Public Assessment Report

Decentralised Procedure

MIDAZOLAM 2 MG/ML AND 5 MG/ML SOLUTION FOR INJECTION

UK/H/2511/001-2/DC
UK Licence No: PL 17507/0030-1

AUDEN MCKENZIE LIMITED
Lay Summary

On 6th June 2011, the UK granted Auden McKenzie Limited Marketing Authorisations (licences) for the medicinal products Midazolam 2 mg/ml and 5 mg/ml Solution for Injection.

Midazolam 2 mg/ml and 5 mg/ml Solution for Injection contain midazolam which belongs to a group of medicines called benzodiazepines.

Midazolam is a short-acting medicine that is used to induce sedation (a very relaxed state of calm, drowsiness or sleep) and relieves anxiety and muscle tension.

Midazolam 2 mg/ml and 5 mg/ml Solution for Injection is used for:
• Conscious sedation (an awake but very relaxed state of calm or drowsiness during a medical test or procedure) in adults and children.
• Sedation of adults and children, in intensive care units.
• Anaesthesia in adults, used alone or with other medicines.
• Premedication (medicine used to cause relaxation, calm and drowsiness before an anaesthetic) in adults and children.

Midazolam 2 mg/ml and 5 mg/ml Solution for Injection should be given only by experienced healthcare professionals (doctor or nurse). It should be given in a place (hospital, clinic or surgery) equipped to monitor and support the patient’s breathing, heart and circulation (cardiovascular function) and recognise the signs of and manage the expected side effects of anaesthesia.

Midazolam 2 mg/ml and 5 mg/ml Solution for Injection may be given in one of four different ways:
• by slow injection into a vein (intravenous injection)
• through a tube into one of your veins (intravenous infusion)
• by injection into a muscle (intramuscular injection)
• into your back passage (rectum).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Midazolam 2 mg/ml and 5 mg/ml Solution for Injection outweigh the risks; hence these Marketing Authorisations have been granted.
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## Module 1

<table>
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<th><strong>Product Name</strong></th>
<th>Midazolam 2 mg/ml and 5 mg/ml Solution for Injection</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
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<td><strong>Active Substance</strong></td>
<td>Midazolam</td>
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<td><strong>Form</strong></td>
<td>2mg/ml and 5mg/ml Solution for Injection</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Auden McKenzie Limited</td>
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<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
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<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>Ireland (IE)</td>
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<td><strong>Procedure Number</strong></td>
<td>UK/H/2511/001-2/DC</td>
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<tr>
<td><strong>End of Procedure</strong></td>
<td>Day 210 – 5th May 2011</td>
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</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Midazolam 2 mg/ml Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml of Midazolam solution for injection contains 2 mg midazolam as midazolam hydrochloride. Also contains 8 mg of sodium chloride in each ml of Midazolam solution for injection. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection.
A clear colourless solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Midazolam is a short-acting sleep-inducing drug that is indicated:

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 children

- 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

4.2 Posology and method of administration
STANDARD DOSAGE

Midazolam is a potent sedative agent that requires titration and slow administration. Titration is strongly recommended to safely obtain the desired level of sedation according to the clinical need, physical status, age and concomitant medication. In adults over 60 years, debilitated or chronically ill patients and paediatric patients, dose should be determined with caution and risk factors related to each patient should be taken into account. Standard dosages are provided in the table below. Additional details are provided in the text following the table.
<table>
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<tr>
<th>Indication</th>
<th>Adults &lt; 60 y</th>
<th>Adults ≥ 60 y / debilitated or chronically ill</th>
<th>Children</th>
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</thead>
<tbody>
<tr>
<td><strong>Conscious sedation</strong></td>
<td>i.v.</td>
<td>i.v.</td>
<td>i.v. in patients 6 months - 5 years</td>
</tr>
<tr>
<td></td>
<td>Initial dose: 2 - 2.5mg</td>
<td>Initial dose: 0.5 - 1mg</td>
<td>Initial dose: 0.05 - 0.1mg/kg</td>
</tr>
<tr>
<td></td>
<td>Titration doses: 1mg</td>
<td>Titration doses: 0.5 - 1mg</td>
<td>Total dose: &lt; 6mg</td>
</tr>
<tr>
<td></td>
<td>Total dose: 3.5 - 7.5mg</td>
<td>Total dose: &lt; 3.5mg</td>
<td><strong>i.v. in patients 6-12 years</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial dose: 0.025 - 0.05mg/kg</td>
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<td></td>
<td></td>
<td></td>
<td>Total dose: &lt; 10mg</td>
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<tr>
<td></td>
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<td></td>
<td><strong>rectal &gt; 6 months</strong></td>
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<td></td>
<td></td>
<td></td>
<td>0.3 - 0.5mg/kg</td>
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<td></td>
<td></td>
<td><strong>i.m. 1 - 15 years</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.08 - 0.2mg/kg</td>
</tr>
<tr>
<td>Anaesthesia premedication</td>
<td>i.v.</td>
<td>i.v.</td>
<td>rectal &gt; 6 months</td>
</tr>
<tr>
<td></td>
<td>1-2 mg repeated</td>
<td>Initial dose: 0.5mg</td>
<td>0.3 - 0.5mg/kg</td>
</tr>
<tr>
<td></td>
<td>i.m.</td>
<td>Slow up titration as needed</td>
<td><strong>i.m. 1 - 15 years</strong></td>
</tr>
<tr>
<td></td>
<td>0.07 - 0.1mg/kg</td>
<td>i.m.</td>
<td>0.08 - 0.2mg/kg</td>
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<tr>
<td></td>
<td></td>
<td>0.025 - 0.05mg/kg</td>
<td><strong>rectal &gt; 6 months</strong></td>
</tr>
<tr>
<td>Anaesthesia induction</td>
<td>i.v.</td>
<td>i.v.</td>
<td>0.3 - 0.5mg/kg</td>
</tr>
<tr>
<td></td>
<td>0.15 - 0.2mg/kg (0.3 -0.35 without premedication)</td>
<td>0.05-0.15 mg/kg (0.15 -0.3 without premedication)</td>
<td><strong>i.m. 1 - 15 years</strong></td>
</tr>
<tr>
<td>Sedative component in combined anaesthesia</td>
<td>i.v.</td>
<td>i.v.</td>
<td>0.08 - 0.2mg/kg</td>
</tr>
<tr>
<td></td>
<td>intermittent doses of 0.03 - 0.1mg/kg or continuous infusion of 0.03 - 0.1mg/kg/h</td>
<td>lower doses than recommended for adults &lt;60 years</td>
<td><strong>rectal &gt; 6 months</strong></td>
</tr>
<tr>
<td>Sedation in ICU</td>
<td>i.v.</td>
<td>i.v.</td>
<td>i.v. in neonates &lt; 32 weeks gestational age</td>
</tr>
<tr>
<td></td>
<td>Loading dose: 0.03 - 0.3mg/kg in increments of 1 - 2.5mg</td>
<td>0.03mg/kg/h</td>
<td>0.03mg/kg/h</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: 0.03 - 0.2mg/kg/h</td>
<td>i.v in neonates&gt; 32 weeks and children up to 6 months</td>
<td><strong>i.v in neonates&gt; 32 weeks and children up to 6 months</strong></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.06mg/kg/h</td>
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<td></td>
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<td></td>
<td><strong>i.v. in patients&gt; 6 months of age</strong></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Loading dose: 0.05 - 0.2mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintenance dose: 0.06 - 0.12mg/kg/h</td>
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</tbody>
</table>

**CONSCIOUS SEDATION DOSAGE**

For conscious sedation prior to diagnostic or surgical intervention, midazolam is administered i.v. The
dose must be individualised 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. The onset of action is about 2 minutes after the injection. Maximum effect is obtained in about 5 to 10 minutes.

**Adults**

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

**In adults below the age of 60** the initial dose is 2 to 2.5 mg given 5 to 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 to 7.5 mg. A total dose greater than 5 mg is usually not necessary.

**In adults over 60 years of age,** debilitated or chronically ill 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 to 1 mg may be given as necessary. Since in these patients the peak effect may be reached less rapidly, additional midazolam should be titrated very slowly and carefully. A total dose greater than 3.5 mg is usually not necessary.

**Children**

**I.V. administration:** midazolam should be titrated slowly to the desired clinical effect. The initial dose of midazolam should be administered over 2 to 3 minutes. One must 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 (mg/kg) 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.

- **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 6 mg. Prolonged sedation and risk of hypoventilation 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 of up to 0.4 mg/kg to a maximum of 10 mg may be necessary. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.

- **Paediatric patients 12 to 16 years of age:** should be dosed as adults.

**Rectal administration:** the total dose of midazolam usually ranges from 0.3 to 0.5 mg/kg. 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. Total dose should be administered at once and repeated rectal administration avoided.

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

**I.M. administration:** the doses used range between 0.05 and 0.15 mg/kg. A total dose greater than 10.0 mg is usually not necessary. This route should only be used in exceptional cases. Rectal administration should be preferred as i.m. injection is painful.

In children 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.

**ANAESTHESIA DOSAGE**

**PREMEDICATION**

Premedication with midazolam given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of apprehension) and preoperative impairment of memory.
Midazolam can also be administered in combination with anticholinergics. For this indication midazolam should be administered i.v. or i.m., deep into a large muscle mass 20 to 60 minutes before induction of anaesthesia, or preferably via the rectal route in children (see below). Close and continuous monitoring of the patients after administration of premedication 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 and II and below 60 years is 1-2 mg i.v. repeated as needed, or 0.07 to 0.1 mg/kg administered i.m.

The dose must be reduced and individualised when midazolam is administered to adults over 60 years of age, debilitated or chronically ill patients. The recommended initial i.v. dose is 0.5 mg and should be slowly uptitrated as needed. A dose of 0.025 to 0.05 mg/kg administered i.m. 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 total dose of midazolam, usually ranging from 0.3 to 0.5 mg/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 10 ml.

**I.M. administration:** As i.m. 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 0.2 mg/kg of midazolam administered i.m. 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 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.

**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 i.v. 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 i.v. induction dose of midazolam should be given slowly in increments. Each increment of not more than 5 mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments.

- In **premedicated adults below the age of 60 years**, an i.v. dose of 0.15 to 0.2 mg/kg will usually suffice.

- In **non-premedicated adults below the age of 60** the dose may be higher (0.3 to 0.35 mg/kg i.v.). 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 0.6 mg/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 significantly be reduced, eg., down to 0.05-0.15 mg/kg administered i.v. 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 0.3 mg/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 0.25 mg/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 i.v. doses (range between 0.03 and 0.1 mg/kg) or continuous infusion of i.v. midazolam (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, 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**

I.V. 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.

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.

I.V. 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 i.v. infusion, starting at 0.03 mg/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 is 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 i.v. 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 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 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 body weight, midazolam solutions with concentrations higher than 1mg/ml are not recommended. Higher concentrations should be diluted to 1mg/ml.

*Use in Special Populations*

*Renal Impairment*

In patients with renal impairment (creatinine clearance < 10 ml/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 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 30 ml/min) receiving midazolam for induction of anaesthesia.

*Hepatic Impairment*

Hepatic impairment reduces the clearance of i.v. 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.

Midazolam is essentially ‘sodium free’ as it contains less than 1 mmol sodium (23 mg) per ampoule.

4.3 Contraindications

Use of this drug in patients with known hypersensitivity to benzodiazepines or to any excipient of the product.

Use of this drug for conscious sedation in patients with severe respiratory failure or acute respiratory depression.

4.4 Special warnings and precautions for use

Midazolam should be administered only by experienced physicians in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function and by persons specifically trained in the recognition and management of expected adverse events including respiratory and cardiac resuscitation.

Severe cardiorespiratory adverse events have been reported. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest. Such life-threatening incidents are more likely to occur when the injection is given too rapidly or when a high dosage is administered (see section 4.8).

Special caution is required for the indication of conscious sedation in patients with impaired respiratory function.

Paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful respiratory rate and oxygen saturation monitoring are essential.

When midazolam is used for premedication, adequate observation of the patient after administration is mandatory as interindividual sensitivity varies and symptoms of overdose may occur.

Special caution should be exercised when administering midazolam to high-risk patients:

- adults over 60 years of age
- chronically ill or debilitated patients, e.g.
- patients with chronic respiratory insufficiency
- patients with chronic renal failure, impaired hepatic function or with impaired cardiac function
• paediatric patients specially those with cardiovascular instability.

These high-risk patients require lower dosages (see section 4.2) and should be continuously monitored for early signs of alterations of vital functions.

As with any substance with CNS depressant and/or muscle-relaxant properties, particular care should be taken when administering midazolam to a patient with myasthenia gravis.

_Tolerance_

Some loss of efficacy has been reported when midazolam was used as long-term sedation in intensive care units (ICU).

_Dependence_

When midazolam is used in long-term sedation in ICU, it should be borne in mind that physical dependence on midazolam may develop. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse (see section 4.8).

_Withdrawal symptoms_

During prolonged treatment with midazolam in ICU, physical dependence may develop. Therefore, abrupt termination of the treatment will be accompanied by withdrawal symptoms. The following symptoms may occur: headaches, muscle pain, anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood changes, hallucinations and convulsions. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, it is recommended to decrease doses gradually.

_Amnesia_

Midazolam causes anterograde amnesia (frequently this effect is very desirable in situations such as before and during surgical and diagnostic procedures), the duration of which is directly related to the administered dose. Prolonged amnesia can present problems in outpatients, who are scheduled for discharge following intervention. After receiving midazolam parenterally, patients should be discharged from hospital or consulting room only if accompanied by an attendant.

_Paradoxical reactions_

Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, have been reported to occur with midazolam. These reactions may occur with high doses and/or when the injection is given rapidly. The highest incidence to such reactions has been reported among children and the elderly.

_Altered elimination of midazolam_

Midazolam elimination may be altered in patients receiving compounds that inhibit or induce CYP3A4 and the dose of midazolam may need to be adjusted accordingly (see section 4.5).

Midazolam elimination may also be delayed in patients with liver dysfunction, low cardiac output and in neonates (see section 5.2).

_Preterm infants and neonates_

Due to an increased risk of apnoea, extreme caution is advised when sedating preterm and former preterm non intubated patients. Careful monitoring of respiratory rate and oxygen saturation is required.

Rapid injection should be avoided in the neonatal population.

Neonates have reduced and/or immature organ function and are also vulnerable to profound and/or prolonged respiratory effects of midazolam.

Adverse haemodynamic events have been reported in paediatric patients with cardiovascular instability; rapid intravenous administration should be avoided in this population.
Paediatric patients less than 6 months

In this population, midazolam is indicated for sedation in ICU only. Paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful respiratory rate and oxygen saturation monitoring are essential (see also section 'Preterm infants' above).

Concomitant use of alcohol / CNS depressants

The concomitant use of midazolam with alcohol or and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of midazolam possibly including severe sedation or clinically relevant respiratory depression (see section 4.5).

Medical history of alcohol or drug abuse

Midazolam as other benzodiazepines should be avoided in patients with a medical history of alcohol or drug abuse.

Discharging criteria

After receiving midazolam, patients should be discharged from hospital or consulting room only when recommended by treating physician and if accompanied by an attendant. It is recommended that the patient is accompanied when returning home after discharge.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic Interactions

Midazolam is metabolised by CYP3A4. Inhibitors and inducers of CYP3A4 have the potential to respectively increase and decrease the plasma concentrations and, subsequently, the effects of midazolam thus requiring dose adjustments accordingly. Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral as compared to i.v. midazolam, in particular since CYP3A4 also exists in the upper gastro-intestinal tract. This is because for the oral route both systemic clearance and availability will be altered while for the parenteral route only the change in the systemic clearance becomes effective. After a single dose of IV midazolam, the consequence on the maximal clinical effect due to CYP3A4 inhibition will be minor while the duration of effect may be prolonged. However, after prolonged dosing of midazolam, both the magnitude and duration of effect will be increased in the presence of CYP3A4 inhibition.

There are no available studies on CYP3A4 modulation on the pharmacokinetics of midazolam after rectal and intramuscular administration. It is expected that these interactions will be less pronounced for the rectal than for the oral route because the gastro-intestinal tract is by-passed whereas after i.m. administration the effects of CYP3A modulation should not substantially differ from those seen with i.v. midazolam.

It is therefore recommended to carefully monitor the clinical effects and vital signs during the use of midazolam, taking into account that they may be stronger and last longer after co-administration of a CYP3A4 inhibitor, be it given only once. Notably, administration of high doses or long-term infusions of midazolam to patients receiving strong CYP3A4 inhibitors, e.g. during intensive care, may result in long-lasting hypnotic effects, delayed recovery and respiratory depression, thus requiring dose adjustments.

With respect to induction, it should be considered that the inducing process needs several days to reach its maximum effect and also several days to dissipate. Contrary to a treatment of several days with an inducer, a short-term treatment is expected to result in less apparent DDI with midazolam. However, for strong inducers a relevant induction even after short-term treatment cannot be excluded.

Midazolam is not known to change the pharmacokinetics of other drugs.

Drugs that inhibit CYP3A4

Aazole antifungals
• **Ketoconazole** increased the plasma concentrations of intravenous midazolam by 5-fold while the terminal half-life increased by about 3-fold. If parenteral midazolam is co-administered with the strong CYP3A4 inhibitor ketoconazole, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Staggered dosing and dosage adjustment should be considered, especially if more than a single i.v. dose of midazolam is administered. The same recommendation may apply also for other azole antifungals (see further), since increased sedative effects of IV midazolam, although lesser, are reported.

• **Voriconazole** increased the exposure of intravenous midazolam by 3-fold whereas its elimination half-life increased by about 3-fold.

• **Fluconazole and itraconazole** both increased the plasma concentrations of intravenous midazolam by 2 – 3-fold associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole, respectively.

• **Posaconazole** increased the plasma concentrations of intravenous midazolam by about 2-fold.

• It should be kept in mind that if midazolam is given orally, its exposure will drastically be higher than the above-mentioned ones, notably with ketoconazole, itraconazole, voriconazole.

Midazolam ampoules are not indicated for oral administration.

**Macrolide antibiotics**

• **Erythromycin** resulted in an increase in the plasma concentrations of intravenous midazolam by about 1.6 – 2-fold associated with an increase of the terminal half-life of midazolam by 1.5 – 1.8-fold.

• **Clarithromycin** increased the plasma concentrations of midazolam by up to 2.5-fold associated with an increase in terminal half-life by 1.5 – 2-fold.

Additional information from oral midazolam

• **Roxithromycin:** While no information on roxithromycin with IV midazolam is available, the mild effect on the terminal half-life of oral midazolam tablet, increasing by 30%, indicates that the effects of roxithromycin on intravenous midazolam may be minor.

**HIV Protease inhibitors**

• **Saquinavir and other HIV protease inhibitors:** Co-administration with protease inhibitors may cause a large increase in the concentration of midazolam. Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of intravenous midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life. If parenteral midazolam is coadministered with HIV protease inhibitors, treatment setting should follow the description in the above section for azole antifungals, ketoconazole.

Additional information from oral midazolam

Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore protease inhibitors should not be co-administered with orally administered midazolam.

**Calcium-channel blockers**

• **Diltiazem:** A single dose of diltiazem increased the plasma concentrations of intravenous midazolam by about 25% and the terminal half-life was prolonged by 43%.

Additional information from oral midazolam

• **Verapamil / diltiazem** increased the plasma concentrations of oral midazolam by 3- and 4-fold, respectively. The terminal half-life of midazolam was increased by 41% and 49% respectively.

**Various drugs/Herbs**

• **Atorvastatin** showed a 1.4-fold increase in plasma concentrations of IV midazolam compared to control
group.

*Additional information from oral midazolam*

- **Nefazodone** increased the plasma concentrations of oral midazolam by 4.6-fold with an increase of its terminal half-life by 1.6-fold.

- **Aprepitant** dose dependently increased the plasma concentrations of oral midazolam by 3.3-fold after 80 mg/day associated with an increase in terminal half-life by ca. 2-fold.

*Drugs that induce CYP3A4*

- **Rifampicin** decreased the plasma concentrations of intravenous midazolam by about 60% after 7 days of rifampicin 600mg o.d. The terminal half-life decreased by about 50-60%.

*Additional information from oral midazolam*

- **Rifampicin** decreased the plasma concentrations of oral midazolam by 96% in healthy subjects and its psychomotor effects were almost totally lost.

- **Carbamazepine / phenytoin**: Repeat dosages of carbamazepine or phenytoin resulted in a decrease in plasma concentrations of oral midazolam by up to 90% and a shortening of the terminal half-life by 60%.

- **Efavirenz**: The 5-fold increase in the ratio of the CYP3A4 generated metabolite a-hydroxymidazolam to midazolam confirms its CYP3A4-inducing effect.

*Herbs and food*

- **St John's Wort** decreased plasma concentrations of midazolam by about 20 - 40 % associated with a decrease in terminal half-life of about 15 - 17%. Depending on the specific St John's Wort extract, the CYP3A4-inducing effect may vary.

*Pharmacodynamic Drug-Drug Interactions (DDI)*

The co-administration of midazolam with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression.

Examples include opiate derivatives (be they used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; sedative antidepressants, non recent H1-antihistamines and centrally acting antihypertensive drugs.

Alcohol may markedly enhance the sedative effect of midazolam. Alcohol intake should be strongly avoided in case of midazolam administration (see section 4.4).

Midazolam decreases the minimum alveolar concentration (MAC) of inhalational anaesthetics.

### 4.6 Pregnancy and lactation

Insufficient data are available on midazolam to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but fetotoxicity was observed as with other benzodiazepines. No data on exposed pregnancies are available for the first two trimesters of pregnancy.

The administration of high doses of midazolam in the last trimester of pregnancy, during labour or when used as an induction agent of anaesthesia for caesarean section has been reported to produce maternal or fetal adverse effects (inhalation risk in mother, irregularities in the fetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the neonate).

Moreover, infants born from mothers who received benzodiazepines chronically during the latter stage of pregnancy might have developed physical dependence and might be at some risk of developing withdrawal symptoms in the postnatal period.

Consequently, midazolam may be used during pregnancy if clearly necessary but it is preferable to avoid using it for caesarean sections.
The risk for neonate should be taken into account in case of administration of midazolam for any surgery near the term.

Midazolam passes in low quantities into breast milk. Nursing mothers should be advised to discontinue breast-feeding for 24 hours following administration of midazolam.

4.7 Effects on ability to drive and use machines
Midazolam has a major influence on the ability to drive and use machines.

Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive or use machines. Prior to receiving midazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered. The physician should decide when these activities may be resumed. It is recommended that the patient is accompanied when returning home after discharge.

4.8 Undesirable effects
The following undesirable effects have been reported (very rarely) to occur when midazolam is injected:

**Immune System Disorders:** Generalised hypersensitivity reactions (skin reactions, cardiovascular reactions, bronchospasm), anaphylactic shock.

**Psychiatric Disorders:** Confusional state, euphoric mood, hallucinations.

Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, have been reported, particularly among children and the elderly.

**Dependence:** Use of midazolam - even in therapeutic doses - may lead to the development of physical dependence. After prolonged i.v. administration, discontinuation, especially abrupt discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions (see section 4.4).

**Nervous System Disorders:** Prolonged sedation, decreased alertness, somnolence, headache, dizziness, ataxia, postoperative sedation, anterograde amnesia, the duration of which is directly related to the administered dose. Anterograde amnesia may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported.

Convulsions have been reported in premature infants and neonates.

**Cardiac Disorders:** Severe cardiorespiratory adverse events have occurred. These have included cardiac arrest, hypotension, bradycardia, vasodilating effects. Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered (see section 4.4).

**Respiratory Disorders:** Severe cardiorespiratory adverse events including respiratory depression, apnoea, respiratory arrest, dyspnoea, laryngospasm have been reported. Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered (see section 4.4). Hiccup.

**Gastrointestinal System Disorders:** Nausea, vomiting, constipation, dry mouth.

**Skin and Appendages Disorders:** Skin rash urticaria, pruritus.

**General and Application Site Disorders:** Fatigue, erythema and pain on injection site, thrombophlebitis, thrombosis.

**Injury, Poisoning and Procedural Complications:** An increased risk for falls and fractures has been recorded in elderly benzodiazepine users.
4.9 Overdose

Symptoms
Like other benzodiazepines, midazolam commonly causes drowsiness, ataxia, dysarthria and nystagmus. Overdose of midazolam is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnoea, hypotension, cardiorespiratory depression and in rare cases to coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.

Treatment
Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.

If taken orally further absorption should be prevented using an appropriate method e.g. treatment within 1-2 hours with activated charcoal. If activated charcoal is used airway protection is imperative for drowsy patients. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.

If CNS depression is severe consider the use of flumazenil, a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of this drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group:
Hypnotics and sedatives (benzodiazepine derivatives), ATC code: N05CD08.

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 to form water-soluble salts with acids. These produce a stable and well tolerated injection solution.

The pharmacological action of midazolam is characterised by short duration because of rapid metabolic transformation. Midazolam has a 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 remember events that occurred during the maximal activity of the compound).

5.2 Pharmacokinetic properties
Absorption after i.m. injection
Absorption of midazolam from muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. The absolute bioavailability after i.m. 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 i.v., 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.
Metabolism
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 - 500ml/min. Midazolam is excreted mainly by renal route (60 - 80% of the injected dose) and recovered as glucuroconjugated 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 i.v. 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 i.v. 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 (see section 4.4).

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 (see section 4.4).

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 (see section 4.4).

5.3 Preclinical safety data
There are no preclinical data of relevance to the prescriber that are additional to those already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium Chloride
Hydrochloric Acid
Sodium Hydroxide (pH adjustment)
Water for Injections

6.2 Incompatibilities
This medicinal product must not be diluted with other solutions for parenteral use than those mentioned in section 6.6 Special precautions for disposal and other handling.
Midazolam is incompatible with alkaline solutions (due to reduced solubility and precipitation of midazolam) and some medicines. Compatibility must be checked before administration, if intended to be mixed with other drugs.

Published data show that midazolam injection is incompatible with alkaline injections such as some antibiotic and steroid injections, bumetanide, furosemide, omeprazole sodium, sodium bicarbonate and thiopental sodium.

It is also incompatible with aciclovir, albumin, amoxicillin sodium, ampicillin sodium, alteplase, acetzolamide disodium, ceftazidime, dexamethasone sodium phosphate, diazepam, enoximone, flecainide acetate, fluoroacil sodium, furosemide, hydrocortisone sodium succinate, imipenem, mezlocillin sodium, nafcillin, phenobarbital sodium, phenytoin sodium, potassium canrenoate, sulbactam sodium, theophylline, toremifene, urokinase, dimenhydrinate, foscarnet sodium, imipenem with cilastin, pentobarbital sodium, clonidine hydrochloride, perphenazine, prochlorperazine, ranitidine, trimethoprim-sulfamethoxazole, methotrexate sodium and certain parenteral solutions, including parenteral nutrition solutions.

Mixture or dilution with Hartmann's solution is not recommended, as the potency of midazolam decreases.

6.3 Shelf life
24 months (unopened)
24 hours (dilutions)

6.4 Special precautions for storage
Keep the ampoules in the original carton to protect from light.

6.5 Nature and contents of container
Type I clear glass ampoules containing 5 ml.
5 or 10 ampoules per carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
The injection is for single use only and should be used immediately after opening. The injection should not be used if particles are present. Any unused portion should be discarded.

Midazolam ampoule solution is stable, both physically and chemically, for up to 24 hours at room temperature when mixed with 500ml infusion fluids containing Dextrose 4% with Sodium Chloride 0.18%, Dextrose 5% or Sodium Chloride 0.9%.

There is no evidence of the adsorption of midazolam on to the plastic of infusion apparatus or syringes.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, the product 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 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

7 MARKETING AUTHORISATION HOLDER
Auden Mckenzie (Pharma Division) Ltd
McKenzie House
Bury Street
Ruislip
Middlesex
HA4 7TL
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 17507/0031

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/06/2011
DATE OF REVISION OF THE TEXT
06/06/2011
1 NAME OF THE MEDICINAL PRODUCT
Midazolam 5 mg/ml Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml of Midazolam solution for injection contains 5 mg midazolam as midazolam hydrochloride. Also contains 8 mg of sodium chloride in each ml of Midazolam solution for injection. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection.
A clear colourless solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Midazolam is a short-acting sleep-inducing drug that is indicated:

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 children

- 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

4.2 Posology and method of administration
STANDARD DOSAGE
Midazolam is a potent sedative agent that requires titration and slow administration. Titration is strongly recommended to safely obtain the desired level of sedation according to the clinical need, physical status, age and concomitant medication. In adults over 60 years, debilitated or chronically ill patients and paediatric patients, dose should be determined with caution and risk factors related to each patient should be taken into account. Standard dosages are provided in the table below. Additional details are provided in the text following the table.
<table>
<thead>
<tr>
<th>Indication</th>
<th>Adults &lt; 60 y</th>
<th>Adults ≥ 60 y / debilitated or chronically ill</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conscious sedation</td>
<td>i.v.</td>
<td>i.v.</td>
<td>i.v. in patients 6 months - 5 years</td>
</tr>
<tr>
<td></td>
<td>Initial dose: 2 - 2.5mg</td>
<td>Initial dose: 0.5 - 1mg</td>
<td>Initial dose: 0.05 - 0.1mg /kg</td>
</tr>
<tr>
<td></td>
<td>Titration doses: 1mg</td>
<td>Titration doses: 0.5 - 1mg</td>
<td>Total dose: &lt; 6mg</td>
</tr>
<tr>
<td></td>
<td>Total dose: 3.5 - 7.5mg</td>
<td>Total dose: &lt; 3.5mg</td>
<td>i.v. in patients 6-12 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial dose: 0.025 - 0.05mg /kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total dose: &lt; 10mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rectal &gt; 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.3 - 0.5mg /kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>i.m. 1 - 15 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.05 - 0.15mg /kg</td>
</tr>
<tr>
<td>Anaesthesia premedication</td>
<td>i.v.</td>
<td>i.v.</td>
<td>reval &gt; 6 months</td>
</tr>
<tr>
<td></td>
<td>1-2 mg repeated</td>
<td>Initial dose: 0.5mg</td>
<td>0.3 - 0.5mg /kg</td>
</tr>
<tr>
<td>i.m.</td>
<td>0.07 - 0.1mg/kg</td>
<td>Slow uptitration as needed</td>
<td>i.m. 1 - 15 years</td>
</tr>
<tr>
<td></td>
<td>0.025 - 0.05mg/kg</td>
<td></td>
<td>0.08 - 0.2mg /kg</td>
</tr>
<tr>
<td>Anaesthesia induction</td>
<td>i.v.</td>
<td>i.v.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.15 - 0.2mg/kg (0.3 -0.35 without premedication)</td>
<td>0.05-0.15 mg/kg (0.15 -0.3 without premedication)</td>
<td></td>
</tr>
<tr>
<td>Sedative component in combined anaesthesia</td>
<td>i.v.</td>
<td>i.v.</td>
<td>i.v. in neonates &lt; 32 weeks gestational age</td>
</tr>
<tr>
<td></td>
<td>intermittent doses of 0.03 - 0.1mg/kg or continuous infusion of 0.03 - 0.1mg/kg/h</td>
<td>lower doses than recommended for adults &lt;60 years</td>
<td>0.03mg/kg/h</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>i.v.</td>
<td>i.v in neonates &gt; 32 weeks and children up to 6 months</td>
</tr>
<tr>
<td></td>
<td>Loading dose: 0.03 - 0.3mg/kg in increments of 1 - 2.5mg</td>
<td></td>
<td>0.06mg/kg/h</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: 0.03 - 0.2mg/kg/h</td>
<td>i.v. in patients &gt; 6 months of age</td>
<td>Loading dose: 0.05 - 0.2mg /kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintenance dose: 0.06 - 0.12mg /kg</td>
</tr>
</tbody>
</table>

**CONSCIOUS SEDATION DOSAGE**

For conscious sedation prior to diagnostic or surgical intervention, midazolam is administered i.v. The
dose must be individualised 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. The onset of action is about 2 minutes after the injection. Maximum effect is obtained in about 5 to 10 minutes.

**Adults**

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

In adults below the age of 60 the initial dose is 2 to 2.5 mg given 5 to 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 to 7.5 mg. A total dose greater than 5 mg is usually not necessary.

In adults over 60 years of age, debilitated or chronically ill 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 to 1 mg may be given as necessary. Since in these patients the peak effect may be reached less rapidly, additional midazolam should be titrated very slowly and carefully. A total dose greater than 3.5 mg is usually not necessary.

**Children**

**I.V. administration:** midazolam should be titrated slowly to the desired clinical effect. The initial dose of midazolam should be administered over 2 to 3 minutes. One must 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 (mg/kg) 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.

• 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 6 mg. Prolonged sedation and risk of hypoventilation 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 of up to 0.4 mg/kg to a maximum of 10 mg may be necessary. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.

• Paediatric patients 12 to 16 years of age: should be dosed as adults.

**Rectal administration:** the total dose of midazolam usually ranges from 0.3 to 0.5 mg/kg. 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. Total dose should be administered at once and repeated rectal administration avoided.

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

**I.M. administration:** the doses used range between 0.05 and 0.15 mg/kg. A total dose greater than 10.0 mg is usually not necessary. This route should only be used in exceptional cases. Rectal administration should be preferred as i.m. injection is painful.

In children 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.

**ANAESTHESIA DOSAGE**

**PREMEDICATION**

Premedication with midazolam given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of apprehension) and preoperative impairment of memory.
Par Midazolam 2 mg/ml and 5 mg/ml Solution for Injection

Midazolam can also be administered in combination with anticholinergics. For this indication midazolam should be administered i.v. or i.m., deep into a large muscle mass 20 to 60 minutes before induction of anaesthesia, or preferably via the rectal route in children (see below). Close and continuous monitoring of the patients after administration of premedication 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 and II and below 60 years is 1-2 mg i.v. repeated as needed, or 0.07 to 0.1 mg/kg administered i.m.

The dose must be reduced and individualised when midazolam is administered to adults over 60 years of age, debilitated or chronically ill patients. The recommended initial i.v. dose is 0.5 mg and should be slowly uptitrated as needed. A dose of 0.025 to 0.05 mg/kg administered i.m. 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 total dose of midazolam, usually ranging from 0.3 to 0.5 mg/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 10 ml.

I.M. administration: As i.m. 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 0.2 mg/kg of midazolam administered i.m. 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 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.

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 i.v. 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 i.v. induction dose of midazolam should be given slowly in increments. Each increment of not more than 5 mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments.

• In premedicated adults below the age of 60 years, an i.v. dose of 0.15 to 0.2 mg/kg will usually suffice.

• In non-premedicated adults below the age of 60 the dose may be higher (0.3 to 0.35 mg/kg i.v.). 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 0.6 mg/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 significantly be reduced, eg., down to 0.05- 0.15 mg/kg administered i.v. 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 0.3 mg/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 0.25 mg/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 i.v. doses (range between 0.03 and 0.1 mg/kg) or continuous infusion of i.v. midazolam (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, 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*

I.V. 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.

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.

I.V. 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 i.v. infusion, starting at 0.03 mg/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 is 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 i.v. 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 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 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 haodynamic 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 body weight, midazolam solutions with concentrations higher than 1mg/ml are not recommended. Higher concentrations should be diluted to 1mg/ml.

**Use in Special Populations**

**Renal Impairment**

In patients with renal impairment (creatinine clearance < 10 ml/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 was considerably increased most likely due to accumulation of \( \alpha \)-hydroxymidazolam glucuronide.

There is no specific data in patients with severe renal impairment (creatinine clearance below 30 ml/min) receiving midazolam for induction of anaesthesia.

**Hepatic Impairment**

Hepatic impairment reduces the clearance of i.v. 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.

Midazolam is essentially ‘sodium free’ as it contains less than 1 mmol sodium (23 mg) per ampoule.

### 4.3 Contraindications

Use of this drug in patients with known hypersensitivity to benzodiazepines or to any excipient of the product.

Use of this drug for conscious sedation in patients with severe respiratory failure or acute respiratory depression.

### 4.4 Special warnings and precautions for use

Midazolam should be administered only by experienced physicians in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function and by persons specifically trained in the recognition and management of expected adverse events including respiratory and cardiac resuscitation.

Severe cardiorespiratory adverse events have been reported. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest. Such life-threatening incidents are more likely to occur when the injection is given too rapidly or when a high dosage is administered (see section 4.8).

Special caution is required for the indication of conscious sedation in patients with impaired respiratory function.

Paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful respiratory rate and oxygen saturation monitoring are essential.

When midazolam is used for premedication, adequate observation of the patient after administration is mandatory as interindividual sensitivity varies and symptoms of overdose may occur.

Special caution should be exercised when administering midazolam to high-risk patients:
- adults over 60 years of age
- chronically ill or debilitated patients, e.g.
- patients with chronic respiratory insufficiency
- patients with chronic renal failure, impaired hepatic function or with impaired cardiac function
- paediatric patients specially those with cardiovascular instability.

These high-risk patients require lower dosages (see section 4.2) and should be continuously monitored for early signs of alterations of vital functions.

As with any substance with CNS depressant and/or muscle-relaxant properties, particular care should be taken when administering midazolam to a patient with myasthenia gravis.

**Tolerance**

Some loss of efficacy has been reported when midazolam was used as long-term sedation in intensive care units (ICU).

**Dependence**

When midazolam is used in long-term sedation in ICU, it should be borne in mind that physical dependence on midazolam may develop. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse (see section 4.8).

**Withdrawal symptoms**

During prolonged treatment with midazolam in ICU, physical dependence may develop. Therefore, abrupt termination of the treatment will be accompanied by withdrawal symptoms. The following symptoms may occur: headaches, muscle pain, anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood changes, hallucinations and convulsions. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, it is recommended to decrease doses gradually.

**Amnesia**

Midazolam causes anterograde amnesia (frequently this effect is very desirable in situations such as before and during surgical and diagnostic procedures), the duration of which is directly related to the administered dose. Prolonged amnesia can present problems in outpatients, who are scheduled for discharge following intervention. After receiving midazolam parenterally, patients should be discharged from hospital or consulting room only if accompanied by an attendant.

**Paradoxical reactions**

Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, have been reported to occur with midazolam. These reactions may occur with high doses and/or when the injection is given rapidly. The highest incidence to such reactions has been reported among children and the elderly.

**Altered elimination of midazolam**

Midazolam elimination may be altered in patients receiving compounds that inhibit or induce CYP3A4 and the dose of midazolam may need to be adjusted accordingly (see section 4.5).

Midazolam elimination may also be delayed in patients with liver dysfunction, low cardiac output and in neonates (see section 5.2).

**Preterm infants and neonates**

Due to an increased risk of apnoea, extreme caution is advised when sedating preterm and former preterm non intubated patients. Careful monitoring of respiratory rate and oxygen saturation is required.

Rapid injection should be avoided in the neonatal population.

Neonates have reduced and/or immature organ function and are also vulnerable to profound and/or prolonged respiratory effects of midazolam.

Adverse haemodynamic events have been reported in paediatric patients with cardiovascular instability; rapid intravenous administration should be avoided in this population.
Paediatric patients less than 6 months

In this population, midazolam is indicated for sedation in ICU only. Paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful respiratory rate and oxygen saturation monitoring are essential (see also section 'Preterm infants' above).

Concomitant use of alcohol / CNS depressants

The concomitant use of midazolam with alcohol or and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of midazolam possibly including severe sedation or clinically relevant respiratory depression (see section 4.5).

Medical history of alcohol or drug abuse

Midazolam as other benzodiazepines should be avoided in patients with a medical history of alcohol or drug abuse.

Discharging criteria

After receiving midazolam, patients should be discharged from hospital or consulting room only when recommended by treating physician and if accompanied by an attendant. It is recommended that the patient is accompanied when returning home after discharge.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic Interactions

Midazolam is metabolised by CYP3A4. Inhibitors and inducers of CYP3A4 have the potential to respectively increase and decrease the plasma concentrations and, subsequently, the effects of midazolam thus requiring dose adjustments accordingly. Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral as compared to i.v. midazolam, in particular since CYP3A4 also exists in the upper gastro-intestinal tract. This is because for the oral route both systemic clearance and availability will be altered while for the parenteral route only the change in the systemic clearance becomes effective. After a single dose of IV midazolam, the consequence on the maximal clinical effect due to CYP3A4 inhibition will be minor while the duration of effect may be prolonged. However, after prolonged dosing of midazolam, both the magnitude and duration of effect will be increased in the presence of CYP3A4 inhibition.

There are no available studies on CYP3A4 modulation on the pharmacokinetics of midazolam after rectal and intramuscular administration. It is expected that these interactions will be less pronounced for the rectal than for the oral route because the gastro-intestinal tract is by-passed whereas after i.m. administration the effects of CYP3A modulation should not substantially differ from those seen with i.v. midazolam.

It is therefore recommended to carefully monitor the clinical effects and vital signs during the use of midazolam, taking into account that they may be stronger and last longer after co-administration of a CYP3A4 inhibitor, be it given only once. Notably, administration of high doses or long-term infusions of midazolam to patients receiving strong CYP3A4 inhibitors, e.g. during intensive care, may result in long-lasting hypnotic effects, delayed recovery and respiratory depression, thus requiring dose adjustments.

With respect to induction, it should be considered that the inducing process needs several days to reach its maximum effect and also several days to dissipate. Contrary to a treatment of several days with an inducer, a short-term treatment is expected to result in less apparent DDI with midazolam. However, for strong inducers a relevant induction even after short-term treatment cannot be excluded.

Midazolam is not known to change the pharmacokinetics of other drugs.

Drugs that inhibit CYP3A4

Azole antifungals
• Ketoconazole increased the plasma concentrations of intravenous midazolam by 5-fold while the terminal half-life increased by about 3-fold. If parenteral midazolam is co-administered with the strong CYP3A4 inhibitor ketoconazole, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Staggered dosing and dosage adjustment should be considered, especially if more than a single i.v. dose of midazolam is administered. The same recommendation may apply also for other azole antifungals (see further), since increased sedative effects of IV midazolam, although lesser, are reported.

• Voriconazole increased the exposure of intravenous midazolam by 3-fold whereas its elimination half-life increased by about 3-fold.

• Fluconazole and itraconazole both increased the plasma concentrations of intravenous midazolam by 2 – 3-fold associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole, respectively.

• Posaconazole increased the plasma concentrations of intravenous midazolam by about 2-fold.

• It should be kept in mind that if midazolam is given orally, its exposure will drastically be higher than the above-mentioned ones, notably with ketoconazole, itraconazole, voriconazole.

Midazolam ampoules are not indicated for oral administration.

Macrolide antibiotics

• Erythromycin resulted in an increase in the plasma concentrations of intravenous midazolam by about 1.6 – 2-fold associated with an increase of the terminal half-life of midazolam by 1.5 – 1.8-fold.

• Clarithromycin increased the plasma concentrations of midazolam by up to 2.5-fold associated with an increase in terminal half-life by 1.5 – 2-fold.

Additional information from oral midazolam

• Roxithromycin: While no information on roxithromycin with IV midazolam is available, the mild effect on the terminal half-life of oral midazolam tablet, increasing by 30%, indicates that the effects of roxithromycin on intravenous midazolam may be minor.

HIV Protease inhibitors

• Saquinavir and other HIV protease inhibitors: Co-administration with protease inhibitors may cause a large increase in the concentration of midazolam. Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of intravenous midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life. If parenteral midazolam is coadministered with HIV protease inhibitors, treatment setting should follow the description in the above section for azole antifungals, ketoconazole.

Additional information from oral midazolam

Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore protease inhibitors should not be co-administered with orally administered midazolam.

Calcium-channel blockers

• Diltiazem: A single dose of diltiazem increased the plasma concentrations of intravenous midazolam by about 25% and the terminal half-life was prolonged by 43%.

Additional information from oral midazolam

• Verapamil / diltiazem increased the plasma concentrations of oral midazolam by 3- and 4-fold, respectively. The terminal- half-life of midazolam was increased by 41% and 49% respectively.

Various drugs/Herbs

• Atorvastatin showed a 1.4-fold increase in plasma concentrations of IV midazolam compared to control
Additional information from oral midazolam

- **Nefazodone** increased the plasma concentrations of oral midazolam by 4.6-fold with an increase of its terminal half-life by 1.6-fold.

- **Aprepitant** dose dependently increased the plasma concentrations of oral midazolam by 3.3-fold after 80 mg/day associated with an increase in terminal half-life by ca. 2-fold.

**Drugs that induce CYP3A4**

- **Rifampicin** decreased the plasma concentrations of intravenous midazolam by about 60% after 7 days of rifampicin 600mg o.d. The terminal half-life decreased by about 50-60%.

Additional information from oral midazolam

- **Rifampicin** decreased the plasma concentrations of oral midazolam by 96% in healthy subjects and its psychomotor effects were almost totally lost.

- **Carbamazepine / phenytoin**: Repeat dosages of carbamezepine or phenytoin resulted in a decrease in plasma concentrations of oral midazolam by up to 90% and a shortening of the terminal half-life by 60%.

- **Efavirenz**: The 5-fold increase in the ratio of the CYP3A4 generated metabolite a-hydroxymidazolam to midazolam confirms its CYP3A4-inducing effect.

**Herbs and food**

- **St John's Wort** decreased plasma concentrations of midazolam by about 20 - 40 % associated with a decrease in terminal half-life of about 15 - 17%. Depending on the specific St John's Wort extract, the CYP3A4-inducing effect may vary.

**Pharmacodynamic Drug-Drug Interactions (DDI)**

The co-administration of midazolam with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression.

Examples include opiate derivatives (be they used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; sedative antidepressants, non recent H1-antihistamines and centrally acting antihypertensive drugs.

Alcohol may markedly enhance the sedative effect of midazolam. Alcohol intake should be strongly avoided in case of midazolam administration (see section 4.4).

Midazolam decreases the minimum alveolar concentration (MAC) of inhalational anaesthetics.

**4.6 Pregnancy and lactation**

Insufficient data are available on midazolam to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but fetotoxicity was observed as with other benzodiazepines. No data on exposed pregnancies are available for the first two trimesters of pregnancy.

The administration of high doses of midazolam in the last trimester of pregnancy, during labour or when used as an induction agent of anaesthesia for caesarean section has been reported to produce maternal or fetal adverse effects (inhalation risk in mother, irregularities in the fetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the neonate).

Moreover, infants born from mothers who received benzodiazepines chronically during the latter stage of pregnancy might have developed physical dependence and might be at some risk of developing withdrawal symptoms in the postnatal period.

Consequently, midazolam may be used during pregnancy if clearly necessary but it is preferable to avoid using it for caesarean sections.
The risk for neonate should be taken into account in case of administration of midazolam for any surgery near the term.

Midazolam passes in low quantities into breast milk. Nursing mothers should be advised to discontinue breast-feeding for 24 hours following administration of midazolam.

4.7 Effects on ability to drive and use machines
Midazolam has a major influence on the ability to drive and use machines.

Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive or use machines. Prior to receiving midazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered. The physician should decide when these activities may be resumed. It is recommended that the patient is accompanied when returning home after discharge.

4.8 Undesirable effects
The following undesirable effects have been reported (very rarely) to occur when midazolam is injected:

**Immune System Disorders:** Generalised hypersensitivity reactions (skin reactions, cardiovascular reactions, bronchospasm), anaphylactic shock.

**Psychiatric Disorders:** Confusional state, euphoric mood, hallucinations.

Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, have been reported, particularly among children and the elderly.

**Dependence:** Use of midazolam - even in therapeutic doses - may lead to the development of physical dependence. After prolonged i.v. administration, discontinuation, especially abrupt discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions (see section 4.4).

**Cardiac Disorders:** Severe cardiorespiratory adverse events have occurred. These have included cardiac arrest, hypotension, bradycardia, vasodilating effects. Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered (see section 4.4).

**Respiratory Disorders:** Severe cardiorespiratory adverse events including respiratory depression, apnoea, respiratory arrest, dyspnoea, laryngospasm have been reported. Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered (see section 4.4). Hiccup.

**Gastrointestinal System Disorders:** Nausea, vomiting, constipation, dry mouth.

**Skin and Appendages Disorders:** Skin rash urticaria, pruritus.

**General and Application Site Disorders:** Fatigue, erythema and pain on injection site, thrombophlebitis, thrombosis.

**Injury, Poisoning and Procedural Complications:** An increased risk for falls and fractures has been recorded in elderly benzodiazepine users.
4.9 Overdose

Symptoms

Like other benzodiazepines, midazolam commonly causes drowsiness, ataxia, dysarthria and nystagmus. Overdose of midazolam is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnoea, hypotension, cardiorespiratory depression and in rare cases to coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.

Treatment

Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.

If taken orally further absorption should be prevented using an appropriate method e.g. treatment within 1-2 hours with activated charcoal. If activated charcoal is used airway protection is imperative for drowsy patients. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.

If CNS depression is severe consider the use of flumazenil, a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of this drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Hypnotics and sedatives (benzodiazepine derivatives), ATC code: N05CD08.

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 to form water-soluble salts with acids. These produce a stable and well tolerated injection solution.

The pharmacological action of midazolam is characterised by short duration because of rapid metabolic transformation. Midazolam has a 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 remember events that occurred during the maximal activity of the compound).

5.2 Pharmacokinetic properties

Absorption after i.m. injection

Absorption of midazolam from muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. The absolute bioavailability after i.m. 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 i.v., 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.
Metabolism
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 - 500ml/min. Midazolam is excreted mainly by renal route (60 - 80% of the injected dose) and recovered as glucuroconjugated 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 i.v. 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 i.v. 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 (see section 4.4).

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 (see section 4.4).

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 (see section 4.4).

5.3 Preclinical safety data
There are no preclinical data of relevance to the prescriber that are additional to those already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium Chloride
Hydrochloric Acid
Sodium Hydroxide (pH adjustment)
Water for Injections

6.2 Incompatibilities
This medicinal product must not be diluted with other solutions for parenteral use than those mentioned in section 6.6 Special precautions for disposal and other handling.
Midazolam is incompatible with alkaline solutions (due to reduced solubility and precipitation of midazolam) and some medicines. Compatibility must be checked before administration, if intended to be mixed with other drugs.

Published data show that midazolam injection is incompatible with alkaline injections such as some antibiotic and steroid injections, bumetanide, furosemide, omeprazole sodium, sodium bicarbonate and thiopental sodium.

It is also incompatible with aciclovir, albumin, amoxicillin sodium, ampicillin sodium, alteplase, acetzolam disodium, ceftazidime, dexamethasone sodium phosphate, diazepam, enoximone, flecaïnide acetate, fluocoxacillin sodium, fluorouracil, hydrocortisone sodium succinate, imipenem, mezlocillin sodium, nafcilin, phenobarbital sodium, phenytoin sodium, potassium canrenoate, sulbactam sodium, theophylline, trometamol, urokinase, dimenhydrinate, fosfornad sodium, imipenem with cilastin, pentobarbital sodium, clonidine hydrochloride, perphenazine, procilplerazine, ranitidine, trimethoprim-sulfamethoxazole, methotrexate sodium and certain parenteral solutions, including parenteral nutrition solutions.

Mixture or dilution with Hartmann's solution is not recommended, as the potency of midazolam decreases.

6.3 Shelf life
24 months (unopened)
24 hours (dilutions)

6.4 Special precautions for storage
Keep the ampoules in the original carton to protect from light.

6.5 Nature and contents of container
Type I clear glass ampoules containing 2 ml.
5 or 10 ampoules per carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
The injection is for single use only and should be used immediately after opening. The injection should not be used if particles are present. Any unused portion should be discarded.

Midazolam ampoule solution is stable, both physically and chemically, for up to 24 hours at room temperature when mixed with 500ml infusion fluids containing Dextrose 4% with Sodium Chloride 0.18%, Dextrose 5% or Sodium Chloride 0.9%.

There is no evidence of the adsorption of midazolam on to the plastic of infusion apparatus or syringes.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, the product 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 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

7 MARKETING AUTHORISATION HOLDER
Auden Mckenzie (Pharma Division) Ltd
McKenzie House
Bury Street
Ruislip
Middlesex
HA4 7TL
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 17507/0030

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/06/2011
10 DATE OF REVISION OF THE TEXT
06/06/2011
PAR Midazolam 2 mg/ml and 5 mg/ml Solution for Injection
UK/H/2511/001-2/DC

Module 3
Product Information Leaflet

PATIENT INFORMATION LEAFLET

MIDAZOLAM 2 mg/ml or 5 mg/ml Solution for Injection
(Midazolam as Midazolam Hydrochloride)

Please read all of this leaflet carefully before taking your medicine.
• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor, nurse or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet
1. What is MIDAZOLAM and what is it used for?
2. Before you are given MIDAZOLAM
3. How MIDAZOLAM is used
4. Possible side effects
5. Storing MIDAZOLAM
6. Further information

1. What is MIDAZOLAM and what is it used for?

What is MIDAZOLAM?
MIDAZOLAM belongs to a group of medicines known as benzodiazepines. It is a short-acting medicine that is used to induce sedation (a very relaxed state of calm, drowsiness or sleep) and relieves anxiety and muscle tension.

What is MIDAZOLAM used for?
This medicine is used for:
• Conscious sedation (an awake but very relaxed state of calm or drowsiness during a medical test or procedure) in adults and children.
• Sedation of adults and children, in intensive care units.
• Anaesthesia in adults, used alone or with other medicines.
• Premedication (medicine used to cause relaxation, calm and drowsiness before an anaesthetic) in adults and children.

2. Before you are given MIDAZOLAM

Do not use MIDAZOLAM if:
• You are allergic (hypersensitive) to any of the ingredients of the medicine (see section 6, Further information).
• You are allergic to other benzodiazepine medicines, such as diazepam or nitrazepam.
• You have severe breathing problems and you are going to have MIDAZOLAM for conscious sedation

If any of the above applies to you, do not use this medicine and talk to your doctor, nurse or pharmacist.

Special Precautions
Your doctor may take special precautions when giving you MIDAZOLAM if any of the points listed below applies to you:

Children and babies
If your child is going to be given this medicine:
• It is particularly important to tell your doctor or nurse if your child has cardiovascular disease (heart problems). Your child will be carefully monitored and the dose will be adjusted specially.
• Children must be carefully monitored. For infants and babies under 6 months this will include monitoring of breathing and oxygen levels.

Adults
Before MIDAZOLAM is given, let your doctor or nurse know if:
• You are over 60 years of age.
• You have a long term illness (such as breathing problems or kidney, liver or heart problems).
• You are debilitated (have an illness that makes you feel very weak, run down and short of energy).
• You have myasthenia gravis (a neuromuscular disease causing muscle weakness).
• You regularly drink large amounts of alcohol or you have had problems with alcohol use in the past.
• You regularly take recreational drugs or you have had problems with drug use in the past.
• You are pregnant or think you may be pregnant (see ‘Pregnancy and breast-feeding’).

If any of the above applies to you talk to your doctor, nurse or pharmacist.
Taking other medicines
Always tell your doctor if you are taking any other medicines, including medicines obtained without a prescription and herbal medicines because taking some medicines together can be harmful. Remember that the doctor at the hospital may not have been informed if you have recently begun a course of treatment for another illness.

In particular, tell your doctor or nurse if you are taking any of the following medicines:
- tranquilisers (for anxiety or to help you sleep)
- hypnotics (medicines to make you sleep)
- sedatives (to make you feel calm or sleepy)
- antidepressants (medicines for depression)
- narcotic analgesics (very strong pain killers)
- antihistamines (used to treat allergies)
- medicines to treat fungal infections (ketoconazole, voriconazole, fluconazole, itraconazole, posaconazole)
- macrolide antibiotics (such as erythromycin or clarithromycin)
- diuretics (used to treat high blood pressure)
- medicines for HIV called protease inhibitors (such as saquinavir)
- atorvastatin (used to treat high cholesterol)
- rifampicin (used to treat mycobacterial infections such as tuberculosis)
- the herbal medicine St John’s Wort.

If any of the above applies to you talk to your doctor, nurse or pharmacist.

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.

Drinking alcohol
Do not drink alcohol if you have been given MIDAZOLAM. This is because alcohol can increase the sedative effect of MIDAZOLAM and may cause problems with your breathing.

Pregnancy and breast feeding
Talk to your doctor if you are pregnant, or think you are pregnant. Your doctor will decide if this medicine is suitable for you.

Do not breast-feed for 24 hours after being given MIDAZOLAM. This is because MIDAZOLAM may pass into your breast milk.

Driving and using machines
- Do not drive or use machinery until you are completely recovered. Your doctor should advise you when you can start these again.
- MIDAZOLAM may make you sleepy, forgetful or affect your concentration and co-ordination. This may affect your performance at skilled tasks such as driving or using machines.
- You should always be taken home by a responsible adult after your treatment.

Warnings about the ingredients:
MIDAZOLAM is essentially ‘sodium free’ as it contains less than 1 mmol sodium (23 mg) per ampoule (small glass bottle).

3. How you will be given MIDAZOLAM

Important:
MIDAZOLAM should be given only by experienced healthcare professionals (doctor or nurse). It should be given in a place (hospital, clinic or surgery) equipped to monitor and support the patient’s breathing, heart and circulation (cardiovascular function) and recognise the signs of and manage the expected side effects of anaesthesia.

Adults:
Your doctor will decide on a suitable dose for you. The dose you are given will depend on why you are being treated and the type of sedation needed. Your weight, age, your state of health, how you respond to MIDAZOLAM and whether other medicines are needed at the same time will also influence the dose that you are given.

If you need strong painkillers, you will be given these first and then be given MIDAZOLAM. The dose will be adjusted specially for you.

MIDAZOLAM may be given to you in one of four different ways:
- by slow injection into a vein (intravenous injection)
- through a tube into one of your veins (intravenous infusion)
- by injection into a muscle (intramuscular injection)
- into your back passage (rectum).

You should always be taken home by a responsible adult after your treatment.

Children & Babies:
- In infants and babies 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 MIDAZOLAM is used for premedication (to cause relaxation, calm and drowsiness before an anaesthetic) it may be given into the back passage (rectum).
If you think you have been given more MIDAZOLAM than you should:
Your medicine will be given to you by a doctor or nurse. If you are accidentally given too much MIDAZOLAM you may:
- Feel drowsy.
- Lose your co-ordination (ataxia) and reflexes.
- Have problems with your speech (dysarthria).
- Have involuntary eye movements (nystagmus).
- Develop low blood pressure (hypotension).
- Stop breathing (apnoea) and suffer cardiorespiratory depression (slowed or stopped breathing and heart beat) and coma.

Stopping MIDAZOLAM
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 below).

Your doctor will reduce your dose gradually to avoid these effects happening to you.

Withdrawal symptoms:
Benzodiazepine medicines, like MIDAZOLAM, may make you dependent if used for a long time (for instance in intensive care). This means that if you stop treatment suddenly, or lower the dose too quickly, you may get withdrawal symptoms. The symptoms can include:
- Headache
- Muscle pain
- Feeling very worried (anxious), tense, restless, confused or bad-tempered (irritable)
- Problems with sleeping (insomnia)
- Mood changes
- Hallucinations (seeing and possibly hearing things that are not there)
- Fits (convulsions).

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

4. Possible side effects

Like all medicines MIDAZOLAM Injection can cause side effects, although not everybody gets them.

Seek immediate medical help if you have any of the following symptoms. 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 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.

For a list of the side effects associated with the withdrawal of midazolam, please see section 3 of this leaflet.

Other possible side effects:

Immune system problems:
- General allergic reactions (skin reactions, heart and blood system reactions, wheezing)

Effects on behaviour:
- Agitation
- Restlessness
- Hostility, rage or aggression
- Excitement.

Muscle problems:
- Muscle spasms and muscle tremors (shaking of your muscles that you cannot control).

Mental and Nervous system problems:
- Confusion
- Euphoria (an excessive feeling of happiness or excitement)
- Hallucinations (seeing and possibly hearing things that are not really there)
- Drowsiness and prolonged sedation
- Reduced alertness
- Headache
- Dizziness
- Difficulty co-ordinating muscles
- Fits (convulsions) in premature infants 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).
Heart and circulation problems:
- low blood pressure
- slow heart rate
- redness of the face and neck (flushing), fainting or headache.

Breathing problems:
- shortness of breath
- hiccup.

Stomach, gut and mouth problems:
- feeling sick or being sick
- constipation
- dry mouth.

Skin problems:
- rash
- hives (lumpy rash)
- itchiness.

Injection site problems:
- redness
- swelling of the skin
- blood clots or pain at the injection site.

General:
- tiredness (fatigue).

Elderly patients:
- Older patients taking benzodiazepine medicines have a higher risk of falling and breaking bones.
- 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 when the injection is given too quickly or at a high dose.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

5. Storing MIDAZOLAM

Keep out of the reach and sight of children.

Do not use MIDAZOLAM Injection after the expiry date on the carton or the ampoule. The expiry date refers to the last day of that month.

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

Keep the ampoules (small glass bottle) in the outer carton in order to protect from light.

Do not use the medicine if the solution is not clear and colourless.

6. Further Information

What MIDAZOLAM contains:
The active substance is MIDAZOLAM (as midazolam hydrochloride) 2 mg or 5 mg in each 1ml of solution.
- MIDAZOLAM 2 mg/ml Solution for Injection:
  Each ampoule (small glass bottle) contains 10 mg of midazolam in 5 ml of liquid.
- MIDAZOLAM 5 mg/ml Solution for Injection:
  Each ampoule (small glass bottle) contains 10 mg of midazolam in 2 ml of liquid.

The solution for injection also contains sodium chloride, hydrochloric acid, sodium hydroxide (for pH adjustment) and water for injections.

What MIDAZOLAM looks like and contents of the pack:
MIDAZOLAM Injection is a sterile solution for injection in a clear glass container called an ampoule.

MIDAZOLAM Injection is supplied in cartons of 5 or 10 ampoules containing either 2 mg/ml or 5 mg/ml.

Not all pack sizes may be marketed.

Marketing authorisation holder:
Auden Mckenzie (Pharma Division) Ltd.,
Mckenzie House,
Bury Street, Ruislip, Middlesex
HA4 7TJ, UK

Manufacturer:
SNS Pharmaceuticals Ltd.,
Mckenzie House,
Bury Street, Ruislip, Middlesex
HA4 7TJ, UK

This leaflet was last approved in May 2011.

For information in large print, on tape, on CD or in Braille, phone +44 (0) 1895 627 420.
PAR Midazolam 2 mg/ml and 5 mg/ml Solution for Injection

UK/H/2511/001-2/DC

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

(Please detach prior to giving the leaflet to the patient)

MIDAZOLAM 2 mg/ml or 5 mg/ml Solution for Injection
(Midazolam as Midazolam Hydrochloride)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Adults &lt;60y</th>
<th>Adults ≥60y/ debilitated or chronically ill</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conscious sedation</td>
<td>Lv.</td>
<td>Initial dose: 2 - 2.5mg</td>
<td>Initial dose: 0.5 - 1mg</td>
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<td></td>
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<td>Titrations: 0.5 - 1mg</td>
<td>Titrations: 0.5 - 1mg</td>
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<td></td>
<td>Total dose: 3.5 - 7.5mg</td>
<td>Total dose: &lt;3mg</td>
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<tr>
<td>Anesthesia premedication</td>
<td>i.v.</td>
<td>1 - 2mg repeated</td>
<td>i.v.</td>
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<td>Lim.</td>
<td>0.07 - 0.1mg/kg</td>
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<tr>
<td>Anesthesia induction</td>
<td>Lv.</td>
<td>0.15 - 0.2mg/kg</td>
<td>I.v.</td>
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<td>(0.3 - 0.35 without premedication)</td>
<td>Initial dose: 0.05 - 0.15mg/kg</td>
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<tr>
<td>Sedative component in combined anesthesia</td>
<td>Lv.</td>
<td>Intermittent doses of 0.03 - 0.1mg/kg or continuous infusion of 0.03 - 0.1mg/kg/h</td>
<td>I.v.</td>
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<tr>
<td>Sedation in ICU</td>
<td>i.v.</td>
<td>Loading dose: 0.03 - 0.3mg/kg in increments of 1 - 2.5mg</td>
<td>Maintenance dose: 0.03 - 0.2mg/kg/h</td>
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Adults

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

In adults below the age of 60 the initial dose to be given is 2 to 2.5 mg given over 5 to 10 minutes before the beginning of the procedure. Further doses of 0.5 to 1 mg may be given as necessary. A mean total dose has been found to range from 2.5 to 7.5 mg. A total dose greater than 7.5 mg is usually not necessary.

In adults over 60 years of age, debilitated or chronically ill patients, the initial dose should be reduced to 0.5 – 1 mg and given over 5 to 10 minutes before the beginning of the procedure. Further doses of 0.5 to 1 mg may be given as necessary. Since in these patients the peak effect may be reached less rapidly, additional midazolam should be administered very slowly and carefully. A total dose greater than 3.5 mg is usually not necessary.

Children

I.V. administration should be started slowly and should be continued at a rate that provides the desired effect. The initial dose of midazolam should be administered over 2 to 5 minutes. Once started, the additional 2 to 5 minutes to fully evaluate the sedative effect before initiating a procedure or repairing 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 (mg/kg) than older children and adolescents.
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- Pediatric patients less than 6 months of age, pediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoxia. For this reason, the use in conscious sedation in children less than 6 months of age is not recommended.
- Pediatric patients 6 months to 5 years of age: initial dose 0.05 to 0.1 mg/kg. A total dose of up to 0.6 mg/kg may be necessary to reach the desired endpoint, but the total dose should not exceed 0.6 mg. Prolonged sedation and risk of hypoxia may be associated with the higher doses.
- Pediatric patients 6 to 12 years of age: initial dose 0.025 to 0.05 mg/kg. A total dose of up to 0.4 mg/kg to a maximum of 10 mg may be necessary. Prolonged sedation and risk of hypoxia may be associated with the higher doses.
- Pediatric patients 12 to 16 years of age: should be dosed as adults.

**Racial administration:** the total dose of midazolam usually ranges from 0.2 to 0.5 mg/kg. Racial 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. Total dose should be administered at once and repeated racial administration avoided.

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

**1 ML administration:** the doses used range between 0.02 and 0.15 mg/kg. A total dose greater than 10.0 mg/kg is usually not necessary. This route should only be used in exceptional cases. Racial administration should be preferred as I.M. injection is painful.

In children 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.

**ANAESTHESIA DOSAGE PREMEDICATION**

Premedication with midazolam given shortly before a procedure produces sedation (reduction of sleepiness or discomfort and relief of apprehension) and preoperative impairment of memory. Midazolam can also be administered in combination with anticholinergics. For this indication midazolam should be administered I.M. or I.V., deep into a large muscle mass 20 to 60 minutes before induction of anaesthesia, or preferably via the racial route in children (see below). Close and continuous monitoring of the patient after administration of premedication is mandatory as interindividuality variations and symptoms of overdose may occur.

**Adults**

For premedication and to impair memory of preoperative events, the recommended dose for adults of ASA Physical Status I and II is 1-2 mg I.M. repeated as needed, or 0.07 to 0.1 mg/ml administered I.V.

The dose must be reduced and individualised when midazolam is administered to adults over 60 years of age, debilitated or chronically ill patient. The recommended initial I.V. dose is 0.5 mg and should be slowly titrated as needed. A dose of 0.025 to 0.05 mg/ml administered I.V. is recommended. In case of concomitant administration of narcotics, the midazolam dose should be reduced. The usual dose is 2 to 3 mg.

**Pediatric 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**

Racial administration: The total dose of midazolam, usually ranging from 0.3 to 0.5 mg/kg should be administered 15 to 30 minutes before induction of anaesthesia. Racial 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.

1 ML administration: As I.M. injection is painful, this route should only be used in exceptional cases. Racial administration should be preferred. However, a dose range from 0.08 to 0.2 mg/kg of midazolam administered I.M. 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 bodyweight.

In children 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.

**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 I.V. or inhalation agents for induction of anaesthesia, the initial dose of each agent should be significantly reduced, at least to as low as 25% of the usual initial dose of the individual agents.

The desired level of amnesia is reached by repetitive titration. The I.V. induction dose of midazolam should be given slowly in increments. Each increment of not more than 5 mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments.

- In premedicated adults below the age of 60 years, an I.V. dose of 0.15 to 0.3 mg/kg usually suffices.
- In non-premedicated adults below the age of 60 the dose may be higher (0.3 to 0.5 mg/kg I.V.). If needed to complete induction, increments of approximately 25% of the patient's total dose may be used. Induction may instead be commenced with 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.

- In premedicated adults over 60 years of age, debilitated or chronically ill patients, the dose should significantly be reduced, age, down to 0.05 - 0.15 mg/kg administered I.V. 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 0.3 mg/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 0.25 mg/kg usually suffices.

**SEDATIVE COMPONENT IN COMBINED ANAESTHESIA**

**Adults**

Midazolam 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 midazolam (range between 0.03 and 0.1 mg/kg) typically in combination with analgesics. The dose and the interval 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**

I.V. loading dose: 0.03 to 0.3 mg/kg should be given slowly in increments. Each increment of 1 to 3.5 mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments. In hypovolaemic, vasocostricted, or hypertensive patients the loading dose should be reduced or omitted. When midazolam is given with patient paralysis, 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. I.V. maintenance dose can range from 0.01 to 0.2 mg/kg in hypovolaemic, vasocostricted, or hypertensive 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 I.V. infusion, starting at 0.03 mg/kg (0.3 mg/kg/min) in neonates with a gestational age <32 weeks, or 0.1 mg/kg (1 mg/kg/min) in neonates with a gestational age 32 weeks and children up to 6 months.

Intravenous loading doses is 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 pediatric patients, a loading dose of 0.05 to 0.2 mg/kg 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 I.V. infusion at 0.06 to 0.12 mg/kg/h (1 to 2 mg/l/min). The rate of infusion can be increased or decreased (generally by 25% of the final or subsequent infusion rate) as required, or supplemental I.V. doses of midazolam can be administered to increase or maintain the desired effect.

When initiating an infusion with midazolam in hemodynamically compromised patients, the usual loading dose should be infused in small increments and the patient monitored for hemodynamic 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 body weight, midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

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Use in Special Populations

Renal Impairment

In patients with renal impairment (creatinine clearance < 10 ml/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 was considerably increased most likely due to accumulation of 4-hydroxymidazolam glucuronide.

There is no specific data in patients with severe renal impairment (creatinine clearance below 30 ml/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.

Midazolam is essentially sodium free as it contains less than 1 mmol sodium (0.3 mg) per ampoule.

4.3 Contraindications

Use of this drug in patients with known hypersensitivity to benzodiazepines or to any excipient of the product.

Use of this drug for conscious sedation in patients with severe respiratory failure or acute respiratory depression.

4.4 Special warnings and precautions for use

Midazolam should be administered only by experienced physicians in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function and by persons specifically trained in the recognition and management of expected adverse events including respiratory and cardiac resuscitation.

Severe cardiorespiratory adverse events have been reported. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest. Such life-threatening incidents are more likely to occur when the injection is given too rapidly or when a high dosage is administered (see section 4.3).

Special caution is required for the induction of conscious sedation in patients with impaired respiratory function.

Paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoxia because of small increase to clinical effect and careful respiratory rate and oxygen saturation monitoring are essential.

When midazolam is used for premedication adequate observation of the patient after administration is mandatory as interindividual sensitivity varies and symptoms of overdosage may occur.

Special caution should be exercised when administering midazolam to high-risk patients:
- adults over 60 years of age
- with chronic obstructive pulmonary disease, e.g.
- patients with chronic respiratory insufficiency
- patients with chronic renal failure, impaired hepatic function or with impaired cardiac function
- paediatric patients with cardiac insufficiency.

These high-risk patients require lower doses (see section 4.2) and should be continuously monitored for early signs of alteration of vital functions.

As with any substance with CNS depressant and/or muscle relaxant properties, particular care should be taken when administering midazolam to a patient with myasthenia gravis.

Tolerance

Some loss of efficacy has been reported when midazolam was used as long-term sedation in intensive care units (ICU).

Dependence

When midazolam is used in long-term sedation in ICU, it should be borne in mind that physical dependence on midazolam may develop. The risk of dependence increases with dose and duration of treatment. It is also greater in patients with a medical history of alcohol and/or drug abuse (see section 4.4).

 Withdrawal symptoms

During prolonged treatment with midazolam in ICU, physical dependence may develop. Therefore, abrupt termination of the treatment will be accompanied by withdrawal symptoms. The following symptoms may occur: headaches, muscle pain, anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood changes, hallucinations and convulsions. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, it is recommended to decrease doses gradually.

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Anaphylaxis
Midazolam causes anaphylactic anaphylaxis (frequently this effect is very
desirable in situations such as before and during surgical and diagnostic
procedures); the duration of which is directly proportional to the administered
dose. Prolonged anaphylaxis can present problems in patients, who are
scheduled for discharge following intervention. After receiving midazolam
intravenously, patients should be observed from hospital or consulted room
only if accompanied by an attendant.

Paradiscal reactions
Paradiscal reactions such as agitation, involuntary movements (including
tonic-clonic convulsions and myoclonic tremor), hyperactivity, hostility, rage
reactions, aggression, hallucinations and assault, have been reported
to occur with midazolam. These reactions may occur with high
doses and/or if the injection is given rapidly. The highest incidence to
such reactions has been reported among children and the elderly.

Altered elimination of midazolam
Midazolam elimination may be altered in patients receiving compounds
that inhibit or induce CYP3A4 and the dose of midazolam may need to be
adjusted accordingly (see section 4.5).

Midazolam elimination may also be delayed in patients with liver dysfunction,
low cardiac output and in neonates (see section 5.2).

Pregnant infants and neonates
Due to an increased risk of arrhythmia, extreme caution is advised when
administering to premature and/or neonate preterm and/or low birth weight
patients. Careful monitoring of respiratory rate and oxygen saturation
is required (see also section 5.2.5.3. Pregnant infants’ above).

Neonates have reduced renal and/or immature organ function and are also
vulnerable to profound and/or prolonged respiratory effects of midazolam.

Adverse haemodynamic events have been reported in paediatric patients
with cardiovascular instability; rapid intravenous administration should be
avoided in this population.

Paediatric patients less than 6 months
In this population, midazolam is indicated for sedation in ICU only; paediatric
patients less than 6 months of age are particularly vulnerable to airway
obstruction and hypventilation; therefore, increasing with small increments to
clinical effect and careful respiratory rate and oxygen saturation
monitoring are essential (see also section 5.2.3. Pregnant infants’ above).

Concomitant use of alcohol / CNS depressants
The concomitant use of midazolam with alcohol or and CNS depressants
should be avoided. Such concomitant use has the potential to increase the
clinical effects of midazolam possibly including severe sedation or clinically
relevant respiratory depression (see section 4.5).

Medical history of alcohol or drug abuse
Midazolam should not be used in patients with a medical history of alcohol or drug abuse.

Discharge criteria
After receiving midazolam, patients should be discharged from hospital or
consulting room only when recommended by the treating physician and if
accompanied by an attendant. It is recommended that the patient is accompanied
when returning home after discharge.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic Interactions
Midazolam is metabolised by CYP3A4. Inhibitors and inducers of CYP3A4
have the potential to respectively increase and decrease the plasma
concentrations and, subsequently, the effects of midazolam by raising
dose adjustments accordingly. Pharmacokinetic interactions with CYP3A4
inhibitors or inducers are more pronounced for oral as compared to i.v.
midazolam since i.v. midazolam also exists in the upper gastro-intestinal tract. This is because for the oral route both systemic
clarence and availability will be altered while for the parenteral route only
the change in the systemic clearance becomes effective. After a single
dose of IV midazolam, the clearance on the maximal clinical effect due to
CYP3A4 inhibition will be lower while the duration of effect may be prolonged;
however, after prolonged dosing of midazolam, both the magnitude and duration of effect will be increased in the presence of
CYP3A4 inhibition.

There are no available studies on CYP3A4 modulation on the
pharmacodynamics of midazolam after i.v. and intravenous
administration. It is expected that these interactions will be less
pronounced for the oral route because the gastro-intestinal tract is by-passed whereas after i.v. administration the effects
and CYP3A4 modulation should not substantially differ from those seen
with i.v. midazolam.

It is therefore recommended to carefully monitor the clinical effects and vital
signs during the use of midazolam, taking into account that they may be
modified by the presence of CYP3A4 inhibitors or inducers. CYP3A4
inhibition should not substantially differ from those seen
with i.v. midazolam.

With respect to induction, it should be considered that the inductive process
needs several days to reach its maximal effect and also several days to
dissipate. Contrary to a treatment of several days with an inducer, a
short-term treatment is expected to result in less apparent DDI with
midazolam. However, for strong inducers a relevant induction even after
short-term treatment cannot be excluded.

Midazolam is not known to change the pharmacokinetics of other drugs.

Drugs that inhibit CYP3A4

Acute antifibrillatory
Ketorolac increased the plasma concentrations of intravenous midazolam by 5-fold while the terminal half-life increased by about 2 fold.
If parenteral midazolam is co-administered with the strong CYP3A4
inhibitor ketoconazole, it should be dosed to an intensive care unit (ICU)
or similar setting which ensures close clinical monitoring and appropriate
medical management in case of respiratory depression and/or prolonged
sedation. Stratified dosing and dosage adjustment should be considered;
especially if more than a single i.v. dose of midazolam is administered. The
same recommendation may also apply for other azole antifibrillatories (see
further), since increased sedative effects of IV midazolam, although
milder, are also reported.

Voriconazole increased the exposure of intravenous midazolam by 2 fold whereas its elimination half-life increased by about 3 fold.

Fluconazole and itraconazole both increased the plasma concentrations of intravenous midazolam by 2 – 3 fold associated with an increase in
terminal half-life by 2.4 fold for fluconazole and 1.5-3 fold for itraconazole,
respectively.

Ponazurazole increased the plasma concentrations of intravenous midazolam by about 2 fold.

It should be kept in mind that if midazolam is given orally, its exposure will
dramatically be higher than the above mentioned ones, notably with
voriconazole, itraconazole, voriconazole.

Midazolam arnipples are not indicated for oral administration.

Microbiological antibiotics

Netilmicin resulted in an increase in the plasma concentrations of
intravenous midazolam by about 1.6 – 3 fold associated with an increase of
the terminal half-life of midazolam by 1.5 – 1.8 fold.

Clarithromycin increased the plasma concentrations of midazolam by up to
2.5 fold associated with an increase in terminal half-life by 1.3 – 2.4 fold.

Additional information from oral midazolam

Rifampicin. While no information on co-administration with IV
midazolam is available, the mild effect on the terminal half-life of oral
midazolam tablets, increasing by 20%, indicates that the effects
of rifampicin on intravenous midazolam may be minor.

HIV Pro tease inhibitors

Saquinavir and other HIV protease inhibitors. Co-administration with
protease inhibitors may cause a large increase in the concentration of
midazolam. Upon co-administration with ritonavir-boosted lopinavir the
plasma concentrations of intravenous midazolam increased by 3.4-fold,
associated with a similar increase in terminal half-life. If parenteral
midazolam is co-administered with HIV protease inhibitors, treatment
setting should follow the description in the above section for oral
antifibrillas, and ketorolac.

Additional information from oral midazolam

Based on data for other CYP3A4 inhibitors, plasma concentrations of
midazolam are expected to be significantly higher when midazolam is
given orally. Therefore protease inhibitors should not be co-administered
with orally administered midazolam.

Calcium-channel blockers

Diltiazem. A single dose of diltiazem increased the plasma concentrations
of intravenous midazolam by about 25% and the terminal half-life was
prolonged by 43%.

Additional information from oral midazolam

Verapamil.intl increased the plasma concentrations of oral
midazolam by 3-4 fold, respectively. The terminal half-life of
midazolam was increased by 41% and 49% respectively.

Various drugs/Harms

Apoprotein showed a 1.4 fold increase in plasma concentrations of IV
midazolam compared to control group.

Additional information from oral midazolam

Fluoxetine increased the plasma concentrations of oral midazolam by 4.6-fold with an increase of its terminal half-life by 1.6 fold.

Ampyramine dose-dependently increased the plasma concentrations of oral midazolam by 3.3-fold after 80 mg daily associated with an increase in
terminal half-life by ca. 2 fold.

Drugs that induce CYP3A4

Rifampicin decreased the plasma concentrations of intravenous midazolam by about 60% after 7 days of rifampicin 600mg o.d. The terminal half-life
decreased by about 50-60%.
PAR Midazolam 2 mg/ml and 5 mg/ml Solution for Injection UK/H/2511/001-2/DC

Additional information from oral midazolam:

- **Hypersensitivity**: decreased the plasma concentrations of oral midazolam by 96% in healthy subjects and its psychomotor effects were almost totally lost.
- **Cardiovascular**: repeat dosages of cardiovascular-phenytoin resulted in a decrease in plasma concentrations of oral midazolam by up to 98% and a shortening of the terminal half-life by 60%.
- **Hepatic**: the 2-fold increase in the ratio of the CYP4A4-mediated metabolism of oral midazolam to midazolam confirms its CYP4A4-inducing effect.

Hydrated and Unhydrated:

- **St John’s Wort**: decreased plasma concentrations of midazolam by about 20 - 40% associated with a decrease in terminal half-life of about 15 - 17%. Depending on whether the specific St John’s Wort extracts the CYP4A4-inducing effect may vary.

Pharmacodynamic Drug-Drug Interactions (DDI): The co-administration of midazolam with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression.

Examples include opiate derivatives (e.g., they used as analgesics, antidepressant, or as antistress treatments), antidepressants, other benzodiazepines used as sedatives or hypnotics, butorphanol, propofol, ketamine, cyclosporine, valproic acid, and centrally acting antihypertensive agents.

Alcohol may markedly enhance the sedative effects of midazolam. Alcohol intake should be strongly avoided in case of midazolam administration (see section 4.4).

Midazolam decreases the minimum alveolar concentration (MAC) of inhalational anaesthetics.

4.6 Pregnancy and lactation

Inadequate data are available on midazolam to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but fetotoxicity was observed in all other benzodiazepines. No data on exposed pregnancies are available for the first 2 trimesters of pregnancy.

The administration of high doses of midazolam in the last trimester of pregnancy during labour or when used as an induction agent of anaesthesia for caesarean section has been reported to produce maternal or fetal adverse effects (inhalation risk in mother, irregularities in the fetal heart rate, hypotension, poor sucking, hypoactivity and respiratory depression in the neonate).

Moreover, infants born from mothers who received benzodiazepines chronically during the latter stage of pregnancy might have developed physical dependence and might be at some risk of developing withdrawal symptoms in the postnatal period.

Consequently, midazolam may be used during pregnancy if clearly necessary but it is preferable to avoid using it for caesarean sections.

The risk for neonate should be taken into account in case of administration of midazolam for any surgery near the term.

Midazolam passes in low quantities into breast milk. Nursing mothers should be advised to discontinue breastfeeding for 24 hours following administration of midazolam.

4.7 Effects on ability to drive and use machines

Midazolam has a major influence on the ability to drive and use machines.

Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive or use machines. Prior to receiving midazolam, the patient should be warned not to drive or operate a machine until completely recovered. The physician should decide when these activities may be resumed. It is recommended that the patient is accompanied when returning home after discharge.

4.8 Undesirable effects

The following undesirable effects have been reported (very rarely) to occur when midazolam is injected:

- **Immune System Disorders**: Generalized hypersensitivity reactions (urticaria, anaphylaxis, anaphylactic shock).
- **Psychiatric Disorders**: Confusional state, anaphylactic shock, hallucinations.

Paroxysmal reactions such as agitation, involutionary movements (including tonic-clonic movements and muscle tension), hyperventilation, hormonal reaction, aggressiveness, paroxysmal excitement and assault, have been reported, particularly among children and the elderly.

- **Dependence**: Use of midazolam - even in therapeutic doses - may lead to the development of physical dependence. After prolonged use, administration, discontinuation, especially abrupt discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions (see section 4.4).

Nervous System Disorders: Prolonged sedation, decreased alertness, somnolence, headache, dizziness, ataxia, postoperative sedation, anterograde amnesia, the duration of which is directly related to the administered dose. Anterograde amnesia may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported.

Convulsions have been reported in premature infants and neonates.

Cardiac Disorders: Severe cardiorespiratory adverse events have occurred. These have included cardiac arrest, hypotension, bradycardia, vasodilating effects. Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered (see section 4.4).

Hiccups:

Gastrointestinal System Disorders: Nausea, vomiting, constipation, dry mouth.

Skin and Appendage Disorders: Skin rash, eczema, pruritus.

General and Administration Site Disorders: Fatigue, erythema and pain on injection site, thrombophlebitis, thrombosis.

Injury, Poisoning and Procedure Complications: An increased risk for falls and fractures has been recorded in elderly benzodiazepine users.

4.9 Overdose

Symptoms

Like other benzodiazepines, midazolam commonly causes drowsiness, ataxia, dysarthria and dysphoria. Overdose of midazolam is seldom life-threatening if the drug is taken alone, but may lead to anesthetics, amnesia, hypotension, cardiorespiratory depression and in rare cases to coma. If it occurs, usually lasts a few hours but it may be more prolonged and lethal, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.

Treatment

Monitor the patient's vital signs and respiratory system. Supportive measures as indicated by the patient's clinical status. In particular, patients may require symptomatic treatment for cardiovascular effects or central nervous system effects.

If taken orally or rectally, further absorption should be prevented using an appropriate method (e.g., treatment within 1-2 hours with activated charcoal). If activated charcoal is used in any treatment, it is impermeable for ethanol. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.

If CNS depression is severe consider the use of flumazenil, a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g., phenytoin, carbamazepine). Refer to the prescribing information for flumazenil for further information on the correct use of this drug.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

- Hypnotics and sedatives (benzodiazepine derivatives), ATC code N05CD08.

Midazolam is a derivative of the midazolam-benzodiazepine group. The free base is a lipophilic substance with low solubility in water.

The basic nitrogen in position 2 of the midazolam benzodiazepine ring system antagonizes the active ingredient of midazolam to form water-soluble salts with acids. These produce a stable and well tolerated injection solution.

The pharmacological action of midazolam is characterised by short duration because of rapid metabolic transformation. Midazolam has a sedative and sleep-inducing effect of pronounced intensity. It also exerts an anxiolytic, an anticonvulsant and a muscle-relaxant effect.

After i.v. or i.m. administration, the initial state of the patient may be accompanied by withdrawal symptoms including withdrawal convulsions (see section 4.4).

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PAR Midazolam 2 mg/ml and 5 mg/ml Solution for Injection

**UK/H/2511/001-2/DC**

Additional information from oral midazolam:
- **Abuse**: decreased the plasma concentrations of oral midazolam by 96% in healthy subjects and its psychomotor effects were almost totally lost.
- **Carbamazepine / phenytoin**: Repeat doses of carbamazepine or phenytoin resulted in a decrease in plasma concentrations of oral midazolam by up to 90% and a shortening of the terminal half-life by 60%.
- **Ethanol**: The 3.5-fold increase in the ratio of the CPYMA generated metabolite 5-hydroxymidazol to midazolam confirms its CPYMA-inducing effect.

**Herbs and foods**
- **St John’s Wort**: decreased plasma concentrations of midazolam by about 20-40% associated with a decrease in the terminal half-life of about 13-17%. Depending on the specific St John’s Wort extract, the CPYMA-inducing effect may vary.

**Pharmacodynamic Drug-Drug Interactions (DDI)**

The co-administration of midazolam with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression.

Examples include: estazolam (as anxiolytics, antidepressants, or antihypertensive agents), benzodiazepines used as sedative/hypnotics, barbiturates, propofol, lorazepam, etomidate, sedative antidepressants, non-steroidal anti-inflammatory drugs.

Alcohol may markedly enhance the sedative effect of midazolam. Alcohol intake should be strongly avoided in case of midazolam administration (see section 4.4).

Midazolam decreases the minimum alveolar concentration (MAC) of inhalational anaesthetics.

### 4.6 Pregnancy and lactation

Insufficient data are available on midazolam to assess its safety during pregnancy. Several studies do not indicate a teratogenic effect, but foetal malformations were observed as with other benzodiazepines. No data on exposed pregnancies are available for the first two trimesters of pregnancy.

The administration of high doses of midazolam in the last trimester of pregnancy during labour or when used as an induction agent of anaesthesia for caesarean section has been reported to produce maternal or fetal adverse effects (adverse effects: increase in the maternal heart rate, hypotension, poor sucking, hypoxic and respiratory depression in the new born).

Moreover, infants born to mothers who received benzodiazepines chronically during the latter stage of pregnancy might have developed physical dependence and might be at some risk of developing withdrawal symptoms in the postnatal period.

Consequently, midazolam may be used during pregnancy if clearly necessary but it is preferable to avoid using it for caesarean sections.

The risk for neonate should be taken into account in case of administration of midazolam for any surgery near the term.

Midazolam passes in low quantities into breast milk. Nursing mothers should be advised to discontinue breastfeeding for 24 hours following administration of midazolam.

### 4.7 Effects on ability to drive and use machines

Midazolam has a major influence on the ability to drive and use machines.

Sedation, amnesia, impaired attention and impaired muscular functions may adversely affect the ability to drive or use machines. Prior to receiving midazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered. The physician should decide when these activities may be resumed. It is recommended that the patient is accompanied when returning home after discharge.

### 4.8 Undesirable effects

The following undesirable effects have been reported (very rarely) to occur when midazolam is injected:

- **Nervous System Disorders**: Prolonged sedation, decreased alertness, somnolence, headache, dizziness, drowsiness, postoperative sedation, anorexia, amnesia, the duration of which is directly related to the administered dose. Anorexia may persist at the end of the procedure and isolated cases prolonged amnesia has been reported.

- **Contraindications**: have been reported in premature infants and neonates.

Cardiovascular Disorders: Severe cardiovascular adverse events have occurred. These have included cardiac arrest, hypotension, bradycardia, vasodilating effects. Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered (see section 4.4).

Respiratory Disorders: Severe cardiorespiratory adverse events including respiratory depression, apnoea, respiratory arrest, dyspnoea, hypotension and cyanosis have been reported. Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered (see section 4.4).

**Hiccups, Gastrointestinal System Disorders**: Nausea, vomiting, constipation, dry mouth.

Skin and Appendage Disorders: Skin rash, urticaria, pruritus.

General and Application Site Disorders: Fatigue, myalgia and pain on injection site, thrombophlebitis, thrombosis.

**Injury, Poisoning and Procedure Complications**: An increased risk for falls and fractures has been recorded in elderly benzodiazepine users.

### 4.9 Overdose

**Symptoms**

Like other benzodiazepines, midazolam commonly causes drowsiness, ataxia, dysarthria and nystagmus. Overdose of midazolam is seldom life-threatening if the drug is taken alone, but may lead to amnesia, speech, hypotension, hypothermia, cardiovascular depression and in rare cases to coma. Coma if occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

**Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.**

**Treatments**

Monitor the patient's vital signs and Institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.

If oral or intravenous absorption should be prevented using an appropriate method (e.g. treatment with 1-2 hours with activated charcoal). If activated charcoal is used, gastric lavage is imperative for drug patients. In case of missed ingestion gastric lavage may be considered, however not as a routine measure.

If CNS depression is severe consider the use of flumazenil, a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about 4 hours), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. antidepressants). Refer to the prescribing information for flumazenil for further information on the correct use of this drug.

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group**: Hypnotics and sedatives (benzodiazepine derivatives). ATC code: N05CD08.

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 to form water-soluble salts with acids. These probes are stable and well tolerated injection solution.

The pharmacological action of midazolam is characterised by short duration because of rapid metabolic transformation. Midazolam has a sedative and sleep-inducing effect of pronounced intensity. It also exerts an anticonvulsant, an antinociceptive and a muscle-relaxant effect.

After i.m. or iv administration anorexia and somnolence of short duration occurs (the patient does not remember events that occurred during the maximal activity of the compound).
5.2 Pharmacokinetic properties

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

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

Distribution
When midazolam is injected i.v., the plasma concentration-time curve shows two or two distinct phases of distribution. The volume of distribution at steady state is 0.7 - 1.2 L/kg - 96% 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.

Metabolism
Midazolam is almost entirely eliminated by biotransformation. The fraction of the dose excreted in the urine has been estimated to be 30 - 60%.

Midazolam is hydroxylated by the cytochrome P450 3A4 isozyme and the major urinary and plasma metabolite is 4-hydroxymidazolam. Plasma concentrations of alpha-hydroxymidazolam is 12% of those of the parent compound. Alpha-hydroxymidazolam is pharmacologically active, but contributes only minimally (above 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 200 - 500 ml/min. Midazolam is excreted mainly by renal route (60% - 80% of the injected dose) and recovered as glucuronon conjugate alpha-hydroxymidazolam. More than 98% 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 i.v. infusion, its elimination kinetics do not differ from those following bolus injection.

Pharmacokinetics in Special Populations

Biliary
In adults over 60 years of age, the elimination half-life may be prolonged up to 10 times.

Children
The rate of oral absorption in children is similar to that in adults but the bioavailability is lower (5 - 18%). The elimination half-life after i.v. and rectal administration is shorter in children 3 - 10 years old (1.1 - 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 (see section 4.4).

Obese
Obesity is associated with midazolam concentrations in 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 clinical practice may be longer and the clearance smaller as compared to those in healthy volunteers (see section 4.4).

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

Cirrhotic patients
The elimination half-life of midazolam is prolonged up to six times in the cirrhosis.

Patients with cardiac insufficiency
The elimination half-life is longer in patients with congestive heart failure compared with that in healthy subjects (see section 4.4).

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber that is additional to those already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Hydrochloric Acid
Sodium Hydroxide (pH adjustment)
Water for Injections

6.2 Incompatibilities

This medicinal product must not be admixed with other solutions for parenteral use or those mentioned in section 4.4 Special precautions for disposal and other handling.

Midazolam is incompatible with alkaline solutions (due to reduced solubility and precipitation of midazolam) and some medicines. Compatibility must be checked before administration, as it should not be mixed with other drugs.

Published data show that midazolam injection is incompatible with alkaline injections such as some antibiotics and narcotic injections, bismuth subnitrate, ferric subnitrate, amprosate sodium, sodium bicarbonate and disodium phosphate.

It is also incompatible with potassium levulinate, meglumine, ammonium chloride, sodium hydroxide, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium acetate, sodium chloride, disodium edrophonium chloride, sodium acetate, sodium bicarbonate, sodium lactate bacteriostatic water for injection, sodium benzoate, sodium metabisulphite, sodium chloride, sodium hydrochloride, merthiolate, benzyl alcohol, dextrose 50% solution, saline 0.9%, sodium chloride, polysorbate 80, and other similar solutions. Stability of the solution will be affected by temperature, pH and amount of preservative present.

6.3 Shelf life

24 months (unopened)
24 hours (dilutions)

6.4 Special precautions for storage

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

6.5 Nature and contents of container

2 mg/ml: Type I Clear glass ampoules containing 5 ml.
3 mg/ml: Type I Clear glass ampoules containing 2 ml.
5 or 10 ampoules per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This is for single use only and should be used immediately after opening. The injection should not be used if particles are present. Any unused portion should be discarded.

Midazolam suspension is stable, both physically and chemically, for up to 24 hours at room temperature when mixed with 500 ml infusion fluids containing Dextrose 5% with Sodium Chloride 0.18%, Dextrose 5% or Sodium Chloride 0.9%.

There is no evidence of the adsorption of midazolam onto the plastic of infusion apparatus or syringes.

Chemical and physical long-term stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, the product should be used immediately or stored immediately in ice storage and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca (Pharmaceuticals) Ltd
Midsomer House
Bury Street
Redhill
Middlesex
RH1 4TT
UK

8. MARKETING AUTHORISATION NUMBER(S)

UK: 5 mg/ml PL 17507/0030
2 mg/ml PL 17507/0031
IE: 5 mg/ml PA 1532/14/1
2 mg/ml PA 1532/14/2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Legal category POM

This healthcare professional leaflet was last approved in May 2011.
Midazolam
2mg/ml
Solution for injection

Each ampoule contains 10mg midazolam (as midazolam hydrochloride). Also contains sodium chloride, hydrochloric acid, sodium hydroxide (for pH adjustment) and water for injections.

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

Please read the enclosed package leaflet before use.

KEEP MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.
Medicinal product subject to medical prescription.

POM
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Ireland and the UK considered that the applications for Midazolam 2 mg/ml and 5 mg/ml Solution for Injection could be approved. These prescription only medicines (POM) are short-acting sleep-inducing drugs that are indicated:

In adults:

- Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia
- Sedation in intensive care units

Anaesthesia:
- Premedication before induction of anaesthesia
- Induction of anaesthesia
- As a sedative component in combined anaesthesia

In children:

- Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia
- Sedation in intensive care units

Anaesthesia:
- Premedication before induction of anaesthesia

These applications for Midazolam 2 mg/ml and 5 mg/ml Solution for Injection are submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC, claiming to be generic medicinal products of Hyponovel 10 mg/5 ml Solution for Injection (PL 00031/0189) and Hyponovel 10 mg/2 ml Solution for Injection (PL 00031/0126), first authorised in the UK to Roche Products Limited on 15th November 1984 and 8th December 1982, respectively.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance.

No clinical studies have been performed and none are required for these applications as the proposed product is an aqueous solution at the time of administration and contains the same concentration of active substance as the reference product, an aqueous solution which is already approved. The pharmacology of midazolam is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Midazolam 2 mg/ml and 5 mg/ml Solution for Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Midazolam</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Hypnotics and sedatives (benzodiazepine derivatives)</td>
</tr>
<tr>
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<td>ATC code: N05CD08.</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>2 mg/ml and 5 mg/ml Solution for Injection</td>
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<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/2511/001-2/DC</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned (CMS)</td>
<td>Ireland (IE)</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 17507/0030-1</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Auden Mckenzie (Pharma Division) Ltd</td>
</tr>
<tr>
<td></td>
<td>McKenzie House</td>
</tr>
<tr>
<td></td>
<td>Bury Street</td>
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<td>UK</td>
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</table>
III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Midazolam

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

Structural formula:

![Chemical Structure]

Molecular formula: C18H13ClFN3

Molecular weight: 325.78

Appearance: White or yellowish, crystalline powder.

Solubility: practically insoluble in water, freely soluble in acetone & in ethanol (96%), soluble in methanol.

Midazolam complies with the European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a Certificate of Suitability.

An appropriate specification is provided for the active substance midazolam, with suitable test methods and limits. Batch analysis data are provided and comply with the proposed specification.

P. Medicinal Product

Other Ingredients

Other ingredients are pharmaceutical excipients sodium chloride, hydrochloric acid, sodium hydroxide (pH adjustment) and water for injections.

All excipients with the exception of hydrochloric acid comply with their European Pharmacopoeia monographs.

Hydrochloric acid complies with the Swiss Pharmacopoeia (Pharmacopoeia Helvetica).

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.
Pharmaceutical Development
The objective of the development programme was to produce medicinal products containing midazolam that could be considered generic medicinal products of Hyponovel 10 mg/5 ml Solution for Injection and Hyponovel 10 mg/2 ml Solution for Injection.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated using commercial-scale batches for each strength and the results are satisfactory.

Finished Product Specification
The finished product specifications proposed for the products is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
These products are packaged in:
2 mg/ml: ampoules composed of clear Type I glass containing 2 ml.
5 mg/ml: ampoules composed of clear Type I glass containing 5 ml.
Pack sizes are 5 and 10 ampoules per carton.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. The primary packaging complies with the European Pharmacopoeia Type I, requirements for glass containers for pharmaceutical use.

Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 24 months for an unopened product with storage instructions, ‘Keep the ampoules in the original carton to protect from light’.
For a diluted product, a shelf-life of 24 hours has been set. This is satisfactory.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labelling are pharmaceutically acceptable.

User testing results have been submitted for a PIL for these products. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.
Conclusion
It is recommended that Marketing Authorisations are granted for these applications from a quality point of view.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of midazolam are well-known. As this is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required. An overview based on a literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

The licensing of these products is not likely to result in an overall increase in environmental exposure to the active substance; therefore an Environmental Risk Assessment is not required.

It is recommended that Marketing Authorisations are granted for these applications from a non-clinical point of view.
III.3 CLINICAL ASPECTS

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

CLINICAL PHARMACOLOGY
No new pharmacokinetic or pharmacodynamic data were submitted with these applications and none were required, as per the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, as the applicant’s products are similar to the reference products in terms of qualitative and quantitative composition and are expected to perform identically \textit{in vivo}.

EFFICACY
No new efficacy data were submitted with these applications and none were required.

SAFETY
No new safety data were submitted with these applications and none were required.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPCs, PIL and labelling are medically satisfactory and consistent with those for the reference products, where appropriate.

CLINICAL EXPERT REPORT
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA FORM
The MAA Forms are medically satisfactory.

CONCLUSIONS
It is recommended that Marketing Authorisations are granted for these applications from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Midazolam 2 mg/ml and 5 mg/ml Solution for Injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
No bioequivalence studies have been performed and none are required for these applications, given the composition of the products and their intended route of administration.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PILs and labelling are satisfactory and consistent with that for the reference products.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with midazolam is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 5

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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