Kalcex

Package leaflet: Information for the user

Midazolam 1 mg/ml solution for injection/infusion
Midazolam 5 mg/ml solution for injection/infusion

midazolam

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Midazolam is and what it is used for

Midazolam belongs to a class of medicines called benzodiazepines (sedatives). It is a short-acting medicine that is used to induce sedation (a state of calm, drowsiness or sleep) and relieves anxiety and muscle tension. This drug is used for:
- Conscious sedation (an awake state of calm or drowsiness) in adults and children.
- Sedation of adults and children, in intensive care units.
- Anaesthesia in adults (premedication before induction, induction of anaesthesia, as a sedative component with other medicines for maintenance of anaesthesia).
- Premedication before induction of anaesthesia in children.

2. What you need to know before you are given Midazolam

You should not be given Midazolam:
- if you are allergic to midazolam, other benzodiazepines or any of the other ingredients of this medicine (listed in section 6),
- for conscious sedation, if you have severe breathing difficulties.

Warnings and precautions
Talk to your doctor or nurse before you are given Midazolam if you:
- are over 60 years of age,
- have a long-term illness or are debilitated (e.g. chronic respiratory problems, kidney, liver or heart diseases),
- have *myasthenia gravis* (a neuromuscular disease characterized by muscle weakness),
- have a history of alcohol or drug abuse,
- are using other medicines, including those not prescribed by your attending physician (see section "Other medicines and Midazolam"),
- if your breathing sometimes stops while you are sleeping,
- are pregnant or if you suspect pregnancy.

Midazolam should be used only when age- and size-appropriate resuscitation facilities are available. Administration of midazolam may depress myocardial contractility and cause apnoea (pauses in breathing). In rare cases severe cardiorespiratory complications have occurred, including respiratory depression, apnoea, respiratory and/or cardiac arrest. To avoid such complications the medicine should be injected slowly and the administered dose must be as low as possible.

Special caution is required when using midazolam in infants or children. Let your doctor know if your child has a cardiovascular disease or breathing problems. Your child will be monitored and the dose will be specially adjusted.
Patients under 6 months of age undergoing sedation in an intensive care unit are more likely to develop breathing problems, so their dosing will be increased very slowly and their breathing and oxygen levels will be observed.

When midazolam is used for premedication, your response to the drug will be checked and the correct dosage for you will be ascertained, as sensitivity varies between patients. Midazolam is not recommended for new-borns or children under 6 months of age.

Paradoxical reactions and anterograde amnesia (loss of memory for recent events) have been reported to occur with midazolam (see section 4).

Long-term treatment
If you receive midazolam for a longer period, you may become tolerant (midazolam becomes less effective) or dependent upon this medicine.
After long-term treatment (e.g. in intensive care unit) the following withdrawal symptoms may occur: headaches, diarrhoea, muscle pain, anxiety, tension, restlessness, confusion, irritability, sleep disturbances, mood changes, hallucinations and convulsions. In severe cases, depersonalisation, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact may occur. In order to avoid getting such adverse reactions your doctor will reduce the dosage gradually.

Other medicines and Midazolam
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. This is extremely important, as using more than one medicine at the same time can strengthen or weaken the effect of the medicines involved.

In particular, tell your doctor or nurse if you are using any of the following medicines:
- tranquilisers (for anxiety or to help you sleep),
- sedatives (to make you feel calm or sleepy),
- hypnotics (sleep medicines),
- antidepressants (medicines for depression, e.g. nefazodone),
- narcotic analgesics (very strong pain killers, e.g. fentanyl),
- anaesthetics (e.g. propofol),
- some antihistamines (allergy drugs),
- antifungal medicines (ketoconazole, voriconazole, fluconazole, itraconazole, posaconazole),
- antibiotics (erythromycin, clarithromycin, telithromycin, roxithromycin),
- blood pressure drugs, calcium channel blocker like diltiazem, verapamil,
- medicines for HIV (human immunodeficiency virus) (efavirenz or saquinavir, lopinavir and other protease inhibitors),
- medicines for treatment of hepatitis C virus (simeprevir, boceprevir and telaprevir),
- medicines for epilepsy (carbamazepine, phenytoin or valproic acid),
- atorvastatin (used to treat high cholesterol),
- rifampicin (used to treat mycobacterial infections such as tuberculosis),
- ticagrelor (used to prevent heart attack),
- aprepitant, netupitant, casoprepitant (used to stop you feeling or being sick),
- some medicines to treat cancer (e.g. imatinib, lapatinib, idelalisib, vermurafenib),
- everolimus, ciclosporin (used to prevent organ transplant rejection),
- propiverine (used for urinary incontinence),
- herbal medicines (e.g. St John's Wort, *Ginkgo biloba* or ginseng).

Concomitant use of midazolam and opioids (strong pain killers, medicines for substitution therapy and some cough medicines) increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible.
However if your doctor does prescribe midazolam together with opioids the dose and duration of concomitant treatment should be limited by your doctor.
Please tell your doctor about all opioid medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

Operations
If you are going to have an inhaled anaesthetic (one that you breathe in) for an operation or for dental treatment, it is important to tell your doctor or dentist that you have been given Midazolam.

Midazolam with alcohol
Alcohol may strengthen the sedative (calming) effect of midazolam therefore you should avoid any alcohol intake.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before this medicine is given to you. Your doctor will decide if this medicine should be given to you or not.
After you have been given Midazolam, do not breastfeed for 24 hours. This is because midazolam may pass into your breast milk.

Driving and using machines
Midazolam has a major influence on the ability to drive and use machines.
This medicine may cause sleepiness and forgetfulness, and affect your concentration and co-ordination. This may affect your performance at skilled tasks such as driving or using machines.
After midazolam administration you should not drive or operate machines until completely recovered. The doctor will tell you when you can recommence these activities. You should always be taken home by a responsible adult after your treatment.
If insufficient sleep occurs or alcohol is consumed, the likelihood of impaired alertness may be increased.

Midazolam contains sodium
Midazolam ***1 mg/ml***
In daily dose up to 6.5 ml this medicine contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium-free'. If daily dose 6.6 ml or more is administered (equivalent to more than 1 mmol sodium) the following should be taken into account: This medicine contains 3.5 mg sodium (main component of cooking/table salt) in each ml of solution. This is equivalent to 0.18 % of the recommended maximum daily dietary intake of sodium for an adult.

Midazolam ***5 mg/ml***
In daily dose up to 7.3 ml this medicine contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium-free'. If daily dose 7.4 ml or more is administered (equivalent to more than 1 mmol sodium) the following should be taken into account: This medicine contains 3.15 mg sodium (main component of cooking/table salt) in each ml of solution. This is equivalent to 0.16 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How Midazolam is given

This medicine should be administered only by experienced physicians in a place that has the equipment needed to monitor and support the respiratory and cardiovascular function, or by persons specifically trained in the recognition and management of adverse reactions.

Dosage and route of administration
Your doctor will decide on a suitable dose for you. The dosages vary depending on the treatment planned and the required sedation. The dose you will receive depends on your weight, age, general condition of health, concomitant medication, response to the drug and whether other medicines are required at the same time.
If you need strong pain killers, you will receive these first and then have your Midazolam dose adjusted specially for you.
This medicine will be injected directly into your vein (intravenously), administered by infusion, injected into the muscle (intramuscularly) or administered rectally.

The following information is intended for healthcare professionals only:

Instructions for use
Midazolam is compatible with the following solutions for infusion:
- sodium chloride 0.9 % solution
- glucose 5 % solution
- glucose 10 % solution
- Ringer's solution
- Hartmann's solution

For intravenous infusion, the content of Midazolam ampoules may be diluted with one of the solution mentioned above in a ratio of 15 mg midazolam per 100 to 1000 ml of infusion solution.

Midazolam solution for injection/infusion must not be diluted with Macrodex 6 % solution in glucose.
Midazolam solution for injection/infusion must not be mixed with alkaline solutions for injection. Midazolam precipitates in solutions containing hydrogen carbonate.
To avoid potential incompatibility, Midazolam solution for injection/infusion must not be mixed with other solutions except those mentioned above.

Midazolam solution for injection/infusion is intended for single use.
The solution should be examined visually before administration. Only clear solution without visible particles may be used.

Children and neonates
In neonates and infants under 6 months of age midazolam is only recommended for sedation in intensive care units. The dose will be given gradually into a vein.

Children 12 years and under will usually be given midazolam into a vein. When this medicine is used for premedication (to cause relaxation, calm and drowsiness before an anaesthetic) it may be given into the back passage (rectum).

If you are given more Midazolam than you should
The medicine is administered by the doctor or nurse.
If you are accidentally given too much midazolam, this could lead to drowsiness, ataxia (coordination disorders of voluntary muscular action), dysarthria (speech disorder) and nystagmus (involuntary eye movements), loss of reflexes, apnoea (suspension of breathing), hypotension (low blood pressure), cardiac and respiratory depression, and coma. In case of overdose careful monitoring of vital signs, symptomatic treatment of cardiorespiratory effects and use of benzodiazepine antagonist may be required.

If you stop using Midazolam
Sudden discontinuation of treatment can be accompanied by withdrawal symptoms such as headache, muscular pain, anxiety, tension, restlessness, confusion, mood swings, hallucinations and convulsions, rebound insomnia, irritability. Since the risk of withdrawal symptoms occurring is greater if treatment is discontinued abruptly, dose should be reduced gradually when treatment is being discontinued.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell a doctor straight away if you notice any of the following side effects. They can be life-threatening and you may need urgent medical treatment:
- Anaphylactic shock (a life-threatening allergic reaction). Signs may include a sudden rash, itching or lumpy rash (hives) and swelling of the face, lips, tongue or other parts of the body. You may also have shortness of breath, wheezing or trouble breathing, or a pale skin, a weak and rapid pulse, or feeling of loss of consciousness. Additionally, you may experience chest pain, which can be a sign of a potentially serious allergic reaction called Kounis syndrome.
- Heart attack (cardiac arrest). Signs may include chest pain which may spread to your neck and shoulders and down your left arm.
- Breathing problems or complications (sometimes causing the breathing to stop).
- Choking and sudden blockage of the airway (laryngospasm).

Life-threatening side effects are more likely to occur in adults over 60 years of age and those who already have breathing difficulties or heart problems, particularly if the injection is given too fast or at a high dose.

Other possible side effects:
The following side effects have been reported but their frequency is not known and cannot be estimated from the available data:

Immune system disorders: general allergic reactions (skin reactions, heart and vascular system reactions, wheezing).

Psychiatric disorders: confusion, disorientation, emotional and mood disturbances, changes in libido. Paradoxical reactions such as restlessness, agitation, irritability, nervousness, muscle spasms and tremors, hostility, delusion, anger, aggressiveness, anxiety, nightmares, abnormal dreams, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, excitement and assault have been reported. These have mostly been observed if the injection is given too fast or at a high dose. The risk of the appearance of these symptoms is greater in children and elderly patients.

Dependence: midazolam may cause development of physical dependence, even if used in therapeutic doses. The withdrawal symptoms, including seizures, which may occur after prolonged administration of midazolam, can be avoided with gradual reduction in dosage (see section 2).

Nervous system disorders: drowsiness and prolonged sedation, decreased alertness, somnolence, headache, dizziness, muscular coordination disorders. Temporary memory loss has been reported. Its duration depends on dosage administered and it may also occur after the treatment. In isolated cases the memory loss has been prolonged. Convulsions have been reported in preterm infants and new-born babies.

Cardiac disorders: severe adverse reactions have occurred, such as low blood pressure, slow heart rate, dilation of blood vessels (e.g. flushing, fainting and headache).

Gastrointestinal disorders: nausea, vomiting, constipation, dry mouth.

Skin disorders: skin rash, allergic reaction, itching.

General disorders and administration site conditions: tiredness, redness, swelling of the skin, blood clots and pain at the injection site (erythema, thrombophlebitis and thrombosis). Patients taking benzodiazepines are at a higher risk of falling and breaking bones, especially the elderly and those taking other sedatives (including alcoholic beverages).

Patients with severe kidney disease are more likely to experience side effects.

Reporting of side effects
If you get any side effects, talk to your anaesthetist or other doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:
Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Midazolam

This medicine does not require any special temperature storage conditions.
Keep the ampoules in the outer carton in order to protect from light.

Keep this medicine out of the sight and reach of children.

After opening the ampoule the product should be used immediately.

Chemical and physical in-use stability has been demonstrated 24 hours at 25 °C and 3 days at 2 - 8 °C temperature with following infusion solutions: sodium chloride 0.9 %, glucose 5 % and 10 %, Ringer`s solution and Hartmann`s solution.
From a microbiological point of view, the dilutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Midazolam contains
- The active substance is midazolam.

Midazolam ***1 mg/ml***
1 ml of solution contains 1 mg of midazolam.
One ampoule with 5 ml of solution contains 5 mg of midazolam.

Midazolam ***5 mg/ml***
1 ml of solution contains 5 mg of midazolam.
One ampoule with 1 ml of solution contains 5 mg of midazolam.
One ampoule with 2 ml of solution contains 10 mg of midazolam.
One ampoule with 3 ml of solution contains 15 mg of midazolam.
One ampoule with 10 ml of solution contains 50 mg of midazolam.

- The excipients are: hydrochloric acid concentrated, sodium chloride, sodium hydroxide (for pH adjustment), water for injections.

What Midazolam looks like and contents of the pack
Clear, colourless solution for injection/infusion of 1 ml, 2 ml, 3 ml or 10 ml (for 5 mg/ml) and 5 ml solution (for 1 mg/ml) filled in Type I colourless glass ampoules with one point cut.

Pack size: 5 or 10 ampoules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
AS KALCEKS
Krustpils iela 71E, Rīga, LV-1057, Latvia

This leaflet was last revised in 10/2024

Place for AS Kalceks internal code
Place for manufacturer internal code

Instruction of ampoule opening:
1) Turn the ampoule with coloured point up. If there is any solution in the upper part of the ampoule, gently tap with your finger to get all the solution to the lower part of the ampoule.
2) Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point (see the pictures below).