NEW ZEALAND DATA SHEET

MYLAN MIDAZOLAM

1. Product Name

Mylan Midazolam, 1 mg/mL or 5 mg/mL, ampoules

2. Qualitative and Quantitative Composition

Each ampoule contains 1 mg/mL or 5 mg/mL of midazolam

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Mylan Midazolam solution for injection is a clear, colourless solution, packaged in a clear colourless ampoule.

4. Clinical Particulars

4.1 Therapeutic indications

Premedication before induction of anaesthesia (intramuscular or, especially in children, rectal, intranasal or oral administration).

Conscious sedation before diagnostic or surgical interventions carried out under local anaesthesia (intravenous administration), or in children intranasal or oral administration.

Long-term sedation in intensive care units (intravenous administration as bolus injection or continuous infusion).

Induction and maintenance of anaesthesia. As an induction agent in inhalation anaesthesia or a sleep-inducing component in combined anaesthesia, including total intravenous anaesthesia (intravenous injection, intravenous infusion).

Ataralgesia in combination with ketamine in children (intramuscular administration).

4.2 Dose and method of administration

This product is for single patient use only. Use once and discard any residue.

In the case of elderly patients with organic cerebral changes or impaired cardiac and respiratory function, the dosage should be determined with caution, the special factors relating to each patient being taken into consideration.

Initial and subsequent intravenous injections must be given slowly (approximately 2.5 mg in 10 seconds for induction of anaesthesia and 1 mg in 30 seconds for conscious sedation). The medicine takes effect about two minutes after the injection is started. Dosage should be individualised.

Premedication before an operation

Intramuscular administration

In patients suffering from pain before an intervention.

Administration alone or in combination with anticholinergics and possibly analgesics. These doses should be administered about 30 minutes before induction of anaesthesia.

Adults: 0.07-0.10 mg/kg bodyweight intramuscular according to age and general condition of the patient. Usual dosage about 5 mg.

Children: Proportionately higher doses are required than in adults in relation to bodyweight (0.15-0.20 mg/kg bodyweight intramuscular).

Elderly and debilitated patients: 0.025 - 0.05 mg/kg bodyweight intramuscular

Rectal administration

Children: For preoperative sedation. Rectal administration of the ampoule solution by means of a plastic applicator fixed on the end of a syringe, 0.35-0.45 mg/kg bodyweight 20-30 minutes before induction of general anaesthesia. If the volume to be administered is too small, water may be added up to a total volume of 10 ml.

Intranasal administration

Children: 0.2 mg/kg, 10-15 minutes prior to anaesthesia.

Oral administration

Children: 0.5 mg/kg, 15-30 minutes prior to anaesthesia.

Conscious sedation

Intravenous conscious sedation

For conscious sedation in diagnostic or surgical interventions carried out under local anaesthesia.

Adults: The initial dose should not exceed 2.5 mg intravenous 5-10 minutes before the beginning of the operation. Further doses of 1 mg may be given as necessary. A total dose greater than 5 mg is not usually necessary to reach the desired endpoint. In cases of severe illness, particularly if the patient is in poor general condition or of advanced age, the initial dose must be reduced to 1-1.5 mg. Total doses greater than 3.5 mg are not usually necessary.

Intranasal conscious sedation

Children: 0.2 mg/kg, 10-15 minutes before the intervention.

Oral conscious sedation

Children: 0.2 - 0.5 mg/kg, 15-30 minutes before the intervention.

Sedation in intensive care units

Intravenous sedation

For sedation in ICU, the dosage should be individualised and midazolam titrated to the desired state of sedation according to the clinical need, physical status, age, concomitant medication.

Adults

Loading dose: 0.03 - 0.3 mg/kg.

Maintenance dose: 0.03 - 0.2 mg/kg/hr. The dosage should be reduced or the loading dose should even be omitted in hypovolemic, vasoconstricted and hypothermic patients.

Induction and maintenance of anaesthesia

Intravenous injection

Adults

Induction: the dose is 10-15 mg intravenous in combination with analgesics. A sufficiently deep level of sleep is generally achieved after 2-3 minutes.

Maintenance: for maintenance of the desired level of unconsciousness, further small doses should be injected intravenously. The dose and the intervals between doses vary according to the individual patient's reaction. Alternatively, midazolam can be administered by continuous infusion.

Intravenous continuous infusion

Adults: for intravenous anaesthesia combined with ketamine, 0.03 - 0.1 mg/kg/hr; narcotics, 0.03 - 0.3 mg/kg/hr. High-risk surgical patients, elderly and debilitated patients require lower dosages.

Intramuscular administration

Children: a combination of the sleep-inducing and amnesia-inducing midazolam with ketamine (ataralgesia) is recommended. Midazolam intramuscular (0.15-0.20 mg per kg bodyweight) in combination with 50-100 mg ketamine intramuscular (4-8 mg per kg bodyweight). A sufficiently deep level of sleep is generally achieved after 2-3 minutes.

Rectal administration

Children: see Premedication before an Operation.

Method of administration

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.

When administered orally, the bitter taste of midazolam injection may be masked by small quantities of apple juice, sweetened fruit syrup or powdered soft drink.

4.3 Contraindications

Use of this medicine in patients with known hypersensitivity to benzodiazepines or to any component of the product.

4.4 Special warnings and precautions for use

Intravenous midazolam should only be used when age- and size-appropriate resuscitation facilities are available, as intravenous administration of midazolam may depress myocardial contractility and cause apnoea. Severe cardiorespiratory adverse events have occurred on rare occasions. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest. Such life-threatening incidents are more likely to occur in adults over 60 years of age, those with pre-existing respiratory insufficiency or impaired cardiac function and paediatric patients with cardiovascular instability, particularly when the injection is given too rapidly or when a high dosage is administered.

Beonzodiazepines are not recommended for the primary treatment of psychotic illness.

Premedication

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.

High-risk patients

Special caution should be exercised when administering midazolam parenterally to patients representing a higher risk group:

- adults over 60 years of age
- debilitated or chronically ill patients
- patients with impaired respiratory function
- patients with impaired kidney function,
- impaired hepatic function (benzodiazepines may precipitate or exacerbate encephalopathy in patients with severe hepatic impairment).
- impaired cardiac function
- paediatric patients with cardiovascular instability

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

Tolerance

Some loss of efficacy has been reported when midazolam has been 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.

Withdrawal symptoms

During prolonged treatment with midazolam in ICU, physical dependence may develop. Abrupt cessation of therapy may lead to withdrawal symptoms such as headaches, muscle pain, anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood changes, hallucinations and convulsions. In severe cases, the following symptoms may occur: depersonalization, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact.

Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, it is recommended that the dose is decreased gradually.

Concomitant use of alcohol/CNS depressants

The concomitant use of midazolam with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of midazolam, possibly including severe sedation that could result in coma or death, clinically relevant respiratory and/or cardiovascular depression.

Risks from concomitant use with opioids

Concomitant use of benzodiazepines, including midazolam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe midazolam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when midazolam is used with opioids (see section 4.5).

Medical history of alcohol or drug abuse

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

Amnesia

Midazolam causes anterograde amnesia at therapeutic doses (frequently this effect is very desirable in situations such as before and during surgical and diagnostic procedures), the risk and duration of which is directly related to the administered dose. Prolonged amnesia can present problems in outpatients, who are scheduled for discharge following intervention.

Discharging criteria

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

"Paradoxical" reactions

Paradoxical reactions such as restlessness, agitation, irritability, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, delusion, anger, aggressiveness, anxiety, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, paroxysmal excitement and assault have been reported to occur with midazolam. These reactions may occur with higher doses and/or when the injection in given rapidly. The rare incidence of susceptibility to such reactions has been reported among children and at higher intravenous doses in the elderly. Should such symptoms suggestive of a paradoxical reaction occur, discontinuation of the drug should be considered.

Altered elimination of midazolam

Elimination of midazolam may be delayed in patients receiving compounds that inhibit or induce certain hepatic enzymes (particularly cytochrome P450 3A4) and the dose of midazolam may need to be adjusted accordingly (see section 4.5).

When midazolam is given intravenously for a prolonged period and in combination with saquinavir, an initial dose reduction of midazolam of 50% is recommended (see section 4.5).

It is advisable to lower doses of intravenous midazolam when co-administered with erythromycin (see section 4.5).

Displacement of midazolam from its plasma protein binding sites by sodium valproate may increase the response to midazolam. Care should be taken to adjust the midazolam dose in patients with epilepsy on treatment with sodium valproate (see section 4.5).

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

Sleep apnoea

Midazolam ampoules should be used with extreme caution in patients with sleep apnoea syndrome and patients should be regularly monitored.

Pre-term infants and neonates

Due to an increased risk of apnoea, extreme caution is advised when sedating pre-term and former pre-term patients whose trachea is not intubated.

Rapid injection should be avoided in the neonatal population.

Neonates have reduced and/or immature organ function and are vulnerable to profound and/or prolonged respiratory effects of midazolam. Therefore, careful monitoring of respiratory rate and oxygen saturation is required.

Paediatric patients

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.

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

Other

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, owing to pre-existing muscle weakness.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on midazolam

The metabolism of midazolam is predominantly mediated by cytochrome P450 3A4 (CYP3A4, CYP3A5) isozymes. Approximately 25 % of the total cytochrome P450 system in the adult liver is from the CYP3A4 subfamily. Inhibitors (see section 4.4) and inducers of CYP3A may increase and decrease the plasma concentrations and subsequently, the pharmacodynamic effects of midazolam. No other mechanism than modulation of CYP3A activity has been proven as a source for a clinically relevant pharmacokinetic drug-drug interaction with midazolam. Midazolam is not known to change the pharmacokinetics of other drugs.

When co-administered with a CYP3A inhibitor, the clinical effects of midazolam may be stronger and also longer lasting and a lower dose may be required. Conversely the effect of midazolam may be weaker and of a shorter duration when co- administered with a CYP3A inducer and a higher dose may be required.

Interactions studies conducted with midazolam ampoules

CYP3A4 inhibitors

Azole antifungals

Ketoconazole and voriconazole increased the plasma concentration of intravenous midazolam by 5-fold and by 3-4 fold respectively, while the terminal half-life increased by about 3-fold. If parenteral midazolam is co-administered with the strong CYP3A inhibitor, 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 intravenous dose of midazolam is administered.

Fluconazole and itraconazole both increased the plasma concentrations of intravenous midazolam by 2 – 3-folds 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.

Macrolide antibiotics

Erythromycin: Co-administration of midazolam and erythromycin prolonged the elimination half-life of midazolam from 3.5 to 6.2 hours. Although only relatively minor pharmacodynamic changes were observed, it is advised to adjust doses of intravenous midazolam, especially if high doses are being administered (see section 4.4).

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

Intravenous anaesthetics

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

Cimetidine and ranitidine

Cimetidine increased the steady-state plasma concentration of midazolam by 26%, whereas ranitidine had no effect.

Co-administration of midazolam and cimetidine or ranitidine had no clinically significant effect on the pharmacokinetics and pharmacodynamics of midazolam. These data indicate that intravenous midazolam can be used in usual doses with cimetidine and ranitidine and dosage adjustment is not required.

Cyclosporin

There is no pharmacokinetic and pharmacodynamic interaction between cyclosporin and midazolam. Therefore, the dosage of midazolam needs no adjustment when given concomitantly with cyclosporin.

Nitrendipine

Nitrendipine did not affect the pharmacokinetics and pharmacodynamics of midazolam. Both medicines can be given concomitantly and no dosage adjustment of midazolam is required.

Protease inhibitors

Saquinavir and other HIV protease inhibitors: 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 co-administered with HIV protease inhibitors, treatment setting should follow the description in the section above for ketoconazole within azole antifungals (see section 4.4).

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-life 4-fold.

Oral contraceptives

The pharmacokinetics of intramuscular midazolam was not affected by the use of oral contraceptives. Both medicines can be given concomitantly and no dosage adjustment of midazolam is required.

Other interactions

Sodium valproate

Displacement of midazolam from its plasma protein binding sites by sodium valproate may increase the response to midazolam and, therefore, care should be taken to adjust the midazolam dosage in patients with epilepsy (see section 4.4).

Lidocaine

Midazolam had no effect on the plasma protein binding of lidocaine in patients undergoing anti-arrhythmic therapy or regional anaesthesia with lidocaine.

Halothane

The intravenous administration of midazolam decreases the minimum alveolar concentration (MAC) of halothane required for general anaesthesia.

Fentanyl

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

Alcohol

Alcohol may enhance the sedative effect of midazolam.

Opioids

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. The potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Drugs that induce CYP3A

Rifampicin

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

Ticagrelor is a weak CYP3A inducer [246] but has only small effects on intravenously administered midazolam (-12%) and 4-hydoxy-midazolam (-23%) exposures.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk summary statement

Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. However insufficient data are available on midazolam to assess its safety during pregnancy. Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

The administration of midazolam in the last trimester of pregnancy or at high doses during labour has been reported to produce irregularities in the foetal heart rate, hypotonia, poor sucking and hypothermia and moderate respiratory depression in the neonate. Moreover, infants born to 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.

An increased risk of congenital malformation associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested.

Preclinical data

Published studies in pregnant primates demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (see also section 5.3).

Breast-feeding

Since midazolam passes into breast milk, Mylan Midazolam should not be administered to breast-feeding mothers.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following adverse effects have been reported to occur when midazolam is injected:

Central and peripheral nervous system and psychiatric disorders

Drowsiness and prolonged sedation, reduced alertness, confusion, euphoria, hallucinations, fatigue, 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.

Paradoxical reactions such as restlessness, agitation, irritability, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, nervousness, hostility, anger,, aggressiveness, anxiety, nightmares, abnormal dreams, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, paroxysmal excitement and assault, have been reported, particularly among children and the elderly.

Convulsions have been reported in premature infants and neonates.

Changes in libido have been reported occasionally.

Dependence

Use of midazolam - even in therapeutic doses - may lead to the development of physical dependence. After prolonged intravenous administration, discontinuation, especially abrupt discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions.

Abuse has been reported in poly-drug abusers.

Gastrointestinal system disorders

Nausea, vomiting, constipation, dry mouth.

Cardiorespiratory disorders

Severe cardiorespiratory adverse events have occurred on rare occasions. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest. Such 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).

The following other cardiorespiratory adverse events have been reported: hypotension, slight increase in heart rate, bradycardia, vasodilating effects, dyspnoea and hiccough. In isolated cases laryngospasm has occurred following injection of midazolam.

Skin and appendages disorders

Skin rash, urticarial reaction, pruritus.

Immune system disorders

Generalised hypersensitivity reactions (skin reactions, cardiovascular reactions, bronchospasm), angioedema, anaphylactic shock.

Local reactions

Erythema and pain on injection site, thrombophlebitis, thrombosis.

Injury, poisoning and procedural complications

There have been reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Symptoms

The symptoms of overdose are mainly an intensification of the pharmacological effects; drowsiness, mental confusion, lethargy and muscle relaxation or paradoxical excitation. As with other benzodiazepines, overdosage should not present a threat to life unless combined with other CNS depressants including alcohol. More serious symptoms would be areflexia, hypotension, cardiorespiratory depression, apnoea and, rarely, 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

In most cases only observation of vital functions is required and initiate supportive measures as indicated by the patient's clinical state. In the management of overdose special attention should be paid to the respiratory and cardiovascular functions in intensive care.

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 the benzodiazepine antagonist Anexate® (active ingredient: flumazenil). 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).

For further advice on management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and sedatives, 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 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 characterized by rapid onset and, because of rapid metabolic transformation, short duration. Because of its low toxicity, midazolam has a wide therapeutic range.

Midazolam has a very rapid sedative and sleep-inducing effect of pronounced intensity. It also exerts an anxiolytic, an anticonvulsant and a muscle-relaxant effect.

After intramuscular or intravenous administration anterograde amnesia of short duration occurs (the patient does not recall events that occurred during the peak of activity of the compound).

5.2 Pharmacokinetic properties

Absorption

Absorption after intramuscular injection

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

Absorption after intranasal administration

Midazolam is absorbed quickly. Mean peak plasma concentrations are reached within 10.2 to 12.6 minutes. The bioavailability is between 55% and 57%.

Absorption after oral administration

Oral midazolam is absorbed rapidly from the gastrointestinal tract and undergoes extensive first-pass hepatic metabolism. Peak plasma concentrations are reached within 1 hour. Bioavailability is between 40% and 50%.

Distribution

When midazolam is injected intravenously, 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.

Biotransformation

Midazolam is almost entirely eliminated by biotransformation. Midazolam is hydroxylated by the cytochrome P450 3A4 isozyme. α-hydroxymidazolam is the major urinary and plasma metabolite. 60-80% of the dose is excreted in urine as glucuroconjugated α-hydroxymidazolam. Plasma concentrations of α-hydroxymidazolam are 12% those of the parent compound. α-hydroxymidazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous midazolam. There is no evidence of a genetic polymorphism in the oxidative metabolism of midazolam (see section 4.5).

Elimination

In healthy volunteers, the elimination half-life is between 1.5 - 2.5 hours. Plasma clearance is in the range of 300-500 ml/min. 60-80% of the dose is excreted in urine as glucuroconjugated α-hydroxymidazolam. Less than 1% of the dose is recovered in urine as unchanged drug. The elimination half-life of the metabolite is shorter that 1 hour. When midazolam is given by intravenous 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. However, the elimination half-life ($t_{½}$) after intravenous and rectal administration is shorter in children 3-10 years 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).

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 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

Animal toxicology and/or pharmacology

Published studies in animals demonstrate that the use of anaesthetic and sedative agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory.

In a published study conducted on rhesus monkeys, administration of an anaesthetic dose of ketamine for 24 hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the foetus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing

brain of the offspring of rhesus macaques. With respect to brain development, this time period corresponds to the third trimester of gestation in the human.

The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits. Healthcare providers should balance the benefits of appropriate anaesthesia in pregnant women, neonates and young children who require procedures with the potential risks suggested by the nonclinical data.

6. Pharmaceutical Particulars

6.1 List of excipients

Sodium chloride (9 mg/1 mL sodium chloride in the 5 mg/5 mL Mylan Midazolam ampoule and 5 mg/1 mL sodium chloride in the 15 mg/3 mL Mylan Midazolam ampoule), hydrochloric acid and sodium hydroxide for pH adjustment, and water for injections.

6.2 Incompatibilities

Do not dilute Mylan Midazolam solution for injection with macrodex 6% in dextrose.

Do not mix Mylan Midazolam solution for injection in alkaline solution. Midazolam precipitates in sodium bicarbonate.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package below 25°C.

Protect from light.

Use only once and discard any remaining portion.

6.5 Nature and contents of container

Mylan Midazolam 1 mg/1 mL

5 mg/5 mL: 5 Ampoules and 10 Ampoules

Mylan Midazolam 5 mg /1 mL

5 mg/1 mL: 5 Ampoules and 10 Ampoules
15 mg/3 mL: 5 Ampoules
50 mg/10 mL: 5 Ampoules

Not all pack sizes or presentations may be marketed.

6.6 Special precautions for disposal and other handling

Compatibility with infusion solutions

Midazolam may be mixed in the same syringe with frequently used premedicants: morphine sulfate, pethidine, atropine sulfate or hyoscine. Midazolam is compatible with normal saline, glucose 5% and 10% in water, fructose intravenous infusion (levulose 5%), potassium chloride, sodium chloride and calcium chloride intravenous infusion (Ringer's solution) and compound sodium lactate intravenous infusion (Hartmann's solution).

To avoid potential incompatibility with other solutions, midazolam must not be mixed with any solution except those listed above.

Mylan midazolam contains no antimicrobial preservative. It is for single use in one patient only. To reduce microbiological hazard, it is recommended that the infusion commence as soon as possible after preparation and in any case within 24 hours. Storage of prepared infusion should be at 2°C - 8°C.

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

7. Medicines Schedule

Controlled Drug (C5)

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

19 May 2011

10. Date of Revision of the Text

27 June 2018

Section	Summary of Changes (to align with innovator)
-	Revised to SmPC format
4.4	Additional warnings regarding hepatic encephalopathy, withdrawal symptoms, concomitant use with alcohol and opioids, paradoxical reactions and sleep apnoea
4.5	Additional information on effects of other medicines on midazolam and drug interactions including antifungals, macrolide antibiotics, protease inhibitors, fentanyl, concomitant use of benzodiazepines and opioids, drugs that induce CYP3A
4.6	Additional information regarding risks during pregnancy and fertility added
4.7	Additional situations where alertness may be impaired
4.8	Additional adverse reactions
5.3	Addition of animal toxicology and pharmacology data relating to use in pregnancy