Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Midazolam 5 mg/ml Solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: midazolam as hydrochloride.
Ampoules 5mg/ml; for IV., IM and rectal administration.
Each ml of solution for injection or infusion contains 5mg midazolam (as the hydrochloride).
Each 2ml of solution for injection or infusion contains 10mg midazolam (as the hydrochloride).
Each 5ml of solution for injection or infusion contains 25mg midazolam (as the hydrochloride).

Excipient(s) with known effect:
Sodium 1.97 mg/ml.
For a full list of Excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.
Clear, colourless solution.
pH 2.9-3.7

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Midazolam Solution for Injection or Infusion 5 mg/ml is a short-acting sedative and sleep-inducing drug. The indications are as follows:
In adults and children

- Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia,
- Premedication before induction of anaesthesia,
- Sedation in Intensive Care Units.

In adults

- Induction of anaesthesia,
- As an induction agent or as a sedative component in combined anaesthesia

4.2 Posology and method of administration

Midazolam is a potent sedative that requires dose titration and slow administration. Dose titration is required to optimize safety whilst achieving 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, the dose should be determined with caution and risk factors related to each patient should be taken into account. Standard dosages are shown in the table below; additional details are provided in the text following the table.

Standard Dosage:

Indication	**Adults<60 years**	**Adults 60 years+/debilitated or seriously ill**	**Children**
Conscious sedation	**IV** Initial dose: 2-2.5mg Titration doses: 1mg Total dose: 3.5-7.5mg	**IV** Initial dose: 0.5-1mg Titration doses: 0.5-1mg	**IV in patients 6 months-5 years** Initial dose:

		Total dose: <3.5mg	0.05-0.1mg/kg Total dose: <6mg **IV in patients 6-12 years** Initial dose: 0.025-0.05mg /kg Total dose: < 10mg **Rectal>6 months** 0.3-0.5mg/kg **IM 1-15 years** 0.05-0.15mg/ kg
Anaesthesia premedication	**IV** 1-2 mg repeated **IM** 0.07-0.1mg/kg	**IV** initial dose; 0.5mg Slow uptitration as needed **IM** 0.025-0.05mg/kg	**Rectal> 6 months** 0.3-0.5mg/kg **IM 1-15 years** 0.08-0.2mg/kg
Anaesthesia induction	**IV** 0.15-0.2mg/kg (0.3-0.35 mg/kg without premedication)	**IV** 0.05-015mg/kg (0.15-0.3 mg/kg without premedication)	
Sedative component in combined anaesthesia	**IV** Intermittent doses of 0.03-0.1 mg/kg or continuous infusion of 0.03-0.1 mg/kg/h	**IV** Lower doses than recommended for adults<60 years	
Sedation in ICU	**IV** Loading dose: 0.03-0.3 mg/kg in increments of 1-2.5mg Maintenance dose: 0.03-0.2mg/kg/hr		**IV in neonates<32 weeks gestational age** 0.03 mg/kg/hr **IV in neonates>32 weeks and children up to 6 months** 0.06 mg/kg/hr **IV in patients>6 months** Loading dose: 0.05-0.2mg/kg Maintenance dose: 0.06-0.12mg/ kg/h

Conscious sedation dosage

For conscious sedation prior to diagnostic or surgical intervention, midazolam may be administered IV. The dose must be individualized and titrated, and should not be administered by rapid or single bolus injection. The onset of action is about 2 minutes after the injection. Maximum effect is obtained in about 5 to 10 minutes. However, 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.

Adults
The IV injection of midazolam should be given slowly at a rate of approximately 1mg 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 5mg 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 to 1 mg and given 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 titrated very slowly and carefully. A total dose greater than 3.5 mg is usually not necessary.

Children
IV 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 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, 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 6mg. 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 0.4mg/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 10ml. The 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.

IM administration: the doses used range between 0.05 and 0.15 mg/kg. A total dose greater than 10.0mg is usually not necessary. The IM route should only be used in exceptional cases. Rectal administration is preferred as IM 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 1mg/ml.

ANAESTHESIA DOSAGE

Premedication
Premedication with midazolam given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of apprehension) and pre-operative impairment of memory. Midazolam can also be administered in combination with anticholinergics. For this indication midazolam should be administered IV or IM, 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 pre-operative sedation and to impair memory of pre-operative events, the recommended dose for adults of ASA Physical Status I & II and below 60 years is 1-2 mg IV repeated as needed, or 0.07 to 0.1 mg/kg administered IM. 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 IV dose is 0.5 mg and should be slowly uptitrated as needed. A dose of 0.025 to 0.05 mg/kg administered IM is recommended. In case of concomitant administration of narcotics the midazolam dose should be reduced. The usual dose is 2 to 3 mg.

Paediatric Patients
Neonates and children up to 6 months of age:
The use in children less than 6 months of age is not recommended as available data are limited.

Children over 6 months of age
Rectal administration: The 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.

IM administration: As IM injection is painful, this route should only be used in exceptional cases. Rectal administration is preferred. However, a dose range from 0.08 to 0.2 mg/kg of midazolam administered IM has been shown to be effective and safe. In children between ages 1 and 15 years, proportionally higher doses are required than in adults in relation to body-weight.
In children less than 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 IV or inhalation agents for induction of anaesthesia, the initial dose of each agent should be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents.
The desired level of anaesthesia is reached by stepwise titration. The IV induction dose of midazolam should be given slowly in increments. Each increment of not more than 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 IV 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 IV). If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used. Induction may instead be completed with inhalational anaesthetics. In resistant cases, a total dose of up to 0.6mg/kg may be used for induction, but such larger doses may prolong recovery.
- In premedicated adults over 60 years of age, debilitated or chronically ill patients, the dose should significantly be reduced, e.g., 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 IV doses (range between 0.03 and 0.1 mg/kg) or continuous infusion of IV midazolam (range between 0.03 and 0.1 mg/kg/hr) typically in combination with analgesics. The dose and the intervals between doses vary according to the patient's individual reaction.
In adults over 60 years of age, debilitated or chronically ill patients, lower maintenance doses will be required.

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

Adults

IV loading dose: 0.03 to 0.3 mg/kg should be given slowly in increments. Each increment of 1 to 2.5 mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments. In hypovolaemic, vasoconstricted, or hypothermic patients the loading dose should be reduced or omitted. When midazolam is given with potent analgesics, the latter should be administered first so that the sedative effects of midazolam can be safely titrated on top of any sedation caused by the analgesic.

IV maintenance dose: doses can range from 0.03 to 0.2 mg/kg/h. In hypovolaemic, vasoconstricted, or hypothermic patients the maintenance dose should be reduced. The level of sedation should be assessed regularly. With long-term sedation, tolerance may develop and the dose may have to be increased.
Neonates and children up to 6 months of age
Midazolam should be given as a continuous IV infusion, starting at 0.03 mg/kg/hr (0.5 micrograms/kg/min) in neonates with a gestational age < 32 weeks or 0.06 mg/kg/hr (1 micrograms/kg/min) in neonates with a gestational age > 32 weeks and children up to 6 months.
Intravenous loading doses are not recommended in premature infants, neonates and children up to 6 months, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. The rate of infusion should be carefully and frequently reassessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation.
Careful monitoring of respiratory rate and oxygen saturation is required.

Children over 6 months of age
In intubated and ventilated paediatric patients, a loading dose of 0.05 to 0.2 mg/kg IV should be administered slowly over at least 2 to 3 minutes to establish the desired clinical effect. Midazolam should not be administered as a rapid intravenous dose. The loading dose is followed by a continuous IV infusion at 0.06 to 0.12 mg/kg/hr (1 to 2 micrograms/kg/min). The rate of infusion can be increased or decreased (generally by 25% of the initial or subsequent infusion rate) as required, or supplemental IV doses of midazolam can be administered to increase or maintain the desired effect.
When initiating an infusion with midazolam in haemodynamically compromised patients, the usual loading dose should be titrated in small increments and the patient monitored for haemodynamic instability, e.g., hypotension. These patients are also vulnerable to the respiratory depressant effects of midazolam and require careful monitoring of respiratory rate and oxygen saturation.
In premature infants, neonates and children less than 15 kg of body weight, midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Ideally use a 1mg/ml product but if unavailable this higher strength product should be diluted to 1 mg/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 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 see section 4.4.

4.3 Contraindications

Hypersensitivity to the active substance midazolam or to any of the ingredients listed in section 6.1.
Use of this drug in patients with known hypersensitivity to benzodiazepines.
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 if 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, 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. As with any agent 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 for long-term sedation in intensive care units (ICU).

Dependence
When midazolam is used for 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 the isoenzyme 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 pre-term and former pre-term non-intubated patients. Careful monitoring of respiratory rate and oxygen saturation is required. Rapid injection should be avoided in neonates. 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.

Sodium content:
This medicinal product contains 1.97 mg sodium per ml of solution, equivalent to 0.1% of the WHO recommended maximum daily intake for sodium.
Midazolam Injection 5mg/ml is considered high in sodium. This should be taken into account for those on a low salt diet.

Risk from concomitant use of opioids:
Concomitant use of Midazolam Injection 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 Midazolam Injection with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Midazolam Injection 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).

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.
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 IM administration the effects of CYP3A4 modulation should not substantially differ from those seen with IV 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 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 abovementioned 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 600 mg 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: 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%.
- 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 HI-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.

Opioids:
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Midazolam Injection 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).

4.6 Fertility, pregnancy and lactation

There are insufficient data 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 stage of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period. Consequently, midazolam should not be used during pregnancy unless clearly necessary. It is preferable to avoid using it for caesarean section. The risk for the 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.

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	
frequency not known	Hypersensitivity, angioedema, anaphylactic shock
Psychiatric Disorders	
frequency not known	Confusional state, euphoric mood, hallucinations Agitation*, hostility*, rage*, aggressiveness*, excitement* Physical drug dependence and withdrawal syndrome Abuse
Nervous System Disorders	
frequency not known	Involuntary movements (including tonic/clonic movements and muscle tremor)*, hyperactivity* Sedation (prolonged and postoperative), alertness decreased, somnolence, headache, dizziness, ataxia, anterograde amnesia**, the duration of which is directly related to the administered dose Convulsions have been reported in premature infants and neonates

	Drug withdrawal convulsions
Cardiac Disorders	
frequency not known	Cardiac arrest, bradycardia
Vascular Disorders	
frequency not known	Hypotension, vasodilation, thrombophlebitis, thrombosis
Respiratory Disorders	
frequency not known	Respiratory depression, apnoea, respiratory arrest, dyspnea, laryngospasm, hiccups
Gastrointestinal Disorders	
frequency not known	Nausea, vomiting, constipation, dry mouth
Skin and Subcutaneous Tissue Disorders	
frequency not known	Rash, urticaria, pruritus
General Disorders and Administration Site Conditions	
frequency not known	Fatigue, injection site erythema, injection site pain
Injury, Poisoning and Procedural Complications	
frequency not known	Falls, fractures***
Social Circumstances	
frequency not known	Assault*

*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 few cases prolonged amnesia has been reported (see section 4.4).
***There have been reports of falls and fractures in benzodiazepine users. The risk of falls and fractures is increased in those taking concomitant sedatives (including alcoholic beverages) and in 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). Cases of abuse have been reported.
Severe cardiorespiratory adverse events have occurred. 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).

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.

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. Midazolam has a sedative and sleep-inducing effect of pronounced intensity. It also exerts an anxiolytic, an anticonvulsant and a muscle-relaxing effects. The pharmacological action of midazolam is characterised by short duration because of rapid metabolic transformation. Following IV or IM administration of midazolam, 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 muscle 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 rapidly. Maximum plasma concentration is reached in about 30 minutes. The absolute bioavailability is about 50%.

Distribution
Following IV injection of midazolam, 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. Midazolam is extensively bound (96-98%) to plasma proteins, mainly 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 the 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 isoenzyme and the major urinary and plasma metabolite is alpha-hydroxymidazolam. Plasma concentrations of alpha-hydroxymidazolam are 12% of those of the parent compound. Although pharmacologically active, this metabolite 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 – 500 ml/min. Midazolam is excreted mainly by the kidneys (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 less than 1 hour. When midazolam is given by IV infusion, its elimination kinetics does 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 5-18% lower. 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 being 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 4.4 Special warnings and precautions for use).

Obese
The mean half-life is longer in obese than in non-obese patients (5.9 vs 2.3 hours), 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 4.4 Special warnings and precautions for use).

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 critically ill patients.

Patients with cardiac insufficiency
The elimination half-life is longer in patients with congestive heart failure compared with that in healthy subjects (see 4.4 Special warnings and precautions for use).

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

6.2 Incompatibilities

Admixture with Hartmann's solution is not recommended, as the potency of midazolam decreases.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

Unopened: 2 years
Diluted: 24 hours
Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°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 has taken place in controlled and validated conditions.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the ampoules in the outer carton in order to protect from light.
For the storage condition of the diluted medicinal product see section 6.3

6.5 Nature and contents of container

Clear type I glass ampoules.
2 ml and 5 ml type I glass ampoules in packs of 10.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.
The product should be used immediately after opening.
Diluted product should be discarded if not used within 24 hours. (See section 6.3)
Do not use the product if the solution is discolored (see section 3).
The solution for injection or infusion should be examined visually before administration. Only solutions without visible particles should be used
Compatible solutions for infusions are as follows:

- 5% Glucose Intravenous Infusion BP
- Sodium Chloride Intravenous Infusion BP
- 0.18% Sodium Chloride and 4% Glucose Intravenous Infusion BP

For continuous intravenous infusion, Midazolam solution for injection may be diluted to the range of 0.05mg-1mg/ml with infusion solutions listed above

7 MARKETING AUTHORISATION HOLDER

Martindale Pharmaceuticals Ltd
Bampton Road
Harold Hill
Romford
RM3 8UG
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0361/021/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th January 2011
Date of last renewal: 30th May 2013

10 DATE OF REVISION OF THE TEXT

September 2019