Induction and maintenance of anesthesia. As an induction agent in inhalation anesthesia or a sedative component in combined anesthesia, including total intravenous anesthesia (i.v. injection, i.v. infusion).

Ataradexia in combination with ketamine in children (i.m. administration).

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

Dosage and administration

Standard dosage
Midazolam is a potent sedative agent which requires slow administration with careful titration of dose. The dosage should be individualized and titrated to the desired state of sedation according to the clinical need, physical status, age, and concomitant medication.

In adults over 60 years of age, debilitated or chronically ill patients the dose should be determined with caution, the special factors relating to each patient being taken into consideration.

a) Intravenous conscious sedation

For basal (conscious) sedation prior to diagnostic or surgical intervention, Dormicium is administered i.v. The dose must be individualized and titrated and should not be administered by rapid injection or as a bolus dose. The rate of injection 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). Necessary, subsequent doses may be administered according to the individual need.

The intravenous injection of Dormicium should be given slowly at a rate of approximately 1 mg in 30 seconds. The drug takes effect in about 2 minutes after the injection has been given.

In adults below the age of 60 the initial dose is 2.5 mg given - 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 mg is usually not necessary.

In adults over 60 years of age, debilitated or chronically ill patients the initial dose must be reduced to 1-1.5 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 Dormicium should be titrated very steadily and carefully.

A total dose greater than 3.5 mg is usually not necessary.

b) Anesthesia

Pre-medication: Pre-medication with Dormicium given shortly before a procedure does produce sedation (induction of sleepiness or drowsiness and relief of apprehension) and preoperative impairment of memory.

Dormicium can also be administered in combination with anticholinergics.

The pre-medication is usually administered 20-60 minutes before induction of anesthesia.

Immunosuppressive induction: In adults below the age of 60 the dose of Dormicium ranges from 0.07-0.1 mg/kg according to the general condition of the patient.

The usual dose is 5 mg.

In adults over 60 years of age, debilitated and chronically ill, the dose range 3-5 mg.

The usual dose is 2.3-5 mg. In patients over 70 years i.m. Dormicum should be administered cautiously, under continuous observation, because excessive drowsiness may occur.

Children: In children between ages of 1 and 15 proportionally higher doses are required than in adults in relation to body weight. The dose range from 0.08-0.2 mg/kg bodyweight has been shown to be effective and safe.

Dormicium should be administered deep into a large muscle mass 30-60 minutes prior to the induction of anesthesia.

Rectal administration in children: The total dose of Dormicium ranges from 0.1 to 0.5 mg/kg. Dormicium ampoules should be used only when resuscitation is required and should be administered slowly over 20-30 minutes before induction of anaesthesia.

Rectal administration of the ampoule solution is performed by means of a plastic applicator fixed on the end of the syringe.

If the volume of the ampoule is too small, water may be added up to a total volume of 10 ml.

Induction: If Dormicium is used for induction of anesthesia 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 Dormicium is used before other i.v. agents for induction of anesthesia, the initial dose should be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents.

The desired level of anesthesia is reached by stepwise titration.

The intravenous induction dose of Dormicium should be given slowly in increments of approximately 0.03 mg/kg.

The increment of not more than 5 mg should be injected over 20 - 30 seconds allowing 2 minutes between successive increments.

In pre-medicated adults below the age of 60 the dose can range from 0.15-0.2 mg/kg but a total dose greater than 15 mg is usually not necessary. 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 anesthetics. 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.

In adults over 60 years of age, debilitated and chronically ill patients lower doses will be required.

Dormicium is not recommended for the induction of anesthesia in children, as experience is limited.

Maintenance: The maintenance of the desired level of anesthesia can be achieved by either further intermittent doses or continuous infusion of intravenous Dormicium typically in combination with analgesics.

The maintenance dose usually ranges from 0.03-0.1 mg/kg/hr when used in combination with narcotics or ketamine.

In adults over 60 years of age, debilitated or chronically ill patients lower maintenance doses will be required.

In children receiving ketamine for anesthesia (ataradexia), an initial intravenous dose of Dormicium of 0.15 - 0.20 mg/kg is recommended.

A sufficiently deep level of sleep is generally achieved after 2-3 minutes.

Intravenous sedation in the intensive care unit

The desired level of sedation is reached by stepwise titration of Dormicium followed by either continuous infusion or intermittent boluses.

The intravenous loading dose 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.

The intravenous loading dose can range from 0.03-0.3 mg/kg but a total dose greater than 15 mg is usually not necessary.

In hypovolemic, vasocostricted or hypothermic patients the loading dose should be decreased.

The maintenance dose can range from 0.03-0.2 mg/kg/hr.

The level of sedation should be assessed regularly if permitted by patient's condition.

In hypovolemic, vasocostricted or hypothermic patients the maintenance dose should be reduced, at times to as low as 25% of the usual dose.

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

**Special dosage instructions**

Confusion

Dormicium ampoule solution should be used as a 0.9 %, dextrose 5 %, 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 stable for 24 hours at room temperature, or 3 days at 5 °C (see also Special remarks).

The Dormicum Ampoule solution should not be diluted with Macrobid 6 % in Dextrose or mixed with alkaline injections.

Patients with renal impairment

In patients with severe renal impairment, Dormicium may be accompanied by more pronounced and prolonged sedation possibly including clinically relevant respiratory and cardiovascular depression. Dormicium should therefore be dosed carefully in the patient population described for the desired effect.

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.

**Contraindications**

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

**Precautions**

Dormicum ampoules should be used only when resuscitation facilities are available. Dormicum is not to be used for premedication recommended for the primary treatment of psychiatric illness.

Special caution should be exercised when administering Dormicum parenterally to patients representing a higher risk group:

- adults over 60 years of age.
- patients with a history of drug or alcohol abuse.
- debilitated or chronically ill patients
- patients with obstructive pulmonary disease.
- patients with chronic renal failure.
- patients with impaired hepatic function (benzodiazepines may precipitate or exacerbate end-stage liver disease in patients with severe hepatic impairments)
- patients with congestive heart failure.
- patients with minimal neurological instability.

These higher risk patients require lower doses (see Dosage and administration) and should be continuously monitored for early signs of alterations of vital functions.

**Concomitant use of alcohol or 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 cardiovascular depression (see Drug interactions).

**Medical history of alcohol or drug abuse**

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

**3**
The following undesirable effects have been reported to occur when using Dormicum:

**Immune System Disorders:** generalized hypersensitivity reactions (skin reactions, cardiovascular reactions, bronchospasm), anaphylaxis, angioedema, urticaria.

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

**Paradoxical reactions:** Paradoxic reactions such as restlessness, agitation, irritability, hallucinations, and paranoid thoughts have occurred. Paradoxical effects, especially for paroxysmal excitement and assault, have been reported, particularly among children and the elderly.

**Sedation:** Use of Dormicum - even in therapeutic doses - may lead to the development of physical dependence. After prolonged i.v. administration, the potential to incite discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions. Dormicum has been used as sedative hypnotics, drugs for anxiety, sleep, in situations such as before and during surgical and diagnostic procedures, and as an alternative to thiopental sodium for the induction of general anesthesia in adults. Since the onset of action of Dormicum is greater after discontinuation of treatment, it is recommended that the dose is decreased gradually. In severe cases, the following symptoms may occur: drowsiness, numbness, and tingling of the extremities, hypersensitivity to light, noise and physical contact.

**Anamnese:** Antidepressive and therapeutic doses with the risk increasing at higher dosages (frequently this effect is very desirable in situations such as before and during surgical and diagnostic procedures), the duration of which is directly related to the administered dose. Prolonged anamnese can present problems in outpatients, who are scheduled for discharge following intervention. After receiving Dormicum parenterally, patients should be discharged only hours after leaving hospital or consulting room only if accompanied by an attendant.

**Paradoxical reactions:** Paradoxical reactions such as restlessness, agitation, irritability, hallucinations, paranoid thoughts have occurred. Paradoxical effects, especially for paroxysmal excitement and assault, have been reported to occur with Dormicum. The highest incidence of susceptibility to such reactions has been observed in patients with pre-existing anxiety or depression. Should this be discontinued, the effect of the drug should be considered.

**Cardiac Disorders:** Severe cardiorespiratory adverse events have occurred on rare occasions. These have included cardiac arrest, hypotension, bradycardia, vasodilatory effects, slight increase in heart rate. However, it is more likely to occur in children over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is too rapid or when a high dosage is administered (see Precautions).

**Contraindications:** Dormicum and other benzodiazepines should be avoided during breastfeeding mothers. Use of Dormicum during pregnancy will be accompanied by withdrawal symptoms. The risk has been increased gradually. After prolonged i.v. administration, the potential to incite discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions. Dormicum has been used as sedative hypnotics, drugs for anxiety, sleep, in situations such as before and during surgical and diagnostic procedures, and as an alternative to thiopental sodium for the induction of general anesthesia in adults. Since the onset of action of Dormicum is greater after discontinuation of treatment, it is recommended that the dose is decreased gradually. In severe cases, the following symptoms may occur: drowsiness, numbness, and tingling of the extremities, hypersensitivity to light, noise and physical contact.

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**Dormicum**

**Indication**

Dormicum is an antagonist of the benzodiazepine receptor, which is responsible for the actions of benzodiazepines. Dormicum is prescribed for different indications such as treatment of anxiety, sedation, and preoperative anaesthesia.

**Dosage & Administration**

- **Oral Administration:** Dormicum is available in various strengths and dosages. According to the specific protocol for its use, the dose may vary. The maximum recommended dose is 10 mg orally.
- **Intravenous Administration:** Dormicum is also available for intravenous injection. The recommended dose is 2 mg over 1-2 minutes for inducing sedation.
- **Transdermal Administration:** Dormicum can be administered transdermally as an extended-release patch.

**Contraindications**

- Dormicum should not be used in patients with a history of drug or alcohol addiction, or in patients with a history of seizures.
- It is contraindicated in patients with a history of benzodiazepine hypersensitivity.

**Precautions**

- Dormicum should be used with caution in patients with hepatic or renal impairment.
- It should be used with extreme caution in patients with a history of alcohol or drug dependence.

**Adverse Effects**

- The most common adverse effects of Dormicum include sedation, dizziness, and ataxia.
- More serious adverse effects may include respiratory depression, hypotension, and bradycardia.

**Overdosage**

- Overdosage may result in respiratory depression, hypotension, and cardiovascular collapse.
- In case of an overdose, supportive care should be provided along with specific therapy such as flumazenil.

**Pharmacodynamics**

- Dormicum acts by facilitating the binding of GABA at the GABAA receptor complex, enhancing the inhibitory effect on the neuronal activity.
- The effect is mediated by the increase in the concentration of the GABA receptor-activated chloride conductance.

**Pharmacokinetics**

- Dormicum is rapidly absorbed after oral administration and distributed throughout the body, with high concentrations in the brain and liver.
- It is metabolized primarily in the liver and excreted primarily in the urine.
- The elimination half-life of Dormicum is approximately 2-3 hours.

**Interactions**

- Dormicum can interact with other drugs that affect the central nervous system, such as opioids, alcohol, and other sedatives.
- It can also interact with drugs that affect the hepatic cytochrome P450 enzymes, such as rifampicin and St John’s wort.

**References**

- The information provided is based on the pharmacological properties and usage guidelines of Dormicum. Further details can be obtained from the prescribing information or professional sources.

**Note:**

- The information provided is intended for educational purposes only and should not replace professional medical advice. Always consult a healthcare professional for medical advice.

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**Additional information from oral midazolam**

- *Carbamazepine / phenytoin:* Repeat dosages of carbamazepine or phenytoin may result in decreased plasma concentrations of oral midazolam by up to 90% and a shortening of the terminal half-life by about 60%.
- *Valproic acid:* Increased plasma concentrations of free midazolam due to displacement from plasma protein binding sites by valproic acid result in a profound and long-lasting decrease of oral midazolam (28%) while the terminal half-life is decreased by about 50-60%.
- *Rifampicin,* a strong inducer of the cytochrome P450 3A4/5 isoenzyme, decreased the AUC of oral midazolam (28%) while the terminal half-life was increased by approximately 1.5-fold.
- *Echinacea purpurea root extract:* decreased plasma concentrations of oral midazolam by 23% and increased terminal half-life by about 60%.

**Overdosage**

- 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.

- CNS depression is severe consider the use of flumazenil (Anexate®), a benzodiazepine antagonistic. It should only be administered under closely monitored conditions. It has a short half-life (about 1 hour), therefore if the patient remains comatose for longer than 3 hours the clinical significance of these non-clinical findings is yet to be determined. However, based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

**Special remarks**

- Incompatibilities: Do not dilute Dormicum ampoule solutions with 6% Dextran 70 in dextrose.
- Do not mix Dormicum ampoule solutions in alkaline injections.

**Storage**

- Dormicum ampoules should not be frozen because Dormicum precipitates in sodium bicarbonate.

**Current at Apr 2019**

F. Hoffmann-La Roche Ltd
Basel, Switzerland