Composition

Active ingredient: midazolam

Ampoules 1 ml (5 mg), 3 ml (15 mg), 5 ml (5 mg) and 10 ml (50 mg) for I.V., I.M. and rectal administration (free of organic solvents, ready for injection).

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

Properties

Midazolam, the active ingredient of Dormicum, is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water. The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables the active ingredient of Dormicum to form water soluble salts with acids. These produce a stable injection solution. The pharmacological action of Dormicum is characterized by rapid onset and, because of rapid metabolic transformation, short duration. Because of its low toxicity, Dormicum has a wide therapeutic range. Dormicum has a very rapid sedative and sleep-inducing action of pronounced intensity. It also exerts an anxiolytic, an anticonvulsant and a muscle-relaxant effect. After intramuscular or intravenous administration anterograde amnesia of short duration occurs (the patient does not recall events that occurred during the peak of activity of the compound).

Pharmacokinetics

Absorption after Intramuscular Injection

Absorption of midazolam from the muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. Bioavailability is over 90%.

Absorption after Rectal Administration

Midazolam is absorbed quickly. After rectal administration, the area under the plasma concentration-time curve in children is comparable to that of adults. Bioavailability is about 50%.

Distribution

When Dormicum is injected intravenously, the plasma concentration-time curve shows two distinct phases of distribution. The volume of distribution calculated under steady-state conditions is 50-601. Studies show a protein binding of 96-98%.

Metabolism

Midazolam is completely and rapidly metabolized in the body. The fraction extracted by the liver is 40-50%. The primary metabolite is alpha-hydroxy-midazolam, which can be found in the plasma. Many medicaments have been found to inhibit the production of this metabolite in vitro (see Drug Interactions).

Elimination

In healthy volunteers, the elimination half-life is between 1.5 and 3.5 hours. Plasma clearance is in the range of 300-500 ml/min. When midazolam is given by I.V. infusion, its elimination kinetics do not differ from those following bolus injection. The elimination half-life of the main metabolite, alpha-hydroxy-midazolam, is shorter than that of the parent substance. Immediately after its formation, it is conjugated with glucuronic acid (inactivation), and 50-70% of the dose is then eliminated by the kidneys.

Pharmacokinetics in Special Situations

In elderly patients the elimination half-life may be prolonged up to three times and in some intensive-care patients requiring midazolam by I.V. infusion for long-term sedation, up to six times. In these patients infusion at an unchanged rate results in higher plasma levels at steady state. Consequently, the infusion rate should be adjusted according to the patient’s clinical response. The elimination half-life may also be prolonged in patients with congestive heart failure, with chronic renal failure and with reduced hepatic perfusion. In animals and humans, midazolam has been shown to cross the placenta and to enter fetal circulation. There are indications
that midazolam is excreted in human milk. In children (3-10 years) the elimination half-life is between 1 and 1.5 hours. In neonates the elimination half-life is prolonged with a mean of 6 hours (3-12 hours).

**Indications**

Premedication before induction of anesthesia (I.M. or, especially in children, rectal administration). Basal sedation before diagnostic or surgical interventions carried out under local anesthesia (I.V. administration). Long-term sedation in intensive care units (I.V. administration as bolus injection or continuous infusion). Induction and maintenance of anesthesia. As an induction agent in inhalation anesthesia or a sleep-inducing component in combined anesthesia, including total intravenous anesthesia (I.V. injection, I.V. infusion). Ataralgesia in combination with ketamine in children (I.M. administration).

**Contraindications**

Dormicum must not be given to patients who are hypersensitive to benzodiazepines.

**Side Effects**

Changes in arterial blood pressure, pulse rate and breathing are usually slight. As a rule, the systolic blood pressure falls by a maximum of 15%, while the pulse rate simultaneously shows a corresponding rise. Severe cardiorespiratory side effects have occurred on rare occasions. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest. Such life-threatening incidents are more likely to occur in elderly patients and those with preexisting respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered. Therefore, Dormicum ampoules should be used only when resuscitation facilities are available. In isolated cases, generalized hypersensitivity-including anaphylactoid reactions and skin reactions-have been reported. In rare cases paradoxical reactions such as agitation, hyperactivity and aggressivity have occurred; involuntary movements (including tonic/clonic convulsions and muscle tremor) have also been observed. Should such reactions occur, the response to each dose of Dormicum should be evaluated before proceeding. Anterograde amnesia of short duration may occur. After prolonged I.V. administration of Dormicum, abrupt discontinuation of the product may be accompanied by withdrawal symptoms. Therefore, a gradual reduction of Dormicum is recommended. After rectal administration, a slightly euphoric condition of short duration was observed in individual children. In isolated cases bouts of double vision lasting several minutes were reported. However, this had no effect on preparation for anesthesia.

**Precautions**

Special caution should be exercised when administering Dormicum parenterally to patients representing a higher risk group: elderly and debilitated patients, patients with obstructive pulmonary disease, with chronic renal failure or with congestive heart failure. These higher risk surgical patients require lower and individualized dosages and should be continuously monitored for early signs of alterations of vital functions. Patients with chronic renal failure, impaired hepatic function and congestive heart failure may eliminate midazolam more slowly. Convulsions have been reported in premature infants and neonates. As with other parenteral hypnotic agents, venous access must be maintained when Dormicum is administered intravenously (at least for the duration of the procedure in the case of basal sedation). Dormicum ampoules should be used only when resuscitation facilities are available. After receiving Dormicum parenterally, patients should not be discharged from hospital or consulting room for at least three hours and then only if accompanied by an attendant. They should be warned not to drive a vehicle or operate a machine for at least twelve hours. Particular care is needed when administering Dormicum to a patient with myasthenia gravis, owing to preexisting muscle weakness. (See Drug Interactions section concerning concurrent use of erythromycin or cimetidine).
Dependence
Benzodiazepines have the potential to induce dependence. The risk of dependence increases with long-term therapy and higher doses. Predisposed patients are also at increased risk. Abrupt discontinuation of the drug, in particular, can provoke withdrawal symptoms. In mild cases these are restricted to tremor, restlessness, sleep disturbances, anxiety, headache and poor concentration. In more serious cases, symptoms such as sweating, muscle cramps, abdominal cramps, impaired sensory perception and, rarely, delirium and convulsions may result. Depending on the drug’s duration of action, symptoms may appear a few hours to one week or more after cessation of therapy. In order to reduce the risk of dependence to a minimum, benzodiazepines should be prescribed only after careful evaluation of the indication, and therapy should be restricted to the shortest possible duration (for example, no more than 4 weeks for the treatment of sleep disturbances). The physician must periodically reevaluate the necessity for therapy. Long-term therapy is indicated only in certain patients, for example, those suffering from panic attacks; the risk/benefit ratio is uncertain. To prevent withdrawal symptoms, abrupt discontinuation should be avoided and the dosage gradually tapered off. Close medical supervision and patient support are required should withdrawal symptoms develop.

Pregnancy and Lactation
There is strong evidence that benzodiazepine use during pregnancy is associated with risks for the human fetus. Dormicum like other drugs should therefore not be used in the first three months of pregnancy unless considered absolutely necessary by the physician. Special care must be taken when benzodiazepines are used during labour and delivery, as high single doses may produce irregularities in the fetal heart rate and hypotonia as well as poor sucking, respiratory depression, withdrawal symptoms and hypothermia in the neonate. Midazolam may pass into breast milk and caution should be exercised with its use in nursing mothers.

Overdosage
The symptoms of Dormicum overdosage are mainly an intensification of the therapeutic effects (sedation, muscle weakness, profound sleep) or paradoxical excitation. In most cases only observation of vital functions is required. Extreme overdosage may lead to coma, areflexia, cardiorespiratory depression and apnea, requiring appropriate countermeasures (ventilation, cardiovascular support). The effects of overdoses can be very well controlled with the benzodiazepine antagonist Anexate (active ingredient: flumazenil).

Incompatibilities
Midazolam precipitates in sodium bicarbonate.

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

Drug Interactions
*In vitro* data show that the hydroxylation of midazolam is inhibited by numerous agents that specifically inhibit the cytochrome P-450 IIIA isoenzyme, resulting in a potentiation of midazolam’s effects. These findings have been clinically confirmed for erythromycin, diltiazem, verapamil, ketoconazole, itraconazole and cimetidine, but not for cyclosporin, nitrindipine or ranitidine (after parenteral administration). Dormicum enhances the central sedative effect of neuroleptics, tranquilizers, antidepressants, sleep-inducing agents, analgesics, antiepileptics and anesthetics. This potentiation can be of advantage therapeutically in certain cases. Special attention must be paid to the possibility of potentiation in patients at particular risk. In some cases the mutual potentiation of alcohol and Dormicum can produce unforeseeable reactions. (No alcoholic beverages should be allowed for at least twelve hours after parenteral administration.)

Dosage and Administration

**Standard Dosage**
In the case of elderly patients with organic cerebral changes or impaired cardiac and respiratory function, the dosage should be determined with caution,
the special factors relating to each patient being taken into consideration. Intravenous injections must be given slowly (approximately 2.5 mg in ten seconds for induction of anesthesia and 1 mg in 30 seconds for basal sedation). The drug takes effect about two minutes after the injection is started.

Premedication Before an Operation

Intramuscular Administration
In patients suffering from pain before an intervention: Administration alone or in combination with anticholinergics and possibly analgesics.

*Adults*: 0.07-0.1 mg/kg bodyweight I.M., according to age and general condition of the patient. Usual dose about 5 mg.

*Children*: proportionately higher doses are required than in adults in relation to bodyweight (0.15-0.20 mg/kg).

*Elderly and debilitated patients*: 0.025-0.05 mg/kg I.M.

The doses should be administered 30 min before induction of anesthesia.

Rectal Administration in Children
For Preoperative Sedation: Rectal administration of the ampoule solution by means of a plastic applicator fixed on the end of a syringe, 0.35-0.45 mg/kg 20-30 min before induction of general anesthesia. If the volume to be administered is too small, water may be added up to a total volume of 10 ml.

Basal Sedation and Sedation in Intensive Care Units (ICU)

Intravenous Basal Sedation
For basal sedation in diagnostic or surgical interventions carried out under local anesthesia: The initial dose is 2.5 mg 5-10 min before the beginning of the operation. Further doses of 1 mg may be given as necessary. A total dose greater than 5 mg is not usually necessary to reach the desired endpoint. In cases of severe illness, particularly if the patient is in poor general condition or of advanced age, the initial dose must be reduced to 1-1.5 mg. Total doses greater than 3.5 mg are not usually necessary.

Intravenous Sedation in ICU
For sedation in ICU, the dosage should be individu-