

# Product Secondary Packaging

HIKMA MIDAZOLAM  
Midazolam

## ACTION

Midazolam is a derivative of the imidazobenzodiazepine group. Midazolam 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 doesn't recall events that occurred during the peak of activity of the compound). Because Midazolam is rapidly metabolised, it has a short duration of action. Midazolam has low toxicity and a wide therapeutic range.

## INDICATIONS

- Premedication before the induction of anesthesia (IM or especially in children, rectal administration).
- Basal sedation before diagnostic or surgical interventions carried out under local anesthesia, such as: Bronchoscopy, gastroscopy, cystoscopy, cardiac catheterization and oncology procedure (IV administration).
- Long term sedation in intensive care units (IV 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 (IV injection or IV infusion).
- Ataralgia in combination with ketamine in children (IM 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 10 seconds for induction of anesthesia and one 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, Midazolam can be administered alone or in combination with anticholinergics and possibly analgesics.

**Adults:** 0.07 - 0.1 mg/kg body weight IM, according to age and general condition of the patient. Usual dose is about 5 mg

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

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

The doses should be administered 30 minutes 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 minutes 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:

### 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 minutes before the beginning of the operation. Further doses of 1mg 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 1-1.5mg. Total doses greater than 3.5 mg are not usually necessary.

### Intravenous sedation in ICU:

For sedation in ICU, the dosage should be individualized and Midazolam titrated to the desired state of sedation according to the clinical need, physical status, age and concomitant medication.

**Loading dose:** 0.03-0.3 mg/kg. **Maintenance dose:** 0.03-0.2 mg/kg/hr. The dosage should be reduced or the loading dose should even be omitted in hypovolemic, vasoconstricted and hypothermic patients.

### Induction and maintenance of anesthesia

#### Intravenous injection

**Induction:** The dose is 10-15 mg IV. A sufficiently deep level of sleep is generally achieved after 2-3 minutes.

**Maintenance:** For maintenance of the desired level of unconsciousness, further small doses should be injected IV. The dose and the intervals between doses vary according to the individual patient's reaction. Alternatively, Midazolam can be administered by continuous infusion.

#### Intravenous continuous infusion:

For intravenous anesthesia combined with ketamine: 0.03-0.1 mg/kg/hr. **Narcotics:** 0.03-0.3 mg/kg/hr. **High risk surgical patients, elderly and debilitated patients require lower dosages.**

**Intramuscular administration in children:** A combination of sleep-inducing and amnesia-inducing Midazolam with ketamine (ataralgia) is recommended. Midazolam IM: 0.15-0.2 mg/kg in combination with ketamine IM. A sufficiently deep level of sleep is generally achieved after 2-3 minutes. When Midazolam is given with potent analgesics, the latter should be administered first so that the sedative effects of Midazolam can be safely titrated on top of any sedation caused by the analgesic.

### Special dosage instructions:

## WARNINGS

- Benzodiazepines have the potential to induce dependence. The risk of dependence increases with long-term therapy and higher doses. Abrupt discontinuation of the drug 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 and abdominal cramps, impaired sensory perception and, rarely, delirium and convulsions may occur. Depending on the drug's duration of action, symptoms may appear a few hours to one week or more after stopping therapy.
- In order to decrease 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.
- To prevent withdrawal symptoms, abrupt discontinuation should be avoided and the dosage gradually tapered off.
- Pregnancy and lactation: There is strong evidence that benzodiazepine use during pregnancy is associated with risks for the human fetus, therefore it should not be used in the first trimester unless absolutely necessary. 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, hypotonia, respiratory depression and withdrawal and hypothermia in the neonate. Midazolam may pass into breast milk and caution should be exercised with its use in nursing mothers.

## PRECAUTIONS

Special caution should be exercised when administering Midazolam parenterally to high risk patients: elderly and debilitated patients, patients with obstructive pulmonary disease, with chronic renal failure or with congestive heart failure. These high risk 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 Midazolam is administered intravenously (at least for the duration of the procedure in the case of basal sedation), and Midazolam ampoules should be used only when resuscitation facilities are available. Particular care is needed when administering Midazolam to a patient with myasthenia gravis, owing to preexisting muscle weakness.

## Interactions

The metabolism of Midazolam is inhibited by numerous agents that inhibit the cytochrome P-450 III A isoenzyme, resulting in a potentiation of Midazolam's effects. This has occurred when Midazolam was co-administered with erythromycin, diltiazem, verapamil, ketoconazole, itraconazole and cimetidine, but not with cyclosporin or ranitidine (after parenteral administration). Midazolam enhances the central sedative effect of neuroleptics, tranquilizers, antidepressants, sleep inducing agents, analgesics, anesthetics, antiepileptics and antihistamines. 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. Midazolam and alcohol mutually potentiate each other therefore no alcohol should be ingested for at least 12 hours after parenteral administration.

## 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 adverse events 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, Midazolam 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 Midazolam should be evaluated before proceeding.
- Anterograde amnesia of short duration may occur. After prolonged IV administration of Midazolam, abrupt discontinuation of the product may be accompanied by withdrawal symptoms. Therefore, a gradual reduction of Midazolam 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 of anesthesia.

## OVERDOSAGE

The symptoms of Midazolam 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 flumazenil.

## PRESENTATION