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**Date: 16/04/19**

- reflexes.
- Have problems with speech (dysarthria) and unusual eye movements (nystagmus).
- Develop low blood pressure (hypotension). This may make you feel dizzy or light-headed.
- Stop breathing (apnoea) and suffer cardiorespiratory depression (slowed or stopped breathing and heart beat) and coma.

**If you receive Midazolam in intensive care unit for sedation, for a long time**

If you receive long term treatment with Midazolam (are given the medicine for a long time) you may:

- Become tolerant to Midazolam. The medicine becomes less effective and does not work as well for you.
- Become dependent upon this medicine and get withdrawal symptoms (See "If you stop using Midazolam").

**If you stop using Midazolam**

Risk of Withdrawal symptoms:

If you are given Midazolam for a long time, such as in intensive care, you may get withdrawal symptoms when you stop being given the medicine

- Mood changes
- Fits (convulsions)
- Headache
- Muscle pain
- Problems with sleeping (insomnia)
- Feeling very worried (anxious), tense, restless, confused or bad tempered (irritable).
- Hallucinations (Seeing and possibly hearing things that do not really exist)

Your doctor will gradually reduce the dose to avoid withdrawal symptoms.

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, Midazolam can cause side effects, although not everybody will get them.

The following undesirable effects may occur during the administration of midazolam but their frequency is not known and cannot be estimated from the available data.

**Stop having Midazolam and see 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.
- Heart attack (cardiac arrest). Signs may include chest pain.
- Breathing problems or complications (sometimes causing the breathing to stop).
- Muscle spasm around the throat, causing choking. 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**

Mental and Nervous system problems:

- Being less alert
- Feeling confused
- Feeling very happy or excited (euphoria).
- Feeling tired or sleepy or being sedated for a long time.
- Seeing or possibly hearing things that are not really there (hallucinations).
- Disturbance of consciousness (delirium)
- Headache
- Feeling dizzy
- Difficulty co-ordinating muscles
- Fits (convulsions) in premature and new-born babies.
- Temporary memory loss. How long this lasts depends on how much Midazolam you were given. You may experience this after your treatment. In isolated cases this has been prolonged (lasted for a long time).
- Feeling agitated, restless, angry or aggressive. You may also have muscle spasms or shaking of your muscles that you cannot control (tremors). These effects are more likely if you have been given a high dose of Midazolam or if it has been given too quickly. It is also more likely in children and elderly people.

**Heart and circulation**

- Fainting
- Slow heart rate
- Redness of the face and neck (flushing)
- Low blood pressure. This may make you feel dizzy or light-headed.

**Breathing**

- Hiccups
- Being short of breath

**Mouth, stomach and gut**

- Dry mouth
- Constipation
- Feeling sick (nausea) or being sick (vomiting)

**Skin**

- Feeling itchy
- Rash, including a lumpy rash (hives)
- Redness, pain, blood clots or swelling of the skin where the injection was given.

**General**

- Allergic reactions including skin rash and wheezing.
- Withdrawal symptoms (see 'Stopping Midazolam' in Section 3 above)



The recommended initial IV dose is 0.5mg and should be slowly up titrated as needed. A dose of 0.025 to 0.05mg/kg administered IM is recommended. In case of concomitant administration of narcotics the midazolam dose should be reduced. The usual dose is 2 to 3 mg.

**Paediatric Patients**

Neonates and children up to 6 months of age:

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

Children over 6 months of age:

Rectal administration:  
The product may be used rectally if required.

The total dose of midazolam, usually ranging from 0.3 to 0.5mg/kg should be administered 15 to 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 10ml.

IM administration: As IM injection is painful, this route should only be used in exceptional cases. Rectal administration should be preferred. However, a dose range from 0.08 to 0.2mg/kg of midazolam administered IM has been shown to be effective and safe. In children between ages 1 and 15 years, proportionally higher doses are required than in adults in relation to body-weight.

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

**INDUCTION**

**Adults**

If midazolam 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 is used before or in combination with other IV or inhalation agents for induction of anaesthesia, the initial dose of each agent should 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 IV induction dose of midazolam should be given slowly in increments. Each increment of not more than 5mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments.

- In premedicated adults below the age of 60 years*, an IV dose of 0.15 to 0.2mg/kg will usually suffice.
- In non-premedicated adults below the age of 60* the dose may be higher (0.3 to 0.35mg/kg IV). If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used. Induction may instead be completed with inhalational anaesthetics. In resistant cases, a total dose of up to 0.6mg/kg may be used for induction, but such larger doses may prolong recovery.
- In premedicated adults over 60 years of age*, debilitated or chronically ill patients, the dose should be significantly reduced, e.g., down to 0.05-0.15mg/kg administered IV over 20-30 seconds and allowing 2 minutes for effect.
- Non-premedicated adults over 60 years of age* usually require more midazolam for induction; an initial dose of 0.15 to 0.3mg/kg is recommended. Non-premedicated patients with severe systemic disease or other debilitation usually require less midazolam for induction. An initial dose of 0.15 to 0.25mg/kg will usually suffice.

**SEDATIVE COMPONENT IN COMBINED ANAESTHESIA**

**Adults**

Midazolam can be given as a sedative component in combined anaesthesia by either further intermittent small IV doses (range between 0.03 and 0.1mg/kg) or continuous infusion of IV midazolam (range between 0.03 and 0.1mg/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, debilitated or chronically ill patients, lower maintenance doses will be required.

**SEDATION IN INTENSIVE CARE UNITS**

The desired level of sedation is reached by stepwise titration of midazolam followed by either continuous infusion or intermittent bolus, according to the clinical need, physical status, age and concomitant medication (see section 4.5).

**Adults**

*IV loading dose:* 0.03 to 0.3 mg/kg should be given slowly in increments. Each increment of 1 to 2.5 mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments. In hypovolaemic, vasoconstricted, or hypothermic patients the loading dose should be reduced or omitted.

- Falls and fractures. The risk increases if you take other medicines known to cause drowsiness (for example, sedatives or sleeping pills), or alcohol.

**Elderly patients**

- Use of Midazolam may increase the risk of falling and breaking bones.
- Life-threatening side effects are also more likely to happen in adults over 60 years.

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report any side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

**United Kingdom**

Yellow Card Scheme  
Website: <http://www.mhra.gov.uk/yellowcard>  
[www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)  
or search for MHRA Yellow Card in the Google Play or Apple App Store.

**Ireland**

HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2  
Tel: +353 1 6764971; Fax: +353 1 6762517  
Website: [www.hpra.ie](http://www.hpra.ie); e-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie)

**5. How to store Midazolam**

Your doctor or pharmacist or nurse is responsible for storing Midazolam. They are also responsible for disposing of any unused Midazolam correctly.

Keep this medicine out of the sight and reach of children. Keep the ampoules in the outer carton in order to protect from light.

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

**Do not use this medicine if you notice visible particles.**

Do not dispose of any medication in the sewage system or in the household waste. Ask your pharmacist to eliminate medications that 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. ....5 mg (as midazolam hydrochloride).

Each ml contains 5 mg of midazolam (as hydrochloride).  
Each 1 ml ampoule contains 5 mg of midazolam (as hydrochloride).  
Each 3 ml ampoule contains 15 mg of midazolam (as hydrochloride).  
Each 10 ml ampoule contains 50 mg of midazolam (as hydrochloride).

The other ingredients are:  
Sodium chloride, Sodium hydroxide, Hydrochloric acid and Water for Injections.

**What Midazolam looks like and contents of the pack**  
Midazolam comes in a clear glass ampoule. It is a clear, colourless to pale yellow solution.

The following packs are available:

- 1 ml glass ampoules: pack of 5, 10 and 25.
- 3 ml glass ampoules: pack of 5, 10 and 25.
- 10 ml glass ampoules: pack of 5 and 10.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**

**Ireland:**  
Baxter Holding B.V.  
Kobaltweg 49,  
3542CE Utrecht, Netherlands

**United Kingdom:**

Baxter Healthcare Limited  
Caxton Way  
Thetford, Norfolk IP24 3SE, United Kingdom

**Manufacturer**

**UAB Norameda,**  
Meistru 8a, 02189, Vilnius, Lithuania

**Bieffe Medital S.P.A**

Via Nuova Provinciale, 23034- Grosotto (SO), Italy

**This medicinal product is authorised in the Member States of the EEA under the following names:**

Czech Republic	Midazolam BAXTER
Estonia	Midazolam BAXTER
France	Midazolam Baxter 5mg/ml Solution pour Injection/Perfusion
Hungary	Midazolam Baxter 5mg/ml oldatos injekció/infúzió
Ireland	Midazolam 5mg/ml solution for injection/infusion
Latvia	Midazolam Baxter 5mg/mL šķīdums injekcijām/infūzijām
Lithuania	Midazolam Baxter 5mg/ml injekcinis ar infuzinis tirpalas
Poland	Midazolam BAXTER
Portugal	Midazolam BAXTER
Romania	Midazolam Baxter 5 mg/ml soluție injectabilă/perfuzabilă
Slovakia	Midazolam Baxter 5 mg/ml
The Netherlands	Midazolam Baxter 5mg/ml oplossing voor injectie/infusie
UK	Midazolam 5mg/ml solution for injection/infusion

**This leaflet was last revised in month 04/2019**

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.

*IV maintenance dose:* doses can range from 0.03 to 0.2 mg/kg/h. In hypovolaemic, vasoconstricted, or hypothermic patients the maintenance dose should be reduced. The level of sedation should be assessed regularly. With long-term sedation, tolerance may develop and the dose may have to be increased.

**Neonates and children up to 6 months of age:**

Midazolam should be given as a continuous IV infusion, starting at 0.03mg/kg/h (0.5 µg/kg/min) in neonates with a gestational age <32 weeks, or 0.06 mg/kg/h (1 µg/kg/min) in neonates with a gestational age > 32 weeks and children up to 6 months.

Intravenous loading doses are not recommended in premature infants, neonates and children up to 6 months, 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.

**Children over 6 months of age:**

In intubated and ventilated paediatric patients, a loading dose of 0.05 to 0.2 mg/kg IV should be administered slowly over at least 2 to 3 minutes to establish the desired clinical effect. Midazolam should not be administered as a rapid intravenous dose. The loading dose is followed by a continuous IV 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 IV doses of midazolam can be administered to increase or maintain the desired effect.

When initiating an infusion with midazolam 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 and require careful monitoring of respiratory rate and oxygen saturation.

In premature infants, neonates and children less than 15 kg of bodyweight, midazolam solutions with concentrations higher than 1mg/ml are not recommended. Higher concentrations should be diluted to 1mg/ml.

**Special populations**

Renal Impairment

In patients with renal impairment (creatinine clearance <10ml/min) the pharmacokinetics of unbound midazolam following a single IV dose is similar to that reported in healthy volunteers. However, after prolonged infusion in intensive care unit (ICU) patients, the mean duration of the sedative effect in the renal failure population (shown after prolonged infusion in intensive care unit (ICU) patients) was considerably increased most likely due to accumulation of α-hydroxymidazolam glucuronide. There is no specific data in patients with severe renal impairment (creatinine clearance below 30ml/min) receiving midazolam for induction of anaesthesia.

Hepatic Impairment

Hepatic impairment reduces the clearance of IV midazolam with a subsequent increase in terminal half-life. Therefore the clinical effects may be stronger and prolonged. The required dose of midazolam may be reduced and proper monitoring of vital signs should be established. (See section 4.4).

Paediatric population

See above and section 4.4.

**Incompatibilities**

Do not dilute Midazolam ampoules with dextran glucose 6%. Midazolam should not be mixed with alkaline solutions. Midazolam precipitates with sodium bicarbonate. Midazolam must not be mixed with other medicinal products except those mentioned in section 6.6.

**Shelf life**

3 years  
Chemical and physical in-use stability of the dilutions has been demonstrated for 24 hours at room temperature and for 3 days at 5°C.

From the 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 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. (for dilution, see also section 6.6)

**Special precautions for storage**

Keep the ampoules in the original outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

This healthcare professional leaflet was last approved in 04/2019.