Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Midazolam 2mg/ml Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml solution contains 2mg midazolam.
Each 5ml Ampoule contains 10mg of midazolam

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sterile solution for injection or infusion.
Clear, colourless or slightly yellow sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As intravenous sedative cover before and during minor medical, dental and surgical procedures such as gastroscopy, endoscopy, cystoscopy, bronchoscopy and cardiac catheterisation.

For sedation by continuous infusion in patients in intensive care.

As an alternative intravenous agent for the induction of anaesthesia in high risk and elderly patients, especially where cardiovascular stability is of particular importance.
Induction is more reliable when heavy opiate premedication has been administered or when midazolam is given with a narcotic analgesic such as fentanyl.

4.2 Posology and method of administration

Posology
Intravenous sedation: One or more intravenous administrations over a single operating session.

Adults:An assessment should be made of the degree of sedation necessary for the planned procedure.

The dose should be titrated against the response of the patient. The desired titration end point will depend upon the procedure. Full sedation will be evident by drowsiness, slurred speech but response to commands will be maintained.

As a guide, it is recommended that 1ml of Midazolam 2mg/ml solution (equivalent to 2mg midazolam) be administered intravenously over 30 seconds. If after 2 minutes, sedation is not adequate, incremental doses of 0.25ml to 0.5ml of midazolam 2mg/ml solution (0.5 to 1mg midazolam) should be given.

Usual dose range 2.5mg - 7.5mg total dose (equivalent to around 0.07mg/kg body weight).
Dosages greater than 5.0mg are not usually necessary.

Elderly: **THE ELDERLY ARE MORE SENSITIVE TO THE EFFECTS OF BENZODIAZEPINES. IN THESE PATIENTS DOSES GREATER THAN 3.5MG ARE NOT USUALLY NECESSARY AND LOW DOSES AS LITTLE AS 1MG - 2MG (0.5 – 1.0ML) MAY BE ADEQUATE. THE INITIAL DOSE SHOULD NOT EXCEED 1 - 1.5MG (0.5 - 0.75ML).**

Children:Midazolam Injection has not been evaluated for use as an intravenous sedative in children.

Mode of Administration: For the administration of Midazolam Injection, the patient should be placed in a supine position and remain there throughout the procedure. Resuscitation facilities should always be available, and a second person fully trained in the use of such equipment should always be present.

It is recommended that patients should remain under medical supervision until at least 1 hour has elapsed from the time of injection. They should always be accompanied home by a responsible adult.

Patients who have received Midazolam Injection alone for IV sedation prior to minor procedures should be warned not to drive or operate machinery for 12 hours. 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.

Sedation by continuous infusion in intensive care: For sedation in the intensive care unit, dosages vary considerably, and the dosage of Midazolam Injection should be individualised and titrated to the desired state of sedation according to the clinical need, physical status, age and concomitant medication.

Patients receiving Midazolam Injection for sedation by continuous infusion in the intensive care situation should receive ventilatory support.

Safety of continuous infusion of Midazolam Injection for periods of over fourteen days in duration has not been established in clinical trials.

Adults and children:**Loading dose:** For patients already sedated, a loading dose of midazolam is not required. To induce sedation, a loading dose of 0.03 - 0.3mg/kg is recommended, depending on the level of sedation required. This should be administered over a five-minute period.

Maintenance dose: The dosage varies considerably. A dose between 0.03 - 0.2mg/kg per hour is recommended, commencing at the lower end of the range.
The dosage should be reduced, or the loading dose should even be omitted in hypovolaemic, vasoconstricted and hypothermic patients.

Intravenous bolus sedation:Where analgesia is provided by a narcotic analgesic the latter should be administered first, the dose of midazolam should be carefully titrated and low doses 1 - 2mg (0.5 – 1.0ml) may be adequate. In the elderly, smaller doses as little as 0.5 - 1mg (0.25 - 0.5ml) may be adequate.

Sedation by continuous infusion in intensive care:Where analgesia is provided by narcotic analgesics, the rate of infusion of Midazolam Injection should be titrated carefully to the sedative needs of the patient.

Intravenous induction of anaesthesia:One or more bolus intravenous injections over a single anaesthetic session.
Adults:The dose should be titrated against the individual response of the patient. Midazolam Injection should be given by slow intravenous injection until there is a loss of eyelid reflex, response to commands and voluntary movements.

In anticipating the required dose of midazolam, both the premedication already given and the age of the patient are important. Young, fit unpremedicated patients may require at least 0.3mg/kg body-weight, whereas patients premedicated with an opiate usually require only 0.2mg/kg body-weight.

ELDERLY: **THE ELDERLY ARE MORE SENSITIVE TO THE EFFECTS OF BENZODIAZEPINES. INDUCTION MAY BE ADEQUATE WITH 0.1MG/KG BODY-WEIGHT IN PREMEDICATED PATIENTS AND 0.2MG/KG BODY-WEIGHT IN UNPREMEDICATED PATIENTS.**

Children over 7 years: Midazolam Injection has been shown to be an effective agent for induction of anaesthesia in children over 7 years of age, at a dose of 0.15mg/kg body-weight.

Use in Special Populations:
Renal Impairment:
In patients with renal impairment (creatinine clearance <10ml/min) the pharmacokinetics of unbound midazolam following a single IV dose is similar to that reported in healthy volunteers. However, after prolonged infusion in intensive care unit (ICU) patients, the mean duration of the sedative effect in the renal failure population 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.

Method of administration
Intravenous injection or by intravenous infusion

4.3 Contraindications

- Hypersensitivity to the active substance, benzodiazepines or to any of the excipients listed in section 6.1.
- 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.

When midazolam is used for premedication, adequate observation of the patient after administration is mandatory as inter-individual 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 especially 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 withdrawalsymptoms 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 6months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments toclinical effect and careful respiratory rate and oxygen saturation monitoring are essential (see also '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).

Risk from concomitant use of opioids:
Concomitant use of Midazolam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Midazolamwith opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Midazolam concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (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. This medicinal product contains less than 1mmol sodium (23mg) per ampoule), i.e. essentially sodium free.

4.5 Interaction with other medicinal products and other forms of interactions

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 IV 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.

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 IM administration the effects of CYP3A4 modulation should not substantially differ from those seen with IV midazolam.

Inhibition

- 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.
- 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 with 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.

Induction

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 repiratory depression and/or prolonged sedation.
- Staggered dosing and dosage adjustment should be considered, especially if more than a single IV 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 2mg/ml Solution for Injection/Infusion is not indicated for oral administration.
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.

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.
- Telithromycin increased the plasma levels of oral midazolam 6-fold.

Intravenous anaesthetics

- Disposition of intravenous midazolam was also changed by intravenous propofol (AUC and half-life increased by 1.6-fold).

HIV Protease inhibitors

- **Saquinavir and other HIV protease inhibitors:** Co-administration with protease inhibitors may cause a large increase in the concentration of midazolam.
- Hepatitis C virus (HCV) protease inhibitors: Boceprevir and telaprevir reduce midazolam clearance. This effect resulted in a 3.4-fold increase of midazolam AUC after i.v. administration and prolonged its elimination half-life4-fold.
- 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, the treatment setting should follow the description in the above section for azole antifungals, ketoconazole.

Additional information from oral midazolam

Based on data for other CP3A4 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.

Various drugs/Herbs

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

- Intravenous fentanyl is a weak inhibitor of midazolam elimination: AUC and half-life of i.v. midazolam were increased by 1.5-fold in the presence of fentanyl.

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.
- Tyrosine kinase inhibitors have been shown to be potent inhibitors of CYP3A *in vitro* (imatinib, lapatinib) or *in vivo* (idelalisib). After concomitant administration of idelalisib, oral midazolam exposure was increased on average 5.4-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 600 mg o.d. The terminal half-life decreased by about 50-60%.
- Ticagrelor is a weak CYP3A inducer but has only small effects on intravenously administered midazolam (-12%) and 4-hydroxymidazolam (-23%) exposures.
- The very strong CYP3A4 induction seen after mitotane or enzalutamide resulted in a profound and long-lasting decrease of midazolam levels in cancer patients. AUC of orally administered midazolam was reduced to 5% and 14% of normal values respectively.

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: Repeated 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 about 60%.
- Clobazam and Efavirenz are weak inducers of midazolam metabolism and reduce the AUC of the parent compound by approximately 30%. The 5-fold increase in the ratio of the CYP3A4 generated metabolite α-hydroxymidazolam to midazolam confirms its CYP3A4-inducing effect.
- Vermurafenib modulates CYP isozymes and induces CYP3A4 mildly: Repeat-dose administration resulted in a mean decrease of oral midazolam exposure of 39% (up to 80% in individuals).

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):
Sedative and hypnotics
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, nonrecent H1-antihistamines and centrally acting antihypertensive drugs.

Opioids:

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Midazolam with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Insufficient data are available on midazolam to assess its safety during pregnancy. Animal experiments have not indicated any teratogenic risks with midazolam 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 to mothers who took benzodiazepines chronically during the later stages of pregnancy may have dependence and may be at some risk for 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.

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

Breast-feeding
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.

If insufficient sleep occurs or alcohol is consumed, the likelihood of impaired alertness may be increased (see section 4.5).

4.8 Undesirable effects

The following undesirable effects have been reported(frequency not known cannot be estimated from the available data) to occur when midazolam is injected:

Frequency categories are as follows:
Very common: ≥1/10;
Common ≥1/100 to <1/10;
Uncommon ≥1/1,000 to <1/100
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Immune system disorders:

Not known: Generalised hypersensitivity reactions (skin reactions, cardiovascular reactions, bronchospasm), anaphylactic shock angioedema.

Psychiatric disorders:
Not known: Confusional state, disorientation, changes in libido, euphoric mood, hallucinations
Physical drug dependence and withdrawal syndrome, Abuse.
Paradoxical reactions* such as restlessness, agitation, irritability, nervousness, involuntary movements (including tonic/clonic movements and muscle tremor)*, hyperactivity*, hostility, rage reaction, aggressiveness, anxiety, nightmares, abnormal dreams, psychoses, inappropriate behaviour and other adverse behavioural effects, paroxysmal excitement, have been reported, particularly among children and the elderly (see section 4.4).

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) Cases of abuse have been reported.

Nervous system disorders:
Not known: 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** the duration of which is directly related to the administered dose.
Convulsions have been reported in premature infants and neonates.
Not known: involuntary movements (including tonic/clonic movements and muscle tremor) *, hyperactivity*, Drug withdrawal convulsions

Cardiac disorders:
Not known: Severe cardiorespiratory adverse events have occurred. These have included cardiac arrest, 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:
Not known: Severe cardiorespiratory adverse events including respiratory depression, apnoea, respiratory arrest, dyspnoea, laryngospasm have been reported. Hiccup.

Gastrointestinal system disorders:
Not known: Nausea, vomiting, constipation, dry mouth.

Skin and subcutaneous tissue disorders:
Not known: Skin rash, urticaria, pruritus.

General disorders and administration site disorders:
Not known: Fatigue, erythema and pain on injection site.

Injury, poisoning and procedural complications:
Not known: falls and fractures***

Social circumstances
Not known:Assault*

Vascular disorders:
Not known: Hypotension, vasodilating effects, thrombophlebitis, thrombosis.

*Such paradoxical drug reactions have been reported, particularly among children and the elderly (see section 4.4)
** Anterograde amnesia may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported (see section 4.4).
***An increased risk for falls and fractures has been recorded in benzodiazepine users. The risk of falls and fractures is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.
Renal impairment: There is a greater likelihood of adverse drug reactions in patients with severe renal impairment (see section 4.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail:medsafety@hpra.ie.

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.

Management

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.

Mechanism of action

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 IM or IV 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 IM Injection

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

Absorption after rectal administration

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

Distribution

When midazolam is injected IV, the plasma concentration-time curve shows one or two distinct phases of distribution. The volume of distribution at steady state is 0.7-1.2l/kg. 96-98% of midazolam is bound to plasma proteins. The major fraction of plasma protein binding is due to albumin. There is a slow and insignificant passage of midazolam into the cerebrospinal fluid. In humans, midazolam has been shown to cross the placenta slowly and to enter foetal circulation. Small quantities of midazolam are found in human milk.

Biotransformation
Midazolam is almost entirely eliminated by biotransformation. The fraction of the dose extracted by the liver has been estimated to be 30-60%. Midazolam is hydroxylated by the cytochrome P4503A4 isoenzyme 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-hydroxymidazolam is shorter than 1 hour. When midazolam is given by IV infusion, its elimination kinetics does not differ from that following bolus injection.

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

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

Neonates
In neonates the elimination half-life is on average 6-12 hours, probably due to liver immaturity and the clearance is reduced (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 which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,
Hydrochloric acid,
Sodium hydroxide,
Water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in *section 6.6, Special precautions for disposal of a used medicinal product or waste derived from such medicinal product and other handling of the product.*

6.3 Shelf life

Unopened-:3 years.
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and up to 72 hours at 2 to 8°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 to 8°C, unless reconstitution/ dilution (etc) has been taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C. Keep the ampoules in the outer carton.
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.

6.5 Nature and contents of container

Clear 5ml glass ampoules, glass type I, Ph.Eur.
Pack sizes: 5 x 5ml ampoules, 10 x 5ml ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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.
If only part used, discard the remaining solution.

For single use only.
No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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4045 Kingswood Road
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8 MARKETING AUTHORISATION NUMBER

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