmacokinetic drug interactions

Midazolam is almost exclusively metabolised by cytochrome P450 3A4 (CYP3A4). Inhibitors and inducers of CYP3A may increase or decrease plasma concentrations and hence the pharmacodynamic effects of midazolam. Apart from modulation of CYP3A activity, no other mechanism capable of causing pharmacokinetic drug interactions with midazolam has been demonstrated. Acute displacement from its plasma protein (albumin) binding sites may, however, at least theoretically, cause drug interactions with drugs reaching high serum concentrations, as for example has been suspected with valproic acid (see below). No change due to midazolam is known in the pharmacokinetics of other drugs.

Close monitoring of clinical effects and vital signs is recommended when using midazolam, taking into account the fact that midazolam may have a more marked and sustained clinical effect if coadministered with a CYP3A inhibitor. Depending on the degree of CYP3A inhibition, marked reduction of the dose of midazolam may sometimes be possible. Conversely, when coadministering a CYP3A inducer, it may prove necessary to increased the dose of midazolam to achieve the desired effect.

In CYP3A induction and irreversible inhibition (known as mechanism-based inhibition), the effect of administering the CYP3A inhibitor on the pharmacokinetics of midazolam may last for several days, or even several weeks. Drugs that may cause mechanism-based inhibition of CYP3A include: antibacterials (e.g. clarithromycin, erythromycin, isoniazid), anti-HIV drugs (e.g. HIV protease inhibitors), antihypertensives (e.g. verapamil, diltiazem), steroid sex hormones and modulators of their receptors (e.g. gestoden, raloxifen) and various plant components (e.g. the bergamottin contained in grapefruit). Unlike the other substances causing mechanism-based inhibition (see the list below), use of ethinylestradiol/norgestrel for oral contraception or grapefruit juice (200 ml) has caused no change of note in the plasma concentrations of intravenously administered midazolam.

The intensity of drug-induced CYP3A inhibition or induction is very variable. The antimycotic ketoconazole, a highly potent CYP3A inhibitor, multiplied the plasma concentrations of intravenously administered midazolam approximately 5-fold. The tuberculostatic rifampicin is one of the most potent CYP3A inducers. When coadministered with midazolam, it reduced the plasma concentrations of intravenously administered midazolam by approximately 60%.

The mode of midazolam administration also affects the degree of pharmacokinetic impact caused by CYP3A modulation: a) the impact on plasma concentrations should be slighter when midazolam is administered intravenously rather than orally, since CYP3A modulation affects not only the systemic clearance of midazolam but also its bioavailability after oral administration; b) there are no studies on the effects of CYP3A modulation on the pharmacokinetics of rectally or intramuscularly administered midazolam. Since the drug partially bypasses the liver when administered rectally, and since CYP3A is more weakly expressed in the colon than in the upper gastrointestinal tract, the impact of CYP3A modulation on plasma midazolam concentrations is likely to be weaker after rectal than after oral administration. Since the drug enters the systemic circulation directly after intramuscular injection, CYP3A modulation is likely to have the same effect as after intravenously administered midazolam. Consistent with

pharmacokinetic principles, clinical studies have shown that following the administration of a single intravenous dose of midazolam, the impact of CYP3A modulation on maximum clinical effect is weaker, whereas the duration of effect may be longer. However, after prolonged midazolam administration, both intensity and duration of effect are increased in the presence of CYP3A inhibition.

The following list provides clinical examples of pharmacokinetic drug interactions with intravenously administered midazolam. It is important to note that each drug capable of modulating CYP3A *in vitro* or *in vivo* may in principle modify the plasma concentrations and hence effect of midazolam. Where no information is available on midazolam coadministered intravenously with another drug, the list incorporates data from clinical studies relating to drug interactions with orally administered midazolam. As mentioned above, the impact on plasma concentrations should be slighter when midazolam is administered intravenously than when it is administered orally.

Drugs that inhibit CYP3A4

Azole antifungals

- Ketoconazole multiplied the plasma concentrations of intravenously administered midazolam 5-fold while approximately tripling its terminal half-life.

- Parenteral midazolam should only be coadministered with ketoconazole, a potent CYP3 inhibitor, in an intensive care unit (ICU) or similar setting to ensure close clinical monitoring in the event of respiratory depression and/or prolonged sedation. In particular, incremental dosing and dose adjustment should be considered when administering more than one intravenous dose of midazolam.

- Fluconazole and itraconazole both multiplied the plasma concentrations of intravenously administered midazolam between two- and three-fold and prolonged the terminal half-life 2.4-fold (itraconazole) and 1.5-fold (fluconazole).

- Posaconazole approximately doubled the plasma concentrations of intravenously administered midazolam.

Macrolide antibiotics

- Erythromycin multiplied the plasma concentrations of intravenously administered midazolam approximately 1.6-fold to 2-fold and simultaneously prolonged the terminal half-life of midazolam 1.5-fold to 1.8-fold.

- Clarithromycin multiplied the plasma concentrations of midazolam 2.5-fold while prolonging the terminal half-life 1.5-fold to 2-fold.

Additional information for orally administered midazolam

- Roxithromycin: Roxithromycin has less impact on the pharmacokinetics of midazolam than erythromycin or clarithromycin. It increased the plasma concentrations of orally administered midazolam by approximately 50%, whereas erythromycin and clarithromycin multiplied them 4.4-fold and 2.6-fold, respectively. The relatively slight prolongation of the terminal half-life of midazolam,

approximately 30%, indicates that roxithromycin may have only a slight impact on intravenously administered midazolam.

HIV protease inhibitors

Saquinavir and other HIV protease inhibitors: when coadministered with ritonavir-boosted lopinavir, the plasma concentrations of intravenously administered midazolam were multiplied 5.4-fold and the terminal half-life was correspondingly prolonged.

When coadministering midazolam with HIV protease inhibitors, treatment should comply with the description given in the above paragraph on ketoconazole in the *Azole antifungals* section.

No study on the *in-vivo* interactions of intravenously administered midazolam with other protease inhibitors is available. However, saquinavir is generally a weaker CYP3A4 inhibitor than the other HIV protease inhibitors and it has been shown that HIV protease inhibitors increase exposure to orally administered midazolam and to other CYP3A substrates.

H_2 histamine receptor antagonists

- Cimetidine increases plasma midazolam concentrations at steady state by 26%.

Calcium antagonists

- Diltiazem: A single dose of diltiazem increases the plasma concentrations of intravenously administered midazolam by approximately 25% and the terminal half-life by approximately 43%.

Additional information for orally administered midazolam

- Verapamil and diltiazem multiply the plasma concentrations of orally administered midazolam 3-fold and 4-fold, respectively. They increase the terminal half-life of midazolam by 41% and 49%, respectively.

Miscellaneous drugs/herbal medicines

- Atorvastatin multiplied the plasma concentrations of intravenously administered midazolam approximately 1.4-fold versus the control group.

Additional information for orally administered midazolam

- Fluvoxamine caused a slight increase in the plasma concentrations of orally administered midazolam (28%) and doubled its terminal half-life.

- Nefazodone multiplied the plasma concentrations of orally administered midazolam 4.6-fold and its terminal half-life 1.6-fold.

- Aprepitant dose-dependently increased the concentrations of orally administered midazolam (3.3-fold after a dose of 80 mg/day) this was associated with an approximate doubling of the terminal half-life.

- Chlorzoxazone lowered the ratio between the CYP3A-generated metabolite, α-hydroxymidazolam, and midazolam, indicating that it has an inhibitory effect on CYP3A.

- Bicalutamide had only a weak impact on orally administered midazolam (27% increase in plasma concentrations).

- *Curcuma* rhizome extract lowered the ratio between the CYP3A-generated metabolite, α-hydroxymidazolam, and midazolam, by approximately 40%, indicating that it has an inhibitory effect on CYP3A.

Drugs that induce CYP3A

- Rifampicin 600 mg/day for 7 days reduced the concentrations of intravenously administered midazolam by approximately 60%. It decreased the terminal half-life by 50%–60%.

Additional information for orally administered midazolam

- Carbamazepine/phenytoin: Repeated doses of carbamazepine or phenytoin reduced the plasma concentrations of orally administered midazolam by up to 90%; at the same time they shortened its terminal half-life by approximately 60%.

- Efavirenz: Five-fold multiplication of the ratio between the CYP3A-generated metabolite, α-hydroxymidazolam, and midazolam, confirmed this drug's CYP3A-inducing activity.

Herbal medicines and food

- *Echinacea purpurea* root extract reduced the plasma concentrations of intravenously administered midazolam by 20% and its half-life by approximately 42%.

- St John's wort reduced the plasma concentrations of midazolam by 20%–40%; it also shortened its terminal half-life by 15%–17%.

Acute displacement from plasma protein binding sites

- Valproic acid: One publication has discussed the displacement of midazolam from its plasma protein binding sites by valproic acid as a possible mechanism of drug interaction. However, for methodological reasons the clinical significance of this study has been considered very limited. Given that the therapeutic plasma concentration of valproic acid is high, however, displacement of midazolam from its plasma protein binding sites by the administration of acute doses cannot be excluded, resulting in a more marked clinical effect of midazolam.

Pharmacodynamic drug interactions

Coadministration of midazolam with other sedatives/hypnotics (including alcohol) is likely to have an enhanced sedative or sleep-inducing effect. Examples of such substances include: opiates/opioids (used as analgesics, antitussives or replacement treatments), neuroleptics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate, sedative antidepressants, antihistamines and

centrally-acting antihypertensives. Midazolam decreases the minimum alveolar concentration of inhalational anesthetics.

A more marked effect on sedation, respiration and hemodynamics may occur when coadministering midazolam with centrally-acting antidepressants, including alcohol. Appropriate monitoring of vital functions should be performed for this reason. Alcohol must not be used in any form after midazolam administration (see *Overdose*).

It has been shown that spinal anesthesia may enhance the sedative effect of intravenously administered midazolam. In such cases the dose of midazolam can be reduced. Intramuscular administration of lidocaine and bupivacaine also reduces the dose of intravenously administered midazolam required for sedation.

Drugs that enhance attention and memory, such as physostigmine, an acetylcholinesterase (AchE) inhibitor, suppress the sleep-inducing effect of midazolam. Similarly, 250 mg caffeine also partially inhibits the sedative effect of midazolam.

PREGNANCY AND LACTATION

Pregnancy

There is clear evidence of risk to the human fetus from benzodiazepine administration during pregnancy.

Dormicum must therefore not be used during pregnancy, except if absolutely necessary.

Caution is mandatory when administering benzodiazepines in late pregnancy and during labour, given that irregularities in the heart rate and hypotension may occur in the fetus, while a reduced desire to suck, respiratory depression, reduced activity, floppy infant syndrome, withdrawal symptoms and hypothermia may occur in the neonate.

Lactation

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Sedation, amnesia, concentration difficulties and muscle dysfunction impair the ability to drive and use machines. Before receiving Dormicum, patients should be warned not to drive or use machines until the effect of the drug has fully worn off, but in no case less than 12 hours after the last injection. The physician should decide when the patient may resume these activities.

UNDESIRABLE EFFECTS

The following undesirable effects have been observed in very rare cases after midazolam injection.

Immune system disorders

General hypersensitivity reactions (skin reactions, cardiovascular reactions, bronchospasm), anaphylactic shock.

Psychiatric disorders

Mental confusion, hallucinations, nervousness, euphoria, decreased attention, fatigue.

Paradoxical reactions such as agitation, involuntary movements (such as tonic/clonic movements and muscle tremor), hyperactivity, hostility, rage reactions, aggressiveness, paroxysmal excitement and assault, have been reported, in particular among children and the elderly.

Dependence

Even at therapeutic doses, use of Dormicum may lead to physical dependence. After prolonged intravenous administration, withdrawal symptoms, including withdrawal seizures, may occur after discontinuing treatment, in particular if discontinuation is abrupt.

Nervous system disorders

Prolonged sedation, decreased attention, headache, dizziness, ataxia, postoperative sedation, and anterograde amnesia, the duration of which is directly related to the administered dose. Anterograde amnesia may still persist after the end of the procedure; and prolonged amnesia has been reported in isolated cases.

Seizures have been reported in preterm infants and neonates.

Cardiac disorders

Cardiac arrest, bradycardia.

Severe cardiorespiratory adverse events have occurred in rare cases. These have included: cardiac arrest, hypotension, bradycardia and vasodilatory effects. The probability of life-threatening events is increased in adults over 60 years of age, in patients with pre-existing respiratory disease and in those with heart failure, above all when injection is too rapid or when a high dose is administered (see *Special warnings and precautions for use*).

Respiratory disorders

Severe cardiorespiratory adverse events have occurred in rare cases. These have included: respiratory depression, apnea, respiratory arrest, dyspnea and laryngospasm. Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory or cardiac insufficiency, above all when injection is too rapid or when a high dose is administered (see *Special warnings and precautions for use*). Hiccup.

Gastrointestinal disorders

Nausea, vomiting, constipation, dry mouth.

Skin disorders

Rash, urticaria, pruritus.

Injection site reactions

Erythema and pain at the injection site, thrombophlebitis, thrombosis.

Injury, poisoning and procedural complications

An increased risk of falls and fractures has been recorded in elderly benzodiazepine users.

OVERDOSE

Symptoms

Benzodiazepines generally cause confusion, ataxia, dysarthria and nystagmus. Dormicum overdose is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnea, hypotension, cardiorespiratory depression and, in rare cases, to coma. If coma occurs, it generally lasts a few hours but it may be prolonged and cyclical in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines potentiate the effect of CNS 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 appropriate methods, such as treatment within 1–2 hours with activated charcoal. If activated charcoal is used, the airway must be protected in drowsy patients. Gastric lavage should be considered in the event of mixed intoxication, but not as a routine measure.

The use of Anexate® (active substance flumazenil), a benzodiazepine antagonist, should be considered if central nervous system depression is severe. It should only be administered under closely monitored conditions. Since it has a short half-life (about 1 hour), patients receiving flumazenil must be monitored when its effect wears off. Flumazenil is to be used with extreme caution in conjunction with drugs that reduce the seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for Anexate® (flumazenil) for further information on the correct use of this drug.

PHARMACOLOGICAL PROPERTIES

ATC code: N05CD08.

Mechanism of action / Pharmacodynamics

Midazolam, the active substance in Dormicum, is an imidazobenzodiazepine. The free base is lipophilic and weakly water-soluble.

Thanks to the basic nitrogen in position 2 of the imidazobenzodiazepine ring system, the active substance in Dormicum is able to form water-soluble salts with acids that produce a stable injectable solution.

The pharmacological characteristics of Dormicum are rapid onset of effect and, thanks to rapid metabolic transformation, short duration of effect. The low toxicity of Dormicum confers a wide therapeutic safety margin.

Dormicum has a very rapid sedative and sleep-inducing effect. It also has an anxiolytic, anticonvulsant and muscle-relaxant effect.

Short-lasting anterograde amnesia (patients do not remember events that occur during the phase of maximum drug activity) follows intramuscular or intravenous administration.

Clinical efficacy

Clinical studies conducted in patients confirm the indications for intravenous and rectal Dormicum administration mentioned in *Indications and uses*.

PHARMACOKINETICS

Absorption

Absorption after intramuscular injection

Midazolam absorption from muscle tissue is rapid and complete. Peak plasma concentrations are reached within 30 minutes. Absolute bioavailability exceeds 90%.

Absorption after rectal administration

Midazolam absorption after rectal administration is rapid. Peak plasma concentrations are reached within approximately 30 minutes. Absolute bioavailability is approximately 50%.

Distribution

When Dormicum is administered intravenously, the plasma concentration-time curve shows one or two distinct phases of distribution. The volume of distribution at steady state is 0.7–1.2 l/kg. Midazolam is 96%–98% bound to plasma protein. Protein binding is due mainly to albumin. Midazolam passes slowly but in insignificant amounts into cerebrospinal fluid.

In humans, midazolam has been shown to cross the placental barrier slowly and to enter the fetal circulation. Half to one hour after oral dosing with 15 mg, the ratio between the fetal serum concentration (cord blood) and maternal serum concentration was 0.6–1.0. The elimination half-life of midazolam and its main metabolites in neonates is approximately 6.3 hours. In humans, small quantities of midazolam have also been demonstrated in breast milk.

Metabolism

Midazolam is almost entirely eliminated by biotransformation. Less than 1% of the dose is recovered in urine as unchanged drug. Midazolam is hydroxylated by the cytochrome P450 3A4 isoenzyme. The major urinary and plasma metabolite is α-hydroxymidazolam. Plasma concentrations of α-hydroxymidazolam are 12% those of the parent compound. The fraction of the dose extracted by the liver has been estimated to be 30%–60%. The elimination half-life of the metabolite is less than 1 hour; α-hydroxymidazolam is pharmacologically active, but contributes minimally (approximately 10%) to the effect of intravenously administered midazolam. There is no evidence of genetic polymorphism in oxidative midazolam metabolism (see *Interaction with other medicinal products and other forms of interaction*).

Elimination

In healthy volunteers, the elimination half-life is 1.5–3.5 hours. Plasma clearance is in the range 300–500 ml/min; 60%–80% of the dose is eliminated in the urine as the α-hydroxymidazolam glucuronide conjugate. Less than 1% of the dose is recovered in urine as unchanged drug. The elimination half-life of the metabolite is under 1 hour. When midazolam is given by intravenous infusion, its elimination kinetics do not differ from those observed following bolus injection.

Pharmacokinetics in special patient groups

Elderly patients

In persons over 60 years of age, the elimination half-life may be quadrupled.

Children

In children, the rate of midazolam absorption after rectal administration is similar to that in adults, but bioavailability is lower (5%–18%). However, the elimination half-life (t½) after intravenous and rectal administration in children aged 3–10 years is shorter than in adults (1.0–1.5 h). The difference is consistent with increased metabolic clearance in children.

Neonates

In preterm infants and neonates, the average elimination half-life is 6–12 h, probably due to liver immaturity; clearance is reduced (see *Special warnings and precautions for use*).

Overweight patients

Mean half-life is longer in overweight than in normal-weight patients (8.4 vs 2.7 h). This is due to an increase of approximately 50% in the volume of distribution corrected for total body weight. Clearance does not differ significantly in overweight compared to normal-weight patients.

Patients with hepatic impairment

In cirrhotic patients, the elimination half-life may be longer and clearance lower than in healthy subjects (see *Special warnings and precautions for use*).

Patients with renal impairment

In patients with chronic renal failure, the elimination half-life is similar to that in healthy subjects. It has, however, been shown that α-hydroxymidazolam accumulates and could enhance the clinical effect of midazolam, which could result in prolonged sedation (see *Posology and method of administration*, *Special dosage instructions*, and *Special warnings and precautions for use*).

Critically ill patients

The elimination half-life of midazolam is prolonged in critically ill patients.

Patients with heart failure

In patients with heart failure, the elimination half-life is longer than in healthy subjects (see *Special warnings and precautions for use*).

PRECLINICAL SAFETY DATA

Mutagenic and carcinogenic potential

Liver and thyroid tumours were observed in long-term studies in mice and rats. The consensus view is that these data cannot be extrapolated to humans.

The results of *in-vitro* and *in-vivo* genotoxicity studies show that mutagenic, clastogenic and aneugenic effects are unlikely with the use of midazolam.

Reproductive toxicology

Like all benzodiazepines, midazolam crosses the placental barrier.

Teratogenicity

Studies of midazolam in rats and mice revealed no evidence of teratogenicity.

However, signs of behavioural disturbance were observed in the offspring of females exposed to benzodiazepines.

PHARMACEUTICAL PARTICULARS

Incompatibilities

Midazolam precipitates in sodium bicarbonate.

This medicinal product must not be mixed with other medicinal products except those mentioned under *Special precautions for preparation and handling*.

Shelf-life

This medicinal product must not be used after the expiry date (EXP) shown on the pack.

Infusion solutions (see *Special precautions for preparation and handling*) remain physically and chemically stable for 24 hours at room temperature (or for 3 days at 5°C).

Special precautions for storage

Store at 15–30°C in the original pack protected from light.

Special precautions for preparation and handling

Compatibility with infusion solutions: Dormicum solution can be diluted in 0.9% sodium chloride, 5% and 10% glucose, 5% levulose, Ringer's solution and Hartmann's solution in a 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 for 3 days at 5°C).

Dormicum solution must not be diluted in glucose solution with 6% macrodex nor mixed with alkaline solutions for injection.

Dormicum ampoules are for single use only. Discard all unused residual product.

Inspect the solution before use. Only use clear solutions devoid of particulate matter.

Rectal administration

For rectal administration of the ampoule solution, a plastic applicator (rectal applicator) is fitted onto the syringe tip. If the administration volume is too low, water can be added to a total volume of 10 ml.

PRESENTATION

1 ml ampoules containing 5 mg	10
3 ml ampoules containing 15 mg	5
5 ml ampoules containing 5 mg	10
10 ml ampoules containing 50 mg	5
Rectal applicators	50

Medicine: keep out of the reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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