

pharmaniaga[®]

Pharmaniaga Midazolam 5mg/ml Injection



COMPOSITION

Each 1 ml ampoule contains Midazolam 5 mg.
Each 3 ml ampoule contains Midazolam 15 mg.

PRODUCT DESCRIPTION

A colourless to pale yellow solution.

The compatible infusion solutions for intravenous use are as follows:

- Sodium Chloride 0.9%
- Dextrose 5%
- Dextrose 10%
- Ringer's Solution
- Hartmann's Solution

The solution should be colourless to pale yellow when diluted.

Following dilution in the recommended diluents, chemical and physical in-use stability has been demonstrated for 24 hours at room temperature (<30°C) and at refrigerated condition (2°C to 8°C). However, from a microbiological point of view, the product should be used immediately.

PHARMACODYNAMICS

Midazolam, 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 midazolam injection to form water-soluble salts with acids.

The pharmacological action of midazolam is characterized by rapid onset and, because of rapid metabolic transformation, short duration. Because of its low toxicity, midazolam has a wide therapeutic range.

Midazolam injection has a very rapid sedative and sleep-inducing effect of pronounced intensity. It also exerts an anxiolytic, an anticonvulsant and a muscle-relaxant effect. After i.m. or i.v. 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 IM injection

Absorption of midazolam from the muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. The absolute bioavailability after IM injection is over 90%.

Absorption after rectal administration

After rectal administration midazolam is absorbed quickly. Maximum plasma concentration is reached in about 30 minutes. The absolute bioavailability is about 50%.

Distribution

When midazolam is injected IV, 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. 96-98 % of midazolam is bound to plasma proteins. The major fraction of plasma protein binding is due to albumin. There is a slow and insignificant passage of midazolam into the cerebrospinal fluid. In humans, midazolam has been shown to cross the placenta slowly and to enter foetal circulation. Small quantities of midazolam are found in human milk.

Biotransformation

Midazolam is almost entirely eliminated by biotransformation. The fraction of the dose extracted by the liver has been estimated to be 30-60%. Midazolam is hydroxylated by the cytochrome P4503A4 isozyme and the major urinary and plasma metabolite is alpha-hydroxymidazolam. Plasma concentrations of alpha-hydroxymidazolam are 12% of those of the parent compound. Alpha-hydroxymidazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous midazolam.

Elimination

In healthy volunteers, the elimination half-life of midazolam is between 1.5 -2.5 hours. Plasma clearance is in the range of 300-500 ml/min. Midazolam is excreted mainly by renal route (60-80% of the injected dose) and recovered as glucuronjugated alpha-hydroxymidazolam. Less than 1 % of the dose is recovered in urine as unchanged drug. The elimination half-life of alpha-hydroxy-midazolam is shorter than 1 hour. When midazolam is given by IV infusion, its elimination kinetics do not differ from those following bolus injection.

Pharmacokinetics in special populations

Elderly

In adults over 60 years of age, the elimination half-life may be prolonged up to four times.

Children

The rate of rectal absorption in children is similar to that in adults but the bioavailability is lower (5-18%). The elimination half-life after IV and rectal administration is shorter in children 3-10 years old (1-1.5 hours) as compared with that in adults. The difference is consistent with an increased metabolic clearance in children.

Neonates

In neonates the elimination half-life is on average 6-12 hours, probably due to liver immaturity and the clearance is reduced.

Obese

The mean half-life is greater in obese than in non-obese patients (5.9 vs 2.3 hours). This is due to an increase of approximately 50% in the volume of distribution corrected for total body weight. The clearance is not significantly different in obese and non-obese patients.

Patients with hepatic impairment

The elimination half-life in cirrhotic patients may be longer and the clearance smaller as compared to those in healthy volunteers.

Patients with renal impairment

The elimination half-life in patients with chronic renal failure is similar to that in healthy volunteers.

Critically ill patients

The elimination half-life of midazolam is prolonged up to six times in the critically ill.

Patients with cardiac insufficiency

The elimination half-life is longer in patients with congestive heart failure compared with that in healthy subjects.

INDICATION

Midazolam Injection is a short-acting sleep-inducing drug that is indicated as follows:

In adults:

- Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia.
- Anaesthesia
 - Premedication before induction of anaesthesia
 - Induction of anaesthesia
 - As a sedative component in combined anaesthesia
- Sedation in intensive care units

In paediatric:

- Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia.
- Anaesthesia
 - Premedication before induction of anaesthesia
 - Sedation in intensive care units

RECOMMENDED DOSAGE

Midazolam is a potent sedative agent that requires slow administration and individualisation of dosage.

The dose should be individualized and titration is strongly recommended to safely obtain the desired state of sedation according to the clinical need, physical status, age and concomitant medication.

In adults over 60 years of age, critically ill patients, high risk patients and paediatric patients, the dose should be determined with caution and risk factors related to each patient should be taken into account.

The drug takes effect in about 2 minutes after intravenous injection. Maximum effect is obtained in about 5 to 10 minutes.

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

Table 1 Standard dosage

Indication	Adults < 60 years	Adults ≥ 60 years /critically ill, high-risk patients	Paediatric s
Conscious sedation	<i>i.v</i> Initial dose: 2-2.5mg Titration dose: 1mg Total dose: 3.5-7.5mg	<i>i.v</i> Initial dose: 0.5-1mg Titration dose: 0.5-1mg Total dose: <3.5mg	<i>i.v</i> months-5 6 years: Initial dose: 0.05-0.1mg/kg Total dose: <6mg 6-12 years: Initial dose: 0.025-0.05mg/kg Total dose: <10mg 13-16 years: As adult Rectal >6 months: 0.3-0.5mg/kg i.m. 1-15 years: 0.05-0.15 mg/kg

Anaesthesia premedicati on	<i>i.v</i> 1-2 mg repeated <i>i.m</i> 0.07-0.1 mg/kg	<i>i.v</i> Initial dose: 0.5 mg Slow upitration as needed <i>i.m</i> 0.025-0.05 mg/kg	Rectal >6 months: 0.3-0.5mg/kg i.m 1-15 years: 0.08-0.2 mg/kg
Anaesthesia induction	<i>i.v</i> 0.2mg/kg (0.2-0.35 mg/kg without premedicati n)	<i>i.v</i> 0.05-0.15 mg/kg (0.15-0.2 mg/kg without premedicati n)	Not indicated in paediatrics
Sedative component in combined anaesthesia	<i>i.v</i> Intermittent doses of 0.03-0.1 mg/kg or continuous infusion of 0.03-0.1 mg/kg/h	<i>i.v</i> Lower doses than recommende d for adults <60 years	Not indicated in paediatrics
Sedation in ICU	<i>i.v</i> Loading dose: 0.03-0.3 mg/kg in increments of 1-2.5 mg Maintenance dose: 0.03-0.2 mg/kg/h		<i>i.v.</i> <32 weeks gestationa l age: 0.03 mg/kg/h <i>i.v. in neonates >32 weeks gestationa l age up to 6 months: 0.06 mg/kg/h <i>i.v. > 6 months of age:</i> Loading dose: 0.05-0.2 mg/kg Maintenan ce dose: 0.06-0.12 mg/kg/h</i>

Conscious sedation

For basal (conscious) sedation prior to diagnostic or surgical intervention, Midazolam injection is administered i.v. The dose must be individualized and titrated and should not be administered by rapid or single bolus injection. The onset of sedation 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). If necessary, subsequent doses may be administered according to the individual need. Special caution is required for the indication of conscious sedation in patients with impaired respiratory function. See Warning and Precautions.

Adults

The i.v. injection of Midazolam injection should be given slowly at a rate of approximately 1mg in 30 seconds.

In adults below the age of 60 the initial dose is 2 to 2.5 mg given 5-10 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 5.0 mg is not usually not necessary.

In adults over 60 years of age, critically ill patients, high-risk patients the initial dose must be reduced to 0.5-1.0 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 Midazolam Injection should be titrated very slowly and carefully.

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

Paediatrics

I.V. administration:

Midazolam Injection should be titrated slowly to the desired clinical effect. The initial dose of Midazolam Injection should be administered over 2 to 3 minutes and, it is recommended to wait an additional 2 to 5 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments until the appropriate level of sedation is achieved. Infants and young children less than 5 years of age may require substantially higher doses than older children and adolescents.

- **Paediatric patients less than 6 months of age:** Paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation. For this reason, the use in conscious sedation in children less than 6 months of age is not recommended unless the benefits outweigh the risks. In such cases titration with small increments to clinical effect and careful monitoring are essential.
- **Paediatric patients> 6 months to 5 years of age:** initial dose 0.05 to 0.1 mg/kg. A total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint but the total dose should not exceed 6mg. Prolonged sedation and risk of hyperventilation may be associated with the higher doses.
- **Paediatric patients 6 to 12 years of age:** initial dose 0.025 to 0.05 mg/kg. A total dose up to 0.4 mg/kg to a maximum of 10 mg may be necessary. Prolonged sedation and risk of hyperventilation may be associated with the higher doses.
- **Paediatric patients 13 to 16 years of age:** should be dosed as adults.

I.M. administration (paediatrics 1-16 years):

The recommended dose range is 0.05 and 0.15 mg/kg given 5-10 minutes before the beginning of the procedure. A total dose greater than 10.0 mg is not usually necessary. This route should only be used in exceptional cases. Rectal administration should be preferred as IM injection may be painful.

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

Rectal administration:

The total dose of midazolam usually ranges from 0.3 to 0.5 mg/kg. Total dose should be administered at once and repeated rectal administration avoided. The use in paediatrics less than 6 months of age is not recommended, as available data in this population are limited. Rectal administration of the ampoule/vial solution is performed by means of a plastic applicator fixed on the end of the syringe. If the volume to be administered is too small, water may be added up to a total volume of 10 ml.

Anaesthesia-premedication:

Premedication with Midazolam injection given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of apprehension) and preoperative impairment of memory. Midazolam injection can also be administered in combination with anticholinergics. For this indication Midazolam injection should be administered i.v. or i.m. (deep into a large muscle mass 20-60 minutes before induction of anaesthesia) or preferably via the rectal route in paediatrics. Adequate observation of the patient after administration is mandatory as interindividual sensitivity varies and symptoms of overdose may occur.

Adults

For preoperative sedation and to impair memory of preoperative events, the recommended dose for adults of ASA Physical Status I & II and patients below 60 years is 1-2 mg i.v. repeated as needed, or 0.07-0.1 mg/kg i.m.

The dose must be reduced and individualized when Midazolam injection is administered to adult over 60 years of age, critically ill, high-risk patients. The recommended initial i.v. dose is 0.5 mg and should be slowly upitrated as needed. Allow 2-3 minutes to fully evaluate the effect between doses. An i.m. dose of 0.025-0.05 mg/kg is recommended if there is no concomitant administration of narcotics.

I.M. administration (1-15 years)

As i.m. injection may be painful this route should only be used in exceptional cases. Rectal administration should be preferred. However, a dose range from 0.08-0.2 mg/kg of Midazolam injection administered i.m. has been shown to be effective and safe.

In children between ages 1 and 15, proportionally higher doses are required than in adults in relation to body-weight. It is recommended that Midazolam injection should be administered deep into a large muscle mass 30-60 minutes prior to the induction of anaesthesia.

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

Rectal administration (Children over 6 months of age):

The total dose of midazolam, usually ranging from 0.4 mg/kg, ranging from 0.3-0.5 mg/kg, should be should be administered 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 to be administered is too small, water may be added up to a total volume of 10 ml.

The use in paediatrics less than 6 months of age is not recommended as available data are limited.

Induction of anaesthesia

Adults

If Midazolam injection is used for induction of anaesthesia 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 Midazolam injection is used before or in combination with other i.v. or inhalation agents for induction of anaesthesia, the initial dose of each agent may be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents.

The desired level of anaesthesia is reached by stepwise titration. The i.v. induction dose of Midazolam injection should be given slowly in increments. Each increment of not more than 5 mg should be injected over 20 – 30 seconds allowing 2 minutes between successive increments.

Adults below the age of 60 years

- A dose of 0.15-0.2 mg/kg, administered i.v. over 20-30 seconds and allowing 2 minutes for effect, will usually suffice.
- In non-premedicated patients the dose may be higher (0.3-0.35 mg/kg), administered i.v. over 20-30 seconds and allowing about 2 minutes for effect. 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 anaesthetics. 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.

Adults above the age of 60 years and/or critically ill and/or high-risk patients

- 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 i.v. over 20-30 seconds and allowing 2 minutes for effect, will usually suffice.

Paediatrics

The use of Midazolam injection for the induction of anaesthesia is limited to adults only as there is very limited experience in children.

Sedative component in combined anaesthesia

Adults

Midazolam injection can be given as a sedative component in combined anaesthesia by either further intermittent small i.v. doses (range between 0.03 and 0.1 mg/kg) or continuous infusion of i.v. Midazolam injection (range between 0.03 and 0.1 mg/kg/h) typically in combination with analgesics. The dose and the intervals between doses vary according to the patient's individual reaction.

In adults over 60 years of age, *critically ill and/or high-risk patients* lower maintenance doses will be required.

Paediatrics

The use of Midazolam injection as sedative component in combined anaesthesia is limited to adults only as there is very limited experience in children.

Sedation in the intensive care unit

The desired level of sedation is reached by stepwise titration of Midazolam injection followed by either continuous infusion or intermittent bolus, according to the clinical need, physical status, age and concomitant medication.

Adults

I.V. loading dose: 0.03-0.3 mg/kg 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.

In hypovolemic, vasoconstricted or hypothermic patients the loading dose should be reduced or omitted.

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

I.V. maintenance dose: doses can range from 0.03-0.2 mg/kg/h. In hypovolemic, vasoconstricted or hypothermic patients the maintenance dose should be reduced. The level of sedation should be assessed regularly if the patient's condition permits. With long-term sedation, tolerance may develop and the dose may have to be increased.

Paediatrics

In preterm new born infants, term newborn infants, and paediatrics less than 15 kg of body weight, midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1mg/ml.

Paediatrics up to 6 months of age

Midazolam injection should be given as a continuous i.v. infusion:

- Paediatrics <32 weeks of gestational age: starting dose at 0.03 mg/kg/hr (0.5µg/kg/min)
- Paediatrics >32 weeks of gestational age up to 6 months of age: starting dose 0.06 mg/kg/hr (1µg/kg/min)

Intravenous loading doses should not be used rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. The rate of infusion should be carefully and frequently reassessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation. Careful monitoring of respiratory rate and oxygen saturation is required.

Paediatrics over 6 months of age

In intubated and ventilated patients, a loading dose of 0.05 to 0.2 mg/kg i.v. should be administered slowly over at least 2 to 3 minutes to establish the desired clinical effect. Midazolam injection should not be administered as a rapid intravenous dose. The loading dose is followed by a continuous i.v. infusion at 0.06 to 0.12 mg/kg/h (1 to 2 µg/kg/min). The rate of infusion can be increased or decreased (generally by 25% of the initial or subsequent infusion rate) as required, or supplemental i.v. doses of Midazolam injection can be administered to increase or maintain the desired effect.

When initiating an infusion with Midazolam injection in haemodynamically compromised patients, the usual loading dose should be titrated in small increments and the patient monitored for haemodynamic instability, e.g. hypotension. These patients are also vulnerable to the respiratory depressant effects of Midazolam injection and require careful monitoring of respiratory rate and oxygen saturation.

Instruction for use/handling

The injection is for single patient use and should be used immediately after opening. The injection should not be used if particles are present. Any unused portion should be discarded. With continuous intravenous infusion, midazolam injection solution may be diluted in a ratio of 15mg midazolam to 100-1000ml with one of the infusion solution as below:

- Sodium Chloride 0.9%
- Dextrose 5%
- Dextrose 10%
- Ringer's Solution
- Hartmann's Solution

ROUTE OF ADMINISTRATION

Parenteral

[For IV, IM or rectal administration only.]

CONTRAINDICATIONS

It is contraindicated in patients who have known;

1. Hypersensitivity to the active substance, other benzodiazepines or to one or more of the excipients of this product.
2. Myasthenia gravis.
3. Acute intoxication with alcohol, hypnotics, neuroleptics, antidepressants or lithium.
4. Acute narrow-angle glaucoma.

WARNINGS AND PRECAUTIONS

In view of the potential onset of apnoea, midazolam should preferably be administered by an anaesthetist. Patients, who have received parenteral midazolam, should be assessed carefully before being allowed to leave the hospital - in general not earlier than 3 hours after administration – and should be accompanied home by a responsible adult.

Midazolam causes a dose-dependent anterograde amnesia. Prolonged amnesia can present problems in outpatients.

Inhibitors of the enzyme CYP3A4 such as azole antifungals, macrolide antibiotics etc. markedly increase the plasma concentrations of midazolam. Concomitant treatment should be avoided. If this is not possible, the midazolam dose should be reduced. The patient must not drive, or operate machines, for 12 hours.

WARNING

IV Midazolam has been associated with severe respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy resulted. IV Midazolam should be used only in hospital or ambulatory care settings that provide for continuous monitoring of respiratory and cardiac functions. Assure immediate availability of resuscitative drugs, equipments, appropriate antidote and personnel trained in their use.

Dosage of IV Midazolam must be individualized for each patient. Lower doses are usually required for elderly, debilitated or higher risk surgical patients.

When Midazolam is administered intravenously for conscious sedation, it should be injected slowly (over at least 2 minutes); it should not be administered by rapid or single bolus IV injection because of respiratory depression and/or arrest, especially in elderly or debilitated patients. The initial dose may be as little as 1mg, but should not exceed 2.5mg in a normal healthy adult; administer over at least 2 minutes and allow additional 2 or more minutes to fully evaluate sedative effect. If further titration is necessary, use small increments to the appropriate level of sedation, allowing an additional 2 or more minutes after each increment to fully evaluate sedative effect. See Dosage and Administration for complete dosing information.

Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling) which can occur as early as first time the product is taken.

Complex sleep – related behaviors which many include sleep driving, making phone calls, preparing and eating food while asleep.

Special caution is required if midazolam is administered in high-risk patients:

These include elderly patients, patients in a poor general condition, obese patients, patients with obstructive airways diseases, chronic renal or liver failure, sleep apnoea syndrome, cardiac decompensation and paediatric patients with cardiovascular instability. In these patients, the dose and rate of infusion must be reduced and individually adjusted; the patients must be monitored continuously; particular attention must be paid to early signs of changes in vital functions. In elderly patients and patients with chronic renal insufficiency and cardiac decompensation, the midazolam excretion rate may be reduced. In neonates and infants up to 4-6 months of age (especially in premature infants) the clearance of midazolam is markedly reduced. In this group of patients the administration of midazolam is, therefore, suitable after careful risk/benefit evaluation only. Benzodiazepines are contraindicated in patients with severe liver insufficiency because they may encourage the onset of encephalopathy. As the exacerbation of an acute psychosis cannot completely be ruled out special care is required in patients suffering from schizophrenia or endogene depression.

A current lack of volume should be balanced by infusion before anaesthesia.

As documentation of efficacy and safety of intravenous midazolam in children and adolescents younger than 18 years is limited the expected benefit should carefully be balanced against possible risks.

The risk of severe undesirable effects is particularly great after high doses or rapid administration. There have been reports of reactions such as restlessness, reflex movements (e.g. tonic and clonic movements and muscle tremor), hyperactivity and striking movements. These reactions may be caused by inadequate, excessive or incorrect administration of midazolam; however, the possibility of cerebral hypoxia or paradoxical reactions must also be considered. If such reactions occur, the response to each dose of midazolam, and to all other drugs, including local anaesthetics, must be evaluated.

An intraarterial injection must be avoided in any case as it can cause vasal tissue damage and even necrosis in certain cases.

As in comparable cases of parenteral administered hypnotics a venous access should be ascertained at least during the period of operation under basic sedation.

The risk of dependence increases with dose and duration of treatment and some loss of efficacy has been reported during long-term sedation in intensive care units.

After prolonged intravenous administration, abrupt discontinuation may lead to withdrawal symptoms. Therefore, a gradual reduction is recommended in such cases.

Ability to drive or use machines

The patient must not drive or operate machinery for a period of 12 hours after administration of midazolam and even longer in case of prolonged sedation which may be seen after repeated or continuous dosing or with concomitant use of other CNS depressants. Sedation, amnesia, loss of concentration and diminished muscle function may have adverse effects on the ability to drive, or to use machines.

INTERACTIONS WITH OTHER MEDICATIONS

Midazolam may lead to a potentiation of the anaesthetic or sedative effect of other centrally acting agents, such as neuroleptics, tranquilisers, antidepressants, anticonvulsants, hypnotics, analgesics, anaesthetics and sedative antihistamines; this includes respiratory depression.

The risk of respiratory depression is particularly high with co-administration of narcotic analgesics.

Displacement of midazolam from its plasma protein binding sites by sodium valproate may increase the response to midazolam and, therefore, care should be taken to adjust the midazolam dosage in patients with epilepsy.

The mutual potentiation of midazolam and alcohol may lead to unforeseeable reactions in some cases; patients must therefore not take any alcoholic drinks before and at least 12 hours after injection.

A clinically relevant interaction may occur between midazolam and substances that inhibit specific liver enzymes (principally cytochrome P 450 3A). These substances are known to be capable of influencing midazolam pharmacokinetics and of leading to deeper and longer lasting anaesthesia. The following substances are currently known to produce such reactions: cimetidine, erythromycin, clarithromycin, roxithromycin, diltiazem, verapamil, ketoconazole, itraconazole, fluoxetine, nefazodon. If possible, therefore, administration of midazolam should be avoided in patients concomitantly receiving one of the above substances or other agents inhibiting cytochrome P 450 3A. If this is not possible, the dosage must be reduced to 50 – 75%. These patients must be closely monitored.

The hypotensive effect of antihypertensive and vasodilatory drugs may be potentiated by midazolam.

Incompatibilities

This medicinal product must not be diluted with other solutions for parenteral use other than those mentioned in section 'Recommended Dosage'. Compatibility study must be checked before administration, if intended to be mixed with other drugs.

Midazolam precipitates in solutions containing bicarbonate. Theoretically, the midazolam injection solution is likely to be unstable in solutions of neutral or alkaline pH. If midazolam is mixed with albumin, amoxicillin sodium, ampicillin sodium, bumetamide, dexamethasone sodium phosphate, dimenhydrinate, flouxacinil sodium, furosemide, hydrocortison sodium succinate, pentobarbital sodium, perphenazine, prochlorperazine edisylate, ranitidine or thiopental sodium or trimethoprim-sulfa-methoxazole, a white precipitate forms immediately.

A haze is formed immediately followed by a white precipitate with nafcillin sodium. With ceftazidime a haze is formed.

With methotrexate sodium a yellow precipitate forms. With clonidine hydrochloride an orange discoloration forms. With omeprazole sodium a brown discoloration forms, followed by a brown precipitate. With forscarnet sodium a gas is produced.

Further midazolam should not be mixed with aciclovir, albumin, alteplase, acetazolam disodium, diazepam, enoximone, flecainide acetate, fluorouracil, imipenem, mezlocillin sodium, phenobarbital sodium, phenytoin sodium, potassium canrenoate, sulbactam sodium, theophylline, trometamol, urinkase.

PREGNANCY AND LACTATION

Pregnancy

Because midazolam crosses through the placenta and passes into breast milk, it must not be used during the first three months of pregnancy. Midazolam should not be used during the last six months unless this is considered essential by the treating physician. As with all benzodiazepines, high doses of midazolam must not be administered during the last three months of pregnancy.

Particular caution is required if benzodiazepines are administered during delivery, because high single doses may produce cardiac arrhythmia and hypotonia in the foetus, and cause hypothermia, hypotonia, respiratory depression and poor sucking (floppy infant syndrome) in the neonate.

The risk of abnormalities with ingestion of therapeutic doses of benzodiazepines at an early stage in pregnancy appears to be low, although a number of epidemiological studies have revealed evidence of an increased risk of cleft palate. There have been a few case reports of deformities after overdose and Intoxication.

Lactation

Midazolam passes into breast-milk. Therefore, if midazolam is administered parenterally during lactation, breast-feeding should be interrupted for 1 – 2 days as a precautionary measure.

SIDE EFFECTS

The most common undesirable effects after parenteral administration of midazolam are changes in vital functions, particularly a loss of respiratory volume and/or a fall in respiratory rate or apnoea which are observed frequently. The apnoea is usually a short duration, and respiration resumes rapidly and spontaneously.

However, serious cardiorespiratory undesirable effects, including respiratory depression, apnoea, respiratory and/or cardiac arrest, in many cases fatal, have also been observed after intravenous injection. These life-threatening incidents may occur especially in elderly patients or patients with pre-existing respiratory insufficiency, particularly if excessive or too rapidly-injected doses are administered. At the same time, changes in the blood pressure and heart rate are possible. Changes in cardiovascular parameters are slight but can include a decrease in mean arterial pressure, cardiac output, stroke volume and systemic vascular resistance. Such changes may be important in patients with impaired myocardial oxygen delivery capacity and hypovolaemia.

The following reactions have been reported occasionally (>1%): hiccoughs, nausea, vomiting, dry cough, marked sedation, headache, dizziness, as well as local symptoms such as sensitivity, erythema and induration at the injection site. However, the number of cases or pain following injection and thrombophlebitis was lower.

The following undesirable effects have been reported in less than 1% of cases after intravenous administration:

Respiratory system: Laryngospasm, bronchospasm, dyspnoea, hyperventilation, laboured respiration, shallow respiration, obstructed airways and rapid breathing.

Cardiovascular system: Bigeminal pulse, premature ventricular contractions, vasovagal episodes, tachycardia, nodal rhythm.

Gastrointestinal tract: Sour taste in mouth, increased salivation, vomiting.

CNS/neuromuscular: Retrograde amnesia, euphoria, confusion, quarrelsome behaviour, nervousness, anxiety, feeling or drunkenness, restlessness, sudden delirium or excitation, hallucinations, prolonged waking from anaesthesia and dreams, sleep disturbances, insomnia, nightmares. athetotic movements, muscle twitching, ataxia, dizziness. dysphoria, unclear speech, dysphonia, paraesthesia.

Other sensory organs: Blurred vision, double vision, nystagmus, miosis, fluttering of the eyelids, impaired vision, convergence disorders, impaired hearing, loss of balance, disorientation.

Skin: Urticaria, swelling or burning of the skin, warm or cold feeling, spotty skin, pruritus, particularly at the injection site.

Miscellaneous: Yawning, lethargy, tremor, asthenia, toothache, fainting, haematoma.

General hypersensitivity reactions - shock-like states, amongst others - have been reported only rarely. There have been isolated reports of cerebral convulsions, particularly in neonates.

Patients must be warned that use of the product can cause amnesia.

Withdrawal symptoms have been reported on abrupt cessation after continuous administration (more than 3 to 5 days) of midazolam for long-term sedation. The following symptoms may occur: headaches, muscle pain, anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood changes, hallucinations (some of a sexual nature) and convulsions.

The treatment must therefore be discontinued gradually.

OVERDOSE AND TREATMENT

Symptoms

The symptoms of overdose are mainly an intensification of the therapeutic effects (sedation, muscle weakness, profound sleep) or paradoxical excitation. Confusion, tiredness, ataxia, disorders of vision, at high doses profound sleep or even loss of consciousness, respiratory depression, circulatory collapse. Extreme over-dosage may lead to coma, areflexia, cardiopulmonary depression and apnoea, requiring appropriate counter measures (ventilation, cardiovascular support).

Treatment

In case of mild symptoms of intoxication, the patient should be allowed to regain consciousness naturally, under supervision. If necessary, the circulation must be supported with peripherally acting drugs of the noradrenaline type and volume replacement. In the presence of respiratory insufficiency, which can also be caused by peripheral muscle relaxation, artificial ventilation is used. Forced diuresis, haemodialysis and peritoneal dialysis may be helpful if mixed intoxication cannot be excluded. Insufficient experience is available on the effects of haemoperfusion over activated charcoal. Prophylaxis against infection should be given.

The specific antidote is flumazenil. If mixed intoxication is suspected, for example with other centrally acting drugs, flumazenil is to be used with caution. The toxic effects of other psychotropic substances (in particular convulsions with tricyclic antidepressants) may occur due to neutralisation of the protective effect of the benzodiazepines by flumazenil.

STORAGE CONDITIONS

Store below 30°C. Protect from light.

Retain in carton until time of use.

The solution should be colourless to pale yellow when diluted.

Following dilution in the recommended diluents, chemical and physical in-use stability has been demonstrated for 24 hours at room temperature (<30°C) and at refrigerated condition (2°C to 8°C). However, from a microbiological point of view, the product should be used immediately.

SHELF LIFE

3 years.

The solution should be colourless to pale yellow when diluted.

Following dilution in the recommended diluents, chemical and physical in-use stability has been demonstrated for 24 hours at room temperature (<30°C) and at refrigerated condition (2°C to 8°C). However, from a microbiological point of view, the product should be used immediately.

DOSAGE FORMS AND PACKAGING AVAILABLE

- 10 x 1mL ampoule Solution for Injection
- 10 x 3mL ampoule Solution for Injection

PRODUCT REGISTRATION HOLDER/MANUFACTURER

Pharmaniaga Lifescience Sdn Bhd (198201002939)

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