

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Midazolam Injection 2mg in 1ml.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml solution contains 10mg midazolam
Each 25ml solution contains 50mg midazolam

3 PHARMACEUTICAL FORM

Sterile solution for injection.

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 in to account. Standard dosages are provided in the table below. Additional details are provided in the text following the table.

Indication	Adults<60 y	Adult>=60y/debilitated or chronically ill	Children
Conscious sedation	i.v. initial dose:2-2.5mg Titration doses: 1mg Total dose:3.5-7.5 mg	i.v. Initial dose:0.5-1 mg Titration doses:0.5-1 mg Total dose:<3.5 mg	i.v.in patients 6 months-5 years Initial dose:0.05-0.1mg/kg Total dose:<6 mg i.v.in patients 6-12 years Initial dose:0.025-0.05mg/kg Total dose:<10mg rectal>6 months 0.3-0.5 mg/kg i.m.1-15 years 0.05-0.15mg/kg
Anaesthesia premedication	i.m. 0.07-0.1 mg/kg	i.m. 0.025-0.05mg/kg	Rectal>6months 0.3-0.5mg/kg i.m.1-15 years 0.08-0.2 mg/kg
Anaesthesia induction	i.v. 0.15-0.2mg/kg(0.3-0.35 without premedication)	i.v. 0.1-0.2mg/kg(0.15-0.3 without premedication)	
Sedative component in combined anaesthesia	i.v. intermittent doses of 0.03-0.1 mg/kg or continuous infusion of 0.03-0.1mg/kg/h	i.v. lower doses than recommended for adults<60 years	
Sedation in ICU	i.v. Loading dose:0.03-0.3 mg/kg in increments of 1-2.5 mg Maintenance dose: 0.03-0.2 mg/kg/h		i.v. in neonates <32 weeks gestational age 0.03 mg/kg/h i.v in neonates >32 weeks and children up to 6 months 0.06mg/kg/h i.v. in patients>6 months of age Loading dose:0.05-0.3mg/kg Maintenance dose:0.06-0.12mg/Kg/h

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 1mg 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 10mg 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 1mg/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 inter individual sensitivity varies and symptoms of overdose may occur.

Adults

For preoperative sedation and to impair memory of preoperative events, the recommended dose for adults of ASA Physical Status I & II and 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 up titrated 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.

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 sec 4.8).

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

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' below).

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
- pediatric 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 pediatric patients with cardiovascular instability; rapid intravenous administration should be avoided in this population.

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 metabolized 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 coadministered 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 ritonavirboosted 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 α -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

Midazolam should not be used during pregnancy unless clearly necessary. It is preferable to avoid using it for caesarean.

Insufficient data are available on midazolam to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but foetotoxicity 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 foetal adverse effects (inhalation risk in mother, irregularities in the foetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the neonate).

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

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

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.

Where midazolam is used concurrently with other central nervous system depressants (e.g. potent analgesics) recovery may be prolonged. Patients should therefore be assessed carefully before being allowed to go home or resume normal activities.

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 (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 elderly.

Dependence: Use of midazolam-even in therapeutic doses-may lead to the development of physical dependence. After prolonged i.v. administration, 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: Severe cardiorespiratory adverse events have occurred. These have included cardiac arrest, hypotension, bradycardia, 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 especially 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 4.4). Hiccup.

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

Skin and Appendages Disorders: Skin rash, urticarial reaction, 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 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.

The correct information for using Flumazenil can also be obtained from the UK National Poison Information Service by calling on the following telephone number.

Tel: 0844-892-0111 (directs caller to relevant local centre.)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

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

Midazolam is a potent imidazobenzodiazepine, forming water-soluble salts which are stable and well tolerated by injection. Midazolam possesses the typical pharmacological properties of the benzodiazepines, namely hypnotic, anxiolytic, muscle-relaxant and anticonvulsant activity. In clinical use, the induction of sleep is the main action.

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 the 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

Midazolam did not show any evidence of mutagenic activity in *Salmonella typhimurium*, human lymphocytes or in the micronucleus in mice. In cultured hamster cells, midazolam produced dose-dependent reductions in the number of diploid cells and increases in hypodiploidy and hyperdiploidy.

No evidence of carcinogenic potential was seen in rats or mice given midazolam maleate orally in doses up to 9mg/kg/day (25 times a human dose of 0.35mg/kg) for up to 2 years. When midazolam maleate was administered with diet in rats and mice for 2 years at dosages of 1, 9 and 80mg/kg/day, an increased incidence of hepatic tumors was noted in female mice in the highest dose group.

Reproduction toxicology and teratological studies have shown that midazolam is neither embryotoxic nor teratogenic and exerts no influence on the fertility and post-natal development of animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Hydrochloric acid

Sodium hydroxide

Water for injections

6.2 Incompatibilities

Midazolam Injection when mixed with 500ml infusion fluids containing dextrose 4% with sodium chloride 0.18%, dextrose 5% or sodium chloride 0.9% is chemically and physically stable for up to 24 hours at 25°C and up to 72 hours at 2 to 8°C. However, for pharmaceutical microbiological reasons, the product should be used immediately after dilution. When aseptically prepared, the diluted solution may be kept for not more than 24 hours if stored under refrigeration at a temperature between 2-8°C.

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

6.3 Shelf life

Unopened: 3 years.

After reconstitution: not applicable

After first opening: not applicable

6.4 Special precautions for storage

Protect from light.

Store below 25°C.

6.5 Nature and contents of container

Clear One Point Cut (OPC) 5ml & 25ml glass ampoules, glass type I, Ph. Eur.

Pack sizes: 5 x 5ml ampoules; 10 x 5ml ampoules.

5 x 25ml ampoules; 10 x 25ml ampoules

6.6 Instruction for use, handling and disposal

If only part used, discard the remaining solution.

7. MARKETING AUTHORISATION HOLDER

Antigen International Ltd.

Roscrea

Co. Tipperary

Ireland.

8 MARKETING AUTHORISATION NUMBER(S)

PL 02848/0204

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/12/2005

10 DATE OF REVISION OF THE TEXT

22/04/2010