

DBL[®] MIDAZOLAM INJECTION BP

Midazolam hydrochloride 5mg/ml and 1mg/ml injections ***Sleep-inducing agent***

Composition

Active ingredient

midazolam hydrochloride injections 5 mg/mL and 1 mg/mL

Excipients

5mg sodium chloride per mL (5mg/mL);
9mg sodium chloride (1mg/mL);
sterile water for injections.

Appearance

Colourless ampoules and vials. Clear liquid, colourless, no odour.

Uses

Actions

Midazolam, the active ingredient of DBL[®] Midazolam Injection BP, 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 DBL[®] Midazolam Injection BP to form water-soluble salts with acids. These produce a stable and well tolerated injection solution.

The pharmacological action of DBL[®] Midazolam Injection BP is characterised by a rapid onset and, because of rapid metabolic transformation, a short duration. Because of its very low toxicity, DBL[®] Midazolam Injection BP has a wide therapeutic range.

DBL[®] Midazolam Injection BP 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 after i.m. injection 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. The bioavailability is about 50%.

Absorption after intranasal administration

Midazolam is absorbed quickly. Mean peak plasma concentrations are reached within 10.2 to 12.6 minutes. The bioavailability is between 55 and 57%.

Absorption after oral administration

Oral midazolam is absorbed rapidly from the gastrointestinal tract and undergoes extensive first-pass hepatic metabolism. Peak plasma concentrations are reached within 1 hour. Bioavailability is between 40 and 50%.

Distribution

When DBL[®] Midazolam Injection BP is injected intravenously, the plasma concentration-time curve shows two distinct phases of distribution. The volume of distribution calculated under steady-state conditions is 50-60 litres. Studies show a protein binding of 96-98%.

Metabolism

Midazolam is completely metabolised in the body. The primary metabolite is alpha-hydroxy-midazolam, which can be found in the plasma. The fraction extracted by the liver is 40-50%.

Elimination

In healthy volunteers, the elimination half-life is between 1½ and 3 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, (-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.

Kinetics in special clinical 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 hepatic dysfunction.

Studies have shown that ranitidine has no influence on the pharmacokinetics of midazolam given parenterally.

In animals and humans midazolam has been shown to cross the placenta and to enter foetal circulation. There are indications that midazolam is secreted in human milk.

Indications

Premedication before induction of anaesthesia (i.m. or, especially in children, rectal, intranasal or oral administration).

Conscious sedation before diagnostic or surgical interventions carried out under local anaesthesia (i.v. administration), or in children intranasal or oral administration.

Long-term sedation in intensive care units (i.v. administration as bolus injection or continuous infusion). Induction and maintenance of anaesthesia. As an induction agent in inhalation anaesthesia or a sleep-inducing component in combined anaesthesia, including total intravenous anaesthesia (i.v. injection, i.v. infusion).

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

Dosage and administration

For single patient use. Use once only and discard any residue.

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.

Initial and subsequent intravenous injections must be given slowly (approximately 2.5 mg in 10 seconds for induction of anaesthesia and 1mg in 30 seconds for conscious sedation). The medicine 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.

These doses should be administered about 30 minutes before induction of anaesthesia.

Adults

0.07-0.10 mg per kg bodyweight i.m. according to age and general condition of the patient. Usual dosage about 5mg.

Children

Proportionately higher doses are required than in adults in relation to bodyweight (0.15-0.20 mg per kg bodyweight i.m.).

Elderly and Debilitated Patients

0.025 - 0.05 mg/kg bodyweight i.m.

Rectal Administration**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 bodyweight 20-30 minutes before induction of general anaesthesia. If the volume to be administered is too small, water may be added up to a total volume of 10 ml.

Intranasal Administration**Children**

0.2 mg/kg, 10-15 minutes prior to anaesthesia.

Oral Administration**Children**

0.5 mg/kg, 15-30 minutes prior to anaesthesia.

Conscious sedation**Intravenous conscious sedation**

For conscious sedation in diagnostic or surgical interventions carried out under local anaesthesia.

Adults

The initial dose should not exceed 2.5 mg i.v. 5-10 minutes before the beginning of the operation. Further doses of 1mg may be given as necessary. A total dose greater than 5mg 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 3.5mg are not usually necessary.

Intranasal conscious sedation**Children**

0.2 mg/kg, 10-15 minutes before the intervention.

Oral conscious sedation**Children**

0.2 - 0.5 mg/kg, 15-30 minutes before the intervention.

Sedation in intensive care units**Intravenous sedation**

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

Adults

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 anaesthesia

Intravenous Injection

Adults

Induction

The dose is 10-15 mg i.v. in combination with analgesics. 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 i.v. The dose and the intervals between doses vary according to the individual patient's reaction. Alternatively, DBL[®] Midazolam Injection can be administered by continuous infusion.

Intravenous Continuous Infusion

Adults

For intravenous anaesthesia 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

Children

A combination of the sleep-inducing and amnesia-inducing DBL[®] Midazolam Injection BP with ketamine (ataralgesia) is recommended. DBL[®] Midazolam Injection BP i.m. (0.15-0.20 mg per kg bodyweight) in combination with 50-100 mg ketamine i.m. (4-8 mg per kg bodyweight). A sufficiently deep level of sleep is generally achieved after 2-3 minutes.

Rectal Administration

Children

See Premedication Before an Operation.

Special dosage instructions

When DBL[®] Midazolam Injection BP is given with potent analgesics, the latter should be administered first so that the sedative effects of DBL[®] Midazolam Injection BP can be safely titrated on top of any sedation caused by the analgesic.

Compatibility with infusion solutions. The DBL[®] Midazolam Injection BP ampoule solution can be diluted with sodium chloride 0.9%, dextrose 5% and 10%, levulose 5%, Ringer's solution and Hartmann's solution in a mixing ratio of 15 mg midazolam per 100-1,000 ml infusion solution. These solutions remain physically and chemically stable for 24 hours at room temperature (or three days at 5°C).

When administered orally, the bitter taste of DBL[®] Midazolam Injection BP injection may be masked by small quantities of apple juice, sweetened fruit syrup or powdered soft drink.

Contraindications

Myasthenia gravis. DBL[®] Midazolam Injection BP must not be given to patients who are hypersensitive to benzodiazepines.

Warnings and precautions

Apnoea may occur in 15% of patients following intravenous administration; CNS effects and local reactions may also occur. During intravenous administration of DBL[®] Midazolam Injection BP respiratory depression and cardio-respiratory arrest have occurred, sometimes resulting in death. Life threatening incidents are more likely to occur in elderly patients and those with pre-existing respiratory insufficiency, particularly when the injection is given too rapidly or when a high dosage is administered. Therefore intravenous DBL[®] Midazolam Injection BP should only be given by a skilled person and where adequate resuscitation facilities are available. Patients should be monitored for early signs of underventilation, apnoea or hypoxaemia.

Special caution should be exercised when administering DBL[®] Midazolam Injection BP 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.

DBL[®] Midazolam Injection BP ampoules should be used only when resuscitation facilities are available. After receiving DBL[®] Midazolam Injection BP parenterally, patients should not be discharged from hospital or consulting room for at least three hours, and then, if possible, only if accompanied by a responsible person. They should be warned not to drive a vehicle or operate a machine. The physician should decide when activities such as driving a vehicle or operating a machine may be resumed.

Use in the elderly

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

Carcinogenesis

Animal studies have shown a marked increase in the incidence of hepatic tumours in female mice and in thyroid follicular tumours in male rats following doses of midazolam 25 times the usual human dose. The pathogenesis of induction of these tumours is not known. These tumours were found after chronic administration, whereas human use will ordinarily be of single or several doses.

Mutagenesis

Midazolam did not have mutagenic activity in *Salmonella typhimurium* (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes, or in the micronucleus test in mice.

Pregnancy, nursing mothers

DBL[®] Midazolam Injection BP - like other medicines - should not be used in the first three months of pregnancy unless considered absolutely necessary by the physician. Midazolam may pass into breast milk and caution should be exercised with its use in nursing mothers.

Special care must be taken when benzodiazepines are used during labour and delivery, as high single doses may produce irregularities in the foetal heart rate and hypotonia, poor sucking and hypothermia in the neonate.

Dependence

Dependence may occur during benzodiazepine therapy. The risk is more pronounced in patients on long term use, on high dosage and particularly so in predisposed patients with a history of alcoholism, drug abuse, marked personality or other severe psychiatric disorders.

In order to minimize the risk of dependence, benzodiazepines should only be prescribed after careful consideration of the indication and should be taken for the shortest possible duration. The necessity of continuing treatment should be closely monitored. Prolonged duration of treatment is justified only after careful assessment of the benefit and the risk.

Withdrawal

The onset of withdrawal symptoms is variable, ranging from a few hours to a week or more.

In less severe cases, the symptomatology of withdrawal may remain restricted to tremor, restlessness, insomnia, anxiety, headache and inability to concentrate. However, withdrawal symptoms such as sweating, muscular and abdominal spasms, perceptual changes and, in rare cases, delirium and convulsions may occur.

At the occurrence of withdrawal symptoms, close medical control and support of the patient is necessary. Abrupt discontinuation should generally be avoided and a gradual tapering schedule followed.

Adverse effects

DBL[®] Midazolam Injection BP is well tolerated. 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, apnoea, respiratory arrest and/or cardiac arrest. (See Warnings & Precautions).

In isolated cases, generalized hypersensitivity - including anaphylactoid reactions and skin reactions - have been reported.

In rare cases paradoxical reactions such as agitation, hyperactivity and aggression 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 DBL[®] Midazolam Injection BP should be evaluated before proceeding.

Anterograde amnesia of short duration may occur. After prolonged i.v. administration of DBL[®] Midazolam Injection BP, abrupt discontinuation of the product may be accompanied by withdrawal symptoms.

Therefore, a gradual reduction of dose of DBL[®] Midazolam Injection BP 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 anaesthesia.

After intranasal administration transient irritation of the nasal mucosa may occur and crying may be induced.

Interactions

Special attention must be paid to the possibility of potentiation in patients at particular risk. Respiratory depression and hypoxaemia may occur following the concomitant administration of DBL[®] Midazolam Injection BP with opiate analgesics.

The simultaneous administration of cimetidine (but not ranitidine) has been reported to reduce clearance of midazolam.

Enhancement of the central depressive effect may occur when DBL[®] Midazolam Injection BP is used concomitantly with:

- Antipsychotics
- Hypnotics
- Anxiolytics
- Antidepressants
- Narcotic analgesics
- Antiepileptics
- Anaesthetics
- Sedative antihistamines

There is a potentially relevant interaction between midazolam and compounds which inhibit certain hepatic enzymes (particularly cytochrome P 450 III a). Data clearly indicate that these compounds influence the pharmacokinetics of midazolam **and may lead to prolonged sedation. At present this reaction is known to occur with cimetidine, erythromycin, diltiazem, verapamil, ketoconazole and itraconazole. Therefore patients receiving the above compounds or others which inhibit P 450 III A together with midazolam should be monitored carefully for the first few hours after administration of midazolam. (Studies have shown that ranitidine has no influence on the pharmacokinetics of parenterally given midazolam).**

In some patients, the mutual potentiation of alcohol and DBL[®] Midazolam Injection BP can produce unforeseeable reactions. (No alcoholic beverages should be allowed for at least twelve hours after parenteral administration).

Overdosage

The symptoms of DBL[®] Midazolam Injection BP overdose 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, cardio-respiratory depression and apnoea, requiring appropriate countermeasures (ventilation, cardiovascular support). The effects of overdoses can be very well controlled with the benzodiazepine antagonist is flumazenil. The usual dose is 0.2-0.5mg by slow i.v. injection. Initial dose is 0.2mg i.v. within 15 seconds and further increments of 0.1mg every 60 seconds may be required.

Pharmaceutical precautions

Stability

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

Medicine classification

Prescription Medicine.
Controlled Drug (C5)

Package quantities

Injection, 5mg/ml	5 x 10 mL ampoule
	5 x 3 mL ampoule
Injection, 1mg/ml	5 x 5 mL ampoule

Further information

Chemical Name

Midazolam: 8-chloro-6-(2-fluorophenyl) -1-methyl-4H-imidazo[1,5-a] [1,4]benzodiazepine.

Name and address

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