NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Midazolam 1 mg/mL and 5 mg/mL solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of Midazolam Injection contains 1 mg and 5 mg midazolam.

Each vial of Midazolam Injection 1 mg/mL contains 8 mg/mL sodium.

Each vial of Midazolam Injection 5 mg/mL contains 8 mg/mL sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Midazolam Injection is a sterile, isotonic, clear, colourless to pale yellow solution in a ready-to-use, single dose presentation. Midazolam Injection contains midazolam.

Routes of Administration: Intravenous (i.v.), intramuscular (i.m.), rectal, intranasal or oral (see section 4.1).

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

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

Long-term sedation in intensive care units (i.v. 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 (i.v. injection, i.v. infusion).

Ataralgesia in combination with ketamine in children (i.m. administration).

4.2 Dose and Method of Administration

Dose

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 to 0.10 mg per kg bodyweight i.m 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 to 0.20 mg per kg bodyweight i.m.).

Elderly and debilitated patients: 0.025 to 0.05 mg/kg bodyweight i.m.

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 to 0.45 mg/kg bodyweight 20 to 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 to 15 minutes prior to anaesthesia.

Oral administration

Children: 0.5 mg/kg, 15 to 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 i.v. 5 to 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 to 1.5 mg. Total doses greater than 3.5 mg are not usually necessary.

Intranasal conscious sedation

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

Oral conscious sedation

Children: 0.2 to 0.5 mg/kg, 15 to 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 to 0.3 mg/kg.

Maintenance dose: 0.03 to 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 to 15 mg i.v. in combination with analgesics. A sufficiently deep level of sleep is generally achieved after 2 to 3 minutes.

Maintenance: for maintenance of the desired level of unconsciousness, further small doses should be injected i.v. 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 to 0.1 mg/kg/hr; narcotics, 0.03 to 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 i.m. (0.15 to 0.20 mg per kg bodyweight) in combination with 50 to 100 mg ketamine i.m. (4 to 8 mg per kg bodyweight). A sufficiently deep level of sleep is generally achieved after 2 to 3 minutes.

Rectal administration

Children: see ***Premedication before an Operation***, Rectal administration, *Children*.

Method of Administration

Compatibility with infusion solutions. The midazolam ampoule solution can be diluted with sodium chloride 0.9%, dextrose 5% and 10%, levulose 5%, Ringer's solution and Hartmann's solution in a mixing ratio of 15 mg midazolam per 100 to 1,000 mL infusion solution. These

solutions remain physically and chemically stable for 24 hours at room temperature (or three days at 5°C).

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.

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

Special Dosage Instructions

Renal impairment

In patients with severe renal impairment, Midazolam may be accompanied by more pronounced and prolonged sedation, possibly including clinically relevant respiratory and cardiovascular depression. Midazolam should therefore be dosed carefully in this patient population and titrated for the desired effect (see section 4.4).

Hepatic impairment

The clinical effects in patients with hepatic impairment may be stronger and prolonged. The dose of Midazolam may have to be reduced and vital signs should be monitored (see sections 4.4 and 5.2).

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.

4.3 Contraindications

- Patients with a hypersensitivity to benzodiazepines or any other component of the product.
- Patients with Myasthenia gravis.
- Patients in shock, coma or in acute alcoholic intoxication with depression of vital signs.
- Patients with acute narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma only if they are receiving appropriate therapy. Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with midazolam. Patients with glaucoma have not been studied.

4.4 Special Warnings and Precautions for Use

Risks from concomitant use with opioids

Concomitant use of benzodiazepines, including midazolam, alcohol or/and CNS depressants, including opioids may result in profound sedation, respiratory depression, coma, and death, should be avoided. 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. 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. Opioid premedication also reduces the ventilatory response to carbon dioxide stimulation. Advise both patients and caregivers about the risks of respiratory depression and sedation when midazolam is used with opioids (see section 4.5).

As with other benzodiazepines midazolam may have the potential to cause dependence. Benzodiazepines should be avoided in patients with a history of alcohol or drug abuse. The risk of dependence increases with the duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse. Benzodiazepines are not recommended for the primary treatment of psychotic illness.

General

Intravenous midazolam should only be used where appropriate equipment and personnel are available for continuous monitoring of cardiorespiratory function and for resuscitation procedures when age- and size-appropriate resuscitation facilities are available, as i.v. 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.

Midazolam must never be used without individualisation of dosage. Midazolam should not be administered by rapid or single bolus intravenous administration (see section 4.2). Extravasation should also be avoided. The hazards of intra-arterial injection of midazolam into humans are unknown. Precautions against unintended intra-arterial injection should be taken.

Patients should be continuously monitored for early signs of under-ventilation or apnoea. Vital signs should continue to be monitored during the recovery period. During intravenous application of midazolam respiratory depression, apnoea, respiratory arrest and/or cardiac arrest have occurred. In some cases where this was not recognised promptly and treated, hypoxic encephalopathy or death has resulted. These life-threatening incidents may occur especially in

elderly patients or patients with pre-existing respiratory insufficiency, especially if the injection is given too rapidly or with excessive doses.

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

- adults over 60 years of age
- high-risk surgical patients
- debilitated or chronically ill patients
- patients with chronic respiratory insufficiency and with limited pulmonary reserve because of the possibility of apnoea or respiratory depression may occur.
- patients with chronic renal failure, impaired hepatic function (benzodiazepines may precipitate or exacerbate encephalopathy in patients with severe hepatic impairment) or with congestive heart failure
- 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.

Preoperative sedation

Adequate observation of the patient after preoperative sedation of Midazolam Injection is mandatory as individual sensitivity varies and symptoms of overdose may occur.

Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of midazolam.

Elderly patients frequently have inefficient function of one or more organ systems and dosage requirements have been shown to be reduced with age. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly.

In some intensive care patients, and in some elderly patients given midazolam by intravenous infusion for prolonged sedation, the elimination half-life was found to increase by up to six times (see section 5.2).

Particular care should be exercised in the use of intravenous midazolam in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received midazolam. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with an opioid.

Withdrawal symptoms

During prolonged treatment with midazolam in ICU, physical dependence may develop. Abrupt cessation of therapy may lead to withdrawal symptoms. The following withdrawal symptoms

may occur: headaches, diarrhoea, muscle pain, extreme anxiety, tension, sleep disturbances, 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 that the dose is decreased gradually.

In severe cases, the following symptoms may occur: depersonalisation, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact.

"Paradoxical" reactions

Reactions such as restlessness, agitation, irritability, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, combativeness, delusion, anger, anxiety, nightmares, hallucinations, psychoses, inappropriate behavior, hostility, rage reaction, aggression, paroxysmal excitement and assault or other adverse behavioural effects have been reported. The highest incidence of susceptibility to such reactions has been reported among children and the elderly. Should such reactions occur, the response to each dose of midazolam and all other drugs including local anaesthetics should be evaluated before proceeding. These reactions may be due to inadequate or excessive dosing or improper administration of midazolam, however, consideration should be given to the possibility of cerebral hypoxia or true paradoxical reactions. Should such reactions occur, the response to each dose of midazolam and all other drugs including local anaesthetics should be evaluated before proceeding. If midazolam is the suspected cause, the use of the drug should be discontinued.

The hazards of intra-arterial injection of midazolam solutions into humans are unknown; therefore, precautions against unintended intra-arterial injection should be taken. Extravasation should also be avoided.

After parenteral administration of midazolam, patients should not be discharged from hospital for at least 3 hours, and responsibility for medical supervision of discharge shall lie with a physician (preferably the treating physician) and then, if possible, only if accompanied by a responsible person. The decision as to when patients may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualised. Gross tests of recovery from the effects of midazolam cannot be relied upon to predict reaction time under stress. When midazolam is used with other drugs during anaesthesia, the contribution of these can vary and should also be considered.

Midazolam does not protect against the increase in intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anaesthesia.

Since an increase in cough reflex and laryngospasm may occur with peroral endoscopic procedures, the use of a topical anaesthetic agent and the availability of necessary counter measures are recommended. The use of an opioid premedicant is recommended for bronchoscopies.

Administration of a muscle relaxant may sometimes be necessary to overcome midazolam-associated hiccoughs.

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

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 may develop. The risk of dependence increases with dose and duration of treatment.

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.

Altered elimination

Elimination of midazolam may be delayed in patients receiving compounds that inhibit certain hepatic enzymes (particularly cytochrome P450 3A4) (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).

Use in the elderly

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

Paediatric use

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

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.

Paediatric neurotoxicity

Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anaesthetic agents early in life. These studies have substantial limitations, and it is not clear if the observed effects are due to the anaesthetic/analgesic/sedation drug administration or other factors such as the surgery or underlying illness.

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy. The clinical significance of these nonclinical finding is yet to be determined.

With inhalation or infusion of such drugs, exposure is longer than the period of inhalation or infusion. Depending on the drug and patient characteristics, as well as dosage, the elimination phase may be prolonged relative to the period of administration.

Safety and effectiveness of midazolam in children below the age of 8 have not been established. Pharmacokinetics in children have not been established and may differ from adults.

Nonclinical research has shown that administration of anaesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate GABA activity can increase neuronal cell death in the brain and result in long-term cognitive deficits of juvenile animals when administered at either high doses, or for prolonged periods, or both during the period of peak brain development. The mechanism of action of midazolam includes potentiation of GABA activity.

Use in renal impairment

There is a greater likelihood of adverse drug reactions in patients with severe renal impairment (see section 4.2).

Use in hepatic impairment

Hepatic impairment reduces the clearance of intravenous midazolam with a subsequent increase in terminal half-life. Therefore, the clinical effects may be stronger and prolonged. The required dose of midazolam may have to be reduced and proper monitoring of vital signs should be established (see section 4.2).

Effects on laboratory tests

Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

4.5 Interactions with Other Medicines and Other Forms of Interaction

Specific interaction studies

Midazolam can enhance the central sedative effect of neuroleptics, tranquillisers, antidepressants, sleep-inducing drugs, analgesics, anaesthetics, antipsychotics, anxiolytics,

antiepileptic drugs and sedative antihistamines. This potentiation of effect can in certain cases be of advantage therapeutically.

There is a potentially relevant interaction between midazolam and compounds which inhibit or induce certain hepatic enzymes (particularly CYP3A). Data clearly indicates that these compounds influence the pharmacokinetics of midazolam and this may lead to altered degree and/or duration of prolonged sedation. At present, enzyme induction is known to occur *in vivo* with rifampicin, carbamazepine and phenytoin, and enzyme inhibition occurs with cimetidine, erythromycin, diltiazem, verapamil, ketoconazole, fluconazole, itraconazole, ritonavir and saquinavir.

Therefore patients receiving the above compounds or others which inhibit CYP3A together with midazolam should be monitored carefully for the first few hours after administration of midazolam. During long-term midazolam infusions, a reduction of up to 50% of the initial dose followed by careful titration is recommended. Studies have shown that ranitidine has no influence on the pharmacokinetics of parenterally given midazolam.

In some patients the mutual potentiation of alcohol and midazolam can produce unforeseeable reactions (no alcoholic beverages for at least 12 hours after parenteral administration).

The sedative effect of intravenous midazolam is accentuated by premedication. Consequently, the dosage of midazolam should be adjusted according to the type and amount of premedication administered.

The plasma concentration of midazolam, following oral administration, has been shown to increase when used in combination with erythromycin, which results in a potentiation of midazolam's sedative effect. A much smaller change in plasma concentration with no observed potentiation of the sedative effects was observed following intravenous administration of midazolam, however, caution is advised.

A moderate reduction in induction dosage requirements of thiopentone (about 15%) has been noted following use of intramuscular midazolam for premedication. Simultaneous administration of cimetidine (but not ranitidine) has been reported to reduce clearance of midazolam. 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.

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

The intravenous administration of midazolam decreases the minimum alveolar concentration (MAC) of halothane required for general anaesthesia. This decrease correlates with the dose of midazolam administered. The effects of midazolam can be reversed by the benzodiazepine antagonist flumazenil.

The metabolism of midazolam is predominantly mediated by cytochrome P450 3A4 (CYP3A4) isozyme. 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 this isozyme may lead to interaction with midazolam.

Pharmacokinetic drug-drug interaction (DDI)

Midazolam is almost exclusively metabolised by CYP3A (primarily CYP 3A4 and also CYP 3A5). Inhibitors and inducers of CYP3A have the potential to increase and decrease the plasma concentrations and, subsequently, the pharmacodynamic effects of midazolam. Therefore, it is recommended to carefully monitor the clinical effects and vital signs during the use of midazolam when co-administered with a CYP3A inhibiting or inducing drug.

No mechanism other than modulation of CYP3A activity has been proven as a source for a clinically relevant pharmacokinetic DDI with midazolam. However, acute protein displacement from albumin is a theoretical possibility of drug interaction with drugs that have high therapeutic serum concentrations, as has been hypothesized for valproic acid (see below). 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 the duration of effect shorter when co administered with a CYP3A-inducer and a higher dose may be required.

In case of CYP3A induction and irreversible inhibition (so-called mechanism based inhibition), the effect on the pharmacokinetics of midazolam may persist for a period of several days up to several weeks after administration of the CYP3A modulator. Examples of mechanism based CYP3A inhibitors include antibacterials (e.g. clarithromycin, erythromycin, isoniazid); anti-retroviral agents (e.g. HIV protease inhibitors, such as ritonavir (including ritonavir-boosted protease inhibitors), delavirdine); calcium channel blockers (e.g. verapamil, diltiazem); tyrosine kinase inhibitors (e.g. imatinib, lapatinib, idelalisib, or the oestrogen receptor modulator, raloxifene and several herbal constituents (e.g. bergamottin). In contrast to other mechanism based inhibitors, ethinyloestradiol combined with norgestrel or gestodene (used for oral contraception) and grapefruit juice (200 mL) did not modify exposure to midazolam to a clinically significant degree.

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.

The range of the inhibiting/inducing potency of drugs is wide. The antifungal ketoconazole, a very potent CYP3A inhibitor, increased the plasma concentration of intravenous midazolam by approximately 5-fold. The tuberculostatic drug, rifampicin, belongs to the strongest inducers of CYP3A and its co-administration resulted in a decrease in the $AUC_{0-\infty}$ of intravenous midazolam by approximately 60%.

The administration route of midazolam also determines the magnitude of change in its pharmacokinetics due to CYP3A modulation: (i) The change in plasma concentration is expected to be less for intravenous compared with oral administration of midazolam. This is because CYP3A modulation not only affects the systemic clearance, but also the bioavailability of oral midazolam. (ii) There are no studies available investigating the effect of CYP3A modulation on the pharmacokinetics of midazolam after either rectal or intramuscular administration. After rectal administration the drug partially bypasses the liver and the expression of CYP3A is lower in the colon compared with the upper gastrointestinal tract. Therefore, it is expected that the change in midazolam plasma concentration, due to CYP3A modulation, will be less for the rectal than for the oral route of administration. After intramuscular administration, the drug directly enters the systemic circulation. Therefore, it is expected that the effect of CYP3A modulation will be similar to that for intravenous administration of midazolam. (iii) In line with

pharmacokinetic principles, clinical studies have shown that after a single intravenous dose of midazolam, in the presence of CYP3A inhibition, the change in maximal clinical effect due to CYP3A modulation will be minor, whereas the duration of effect may be prolonged. However, after prolonged dosing of midazolam, both the magnitude and duration of effect may be increased.

The following listing gives examples of clinical pharmacokinetic drug-drug interactions with midazolam after intravenous administration. Importantly, any drug shown to possess CYP3A-modulating effects, either in vitro or in vivo, has the potential to change the plasma concentration of midazolam, and therefore its effects. The listing includes information from clinical drug-drug interaction studies for oral midazolam. As outlined above, the change in plasma concentration is expected to be less for intravenous compared with oral midazolam.

Drugs that inhibit CYP3A

Patients receiving compounds which inhibit CYP3A should not be administered midazolam whenever possible. Otherwise, the dose of midazolam should be adjusted and the patient kept under careful surveillance. There is a potential interaction with the following:

Azole antifungals

- *Ketoconazole and voriconazole:* Increased the $AUC_{0-\infty}$ of intravenous midazolam by 5-fold and 3-4 fold respectively, while the terminal half-life increased by approximately 43-fold.

- *Fluconazole and itraconazole:* Both increased the $AUC_{0-\infty}$ of intravenous midazolam, which was associated with a 2.4-fold and 1.5-fold increase in terminal half-life for itraconazole and fluconazole respectively. A 100 – 300% increase in plasma midazolam at 48 hours after receiving fluconazole was commonly (3/10) seen in intensive care unit patients with a midazolam infusion. Orally, fluconazole increased C_{max} 1.7-fold and $AUC_{0-\infty}$ 3.6-fold, while for itraconazole they increased 2.5- and 6.6-fold, respectively. When bolus doses of midazolam (given for short-term sedation) were administered to patients receiving itraconazole or fluconazole the effect of midazolam was not enhanced to a clinically significant degree, and dosage reduction is not required. However, administration of high doses of midazolam may require dosage adjustments.

- *Posaconazole:* Increased the $AUC_{(tf)}$ (AUC zero to last measurable concentration) of intravenous midazolam by 1.8-fold.

- *Itraconazole*.

Macrolide antibiotics

- *Erythromycin:* Resulted in an increase in the $AUC_{(tf)}$ of intravenous midazolam and was associated with a 1.4 – 1.8-fold increase in the terminal half-life of midazolam. 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 the AUC of intravenous midazolam by approximately 2.5-fold and was associated with a 2.7-fold increase in terminal half-life.

Additional information from oral midazolam

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

- Roxithromycin has less of an effect on the pharmacokinetics of midazolam than erythromycin or clarithromycin. After oral administration with roxithromycin the maximum plasma concentration (C_{max}) of midazolam increased approximately 40% compared with increases of 2.7-fold caused by erythromycin and 2.8-fold with clarithromycin, while the 40% increase in $AUC_{0-\infty}$ is matched by 4.4-fold and 7-fold increases, respectively. The mild effect on the terminal half-life of midazolam (~30%) indicates that the effects of roxithromycin on intravenous midazolam may be minor.

Intravenous anaesthetics

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

Protease inhibitors

- *Saquinavir and other HIV-protease inhibitors:* 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. Co-administration of a single intravenous dose of 0.05 mg/kg midazolam after 3 or 5 days of saquinavir dosing (1200 mg t.i.d.) to 12 healthy volunteers decreased the midazolam clearance by 56% and increased the elimination half-life from 4.1 to 9.5 h. Only the subjective effects to midazolam (visual analogue scales with the item "overall drug effect") were intensified by saquinavir. Therefore, bolus doses of intravenous midazolam can be given in combination with saquinavir. During a prolonged midazolam infusion, an initial dose reduction of 50% is recommended (see section 4.4). Co-administration with other 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.

- *HCV protease inhibitors:* Boceprevir and telaprevir reduce midazolam clearance. This effect resulted in a 3.4-fold increase of midazolam AUC after intravenous administration and prolonged its elimination half-life 4-fold.

Histamine receptor 2 antagonists

- *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.

Calcium-channel blockers

- *Diltiazem:* After pretreatment with lorazepam and a single dose of diltiazem, on cessation of an intravenous infusion of midazolam, the AUC from cessation for 23 h increased approximately 25% and the terminal half-life was prolonged approximately 43%.

Additional information from oral midazolam

- *Verapamil i*ncreased the C_{max} of oral midazolam 2-fold, while $AUC_{0-\infty}$ increased 3- and 4-fold, respectively. The terminal-half-life of midazolam increased 41%.

Various drugs/Herbs

- *Atorvastatin:* Increased the AUC of intravenous midazolam by approximately 1.4-fold compared with control group.

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

Long-term infusions of midazolam to patients receiving systemic antimycotics, e.g., during intensive care treatment, may result in long-lasting hypnotic effects if the dose is not titrated according to the effect.

Additional information from oral midazolam

- Fluvoxamine: Increased the $AUC_{0-\infty}$ and Cmax of oral midazolam 40% and doubled the terminal half-life.

- Nefazodone: Increased the $AUC_{0-\infty}$ of oral midazolam 4.6-fold with an increase in Cmax of 1.8-fold and in terminal half-life of 1.6-fold.

- Tyrosine kinase inhibitors have been shown either in vitro (imatinib, lapatinib or after oral administration in vivo (idelalisib) to be potent inhibitors of CYP3A4. After concomitant administration of idelalisib, oral midazolam exposure was increased on average 5.4-fold.

- NK1 receptor antagonists (aprepitant, netupitant, casoprepitant): Dose-dependently increased the AUC of oral midazolam up to approximately 2.5-3.5 fold and increased terminal half-life by approximately 1.5-2 fold.

- NK1 receptor antagonists (aprepitant, netupitant, casoprepitant): dose-dependently increased the AUC of oral midazolam up to approximately 2.5-3.5 fold and increased terminal half-life by approximately 1.5-2 fold.

- Chlorzoxazone: Decreased the ratio of the CYP3A-generated metabolite α-hydroxymidazolam to midazolam, indicating a CYP3A-inhibiting effect of chlorzoxazone.

- For a number of drugs or herbal medicines, a weak interaction with midazolam's elimination was observed with concomitant changes in its exposure (< 2-fold change in AUC) (bicalutamide, everolimus, cyclosporine, simeprevir, propiverine, berberine as also contained in goldenseal). These weak interactions are expected to be further attenuated after intravenous administration.

- 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.

Drugs that induce CYP3A

- Rifampicin (600 mg o.d.) decreased the AUC of intravenous midazolam by approximately 60% after 7 days. The terminal half-life decreased by approximately 50 - 60%.

- Ticagrelor is a weak CYP3A activator in vitro but has only small effects on intravenously administered midazolam (-12%) and 4-hydoxy-midazolam (-23%) exposures.

Additional information from oral midazolam

- Carbamazepine and phenytoin: Repeat dosages of carbamezepine or phenytoin resulted in a decrease in the AUC and C_{max} of oral midazolam by over 90% and a shortening of the terminal half-life by almost 60%.

- 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.

- Clobazam and Efavirenz: are weak inducers of midazolam metabolism and reduce the AUC of the parent compound by approximately 30%. There is a resulting 4-5-fold increase in the ratio of the active metabolite (α-hydroxy-midazolam) to the parent compound but the clinical significance of this is unknown.

- Vemurafenib modulates CYP isozymes and inhibits CYP3A4 mildly: Repeat-dose administration resulted in a mean decrease of oral midazolam exposure of 39% (up to 80% in individuals).

Herbs and food

- *Echinacea purpurea root extract:* Decreased the AUC of intravenous midazolam 20% and was associated with a decrease in half-life of approximately 42%.

- *St John's wort:* Decreased the AUC of intravenous midazolam by approximately 20% and AUC of oral midazolam by 50% with Cmax decreased by 40 – 50%. It was associated with a decrease in terminal half-life by approximately 16 - 19%.

Additional information from oral midazolam

- Quercetin (also contained in Gingko biloba) and Panax ginseng both have weak enzyme inducing effects and reduced exposure to midazolam after its oral administration to the extent of 20-30%.

Acute protein displacement

- *Valproic acid:* Increased concentrations of free midazolam due to displacement from plasma protein binding sites by valproic acid cannot be excluded although the clinical relevance of such an interaction is not known.

Pharmacodynamic drug-drug interactions (DDI)

The co-administration of midazolam with other sedative/hypnotic agents, including alcohol, is likely to result in increased sedative/hypnotic effects. Examples include opiates/opioids (when they are used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines (used as anxiolytics or hypnotics), barbiturates, propofol, ketamine, etomidate, sedative antidepressants, antihistaminics and centrally acting antihypertensive drugs. Midazolam decreased the minimum alveolar concentration (MAC) of Halothane.

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. Benzodiazepines interact at $GABA_A$ sites, and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, 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.

Enhanced effects such as sedation and cardio-respiratory depression may also occur when midazolam is co-administered with any centrally acting depressants including alcohol. Therefore, adequate monitoring of vital signs should be established. Alcohol should be avoided in patients receiving midazolam (see sections 4.4 and section 4.9).

The sedative effect of intravenous midazolam is likely to be potentiated when either lignocaine or bupivacaine are administered intramuscular.

Physostigmine: may reverse the hypnotic effects of midazolam.

Caffeine: may reverse the sedative effect of midazolam.

4.6 Fertility, Pregnancy and Lactation

Use in pregnancy – Australian Pregnancy Category C

Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. Midazolam crosses the placenta and other benzodiazepines given in the last weeks of pregnancy or at high doses during labour have resulted in neonatal CNS depression and can be expected to cause irregularities in the foetal heart rate, hypothermia, hypotonia, poor sucking and moderate respiratory depression due to the pharmacological action of the product. 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. Midazolam is therefore not recommended for obstetric use.

Teratological studies with midazolam in a number of animal species have not shown association between administration of the drug and disturbances of fetal development, nor has clinical experience so far yielded any evidence of such an association. However, like any other drug, midazolam should not be used in the first three months of pregnancy unless considered absolutely necessary by the physician.

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy.

Published studies in pregnant and juvenile animals demonstrate that the use of anaesthetic/analgesic and sedation drugs that block NMDA receptors and/or potentiate GABA

activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. These studies included anaesthetic agents from a variety of drug classes.

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

Use in lactation

There is evidence that midazolam is excreted in breast milk, and its effects on the new born are not known. Therefore midazolam is not recommended for use in nursing mothers.

Effects on fertility

A reproduction study in male and female rats did not show any impairment of fertility at dosages up to 10 times the human intravenous dose of 0.35 mg/kg.

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 recovered.

After administration of midazolam, patients should not be discharged from hospital for at least three hours and then, if possible, only if accompanied by a responsible person. The decision as to when patients may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualised. Gross tests of recovery from the effects of midazolam cannot be relied upon to predict reaction time under stress. When midazolam is used with other drugs during anaesthesia, the contribution of these can vary and should be considered accordingly.

Patients should be warned to take extra care as a pedestrian and not to drive a vehicle or operate machinery until effects, such as drowsiness, have subsided or until the day after anaesthesia and surgery, whichever is longer. The physician should decide when activities such as driving a vehicle or operating a machine may be resumed. The patient's attendants should be made aware that anterograde amnesia may persist longer than the sedation and therefore patients may not carry out instructions even though they appear to acknowledge them. 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

Fluctuations in vital signs that have been noted following parenteral administration of midazolam include:

- respiratory depression (22.9% following intravenous administration and 10.8% of patients following intramuscular administration)
- apnoea (19% following intravenous administration)
- variations in blood pressure and pulse rate.

These common occurrences during anaesthesia and surgery are affected by the lightening or deepening of anaesthesia, instrumentation, intubation and use of concomitant drugs. Administration of intramuscular midazolam to elderly and/or higher risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiration, especially opioid analgesics (see also Section 4.2 Dose and method of administration).

The following additional adverse effects were reported after intramuscular administration:

- local effects at intramuscular injection site: pain (3.7%)
- headache (1.3%)
- induration (0.5%)
- redness (0.5%)
- muscle stiffness (0.3%)

The following additional adverse effects were reported subsequent to intravenous administration:

- local effects at the intravenous site: tenderness (7%)
- pain during injection (6.2%)
- hiccough (5.5%)
- redness (3.8%)
- nausea (3%)
- vomiting (2.9%)
- coughing (1.9%)
- induration (1.9%)
- drowsiness (1.3%)
- oversedation (1%)
- phlebitis (0.5%)

Post-marketing experience

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

Immune system disorders*:* Generalised hypersensitivity - including anaphylactic reactions, cardiovascular reactions, bronchospasm, and skin reactions - has been reported, angioedema, anaphylactic shock.

Psychiatric disorders: Euphoria, grogginess, emergence delirium, prolonged emergence from anaesthesia, dreaming during emergence, paresthesia, confusional state, disorientation, emotional and mood disturbances, hallucinations, dysphoria, changes in libido.

Paradoxical reactions such as restlessness, agitation, irritability, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, nervousness, hostility, anger, rage reaction, aggressiveness, anxiety, nightmares, abnormal dreams, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, argumentativeness, nervousness, anxiety, irritability, tension, mood changes, restlessness, paroxysmal excitement and assault, have been reported, particularly among children and the elderly. In these cases, discontinuation of the drug should be considered.

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.

Nervous system disorder: Drowsiness and prolonged sedation, reduced alertness, confusion, fatigue, headache, dizziness, ataxia, , dreaming during sleep, sleep disturbance, insomnia, athetoid movements, slurred speech, dysphonia, parasthesia, postoperative sedation, anterograde amnesia, the duration and risk of which is directly related to the administered dose, with the risk increasing at higher doses. Anterograde amnesia may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported.

Convulsions have been reported in premature infants and neonates.

Cardiac disorders: Severe cardiorespiratory adverse events have occurred on rare occasions. These have included cardiac arrest, hypotension, slight increase in heart rate, bradycardia, vasodilating effects, bigeminy, premature ventricular contractions, tachycardia, nodal rhythm, cardiovascular collapse, and vasovagal episode, dyspnoea. In isolated cases laryngospasm has occurred following injection of midazolam. 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: Larynogspasm, bronchospasm, tachypnoea, severe cardio-respiratory adverse effects have occurred on rare occasions. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest, dyspnoea, laryngospasm, hyperventilation, wheezing, shallow respirations, airway obstruction, tachyponea. 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).

Gastrointestinal system disorders: Nausea, vomiting, hiccough, constipation, dry mouth, acid taste, retching, excessive salivation.

Skin and appendages disorders: Skin rash, urticarial reaction, pruritus.

General and application site disorders: Erythema and pain on injection site, redness, tenderness, induration, thrombophlebitis, thrombosis, hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site. In isolated cases, generalized hypersensitivity from skin reactions to anaphylactoid reactions, have been reported.

Ophthalmic disorders: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, difficulty in focusing.

Miscellaneous: Yawning, lethargy, chills, weakness, continued phonation, ears blocked, loss of balance, light-headedness, toothache, faint feeling, haematoma.

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; Overdosage of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. Overdose of midazolam is seldom life-threatening if the medicine is taken alone, but in mild cases, may lead to symptoms including drowsiness, mental confusion, muscle relaxation or paradoxical excitation and lethargy. As with other benzodiazepines, overdosage should not present a threat to life unless combined with other CNS depressants including alcohol. In more serious cases, symptoms may include ataxia, areflexia, apnoea, hypotonia, hypotension, cardiorespiratory depression, respiratory depression, and, rarely, coma, cerebrovascular perfusion and very rarely death. Coma 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. When combined with other CNS depressants, the effects of overdosage are likely to be severe and may prove fatal.

Treatment

Treatment of midazolam overdosage is the same as that followed for overdosage with other benzodiazepines.

Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed as indicated by the patient's clinical state. If the overdosage is known to be small, observation of the patient and monitoring of their vital signs only may be appropriate. In adults or children who have taken an overdose of benzodiazepines within 1 - 2 hours, consider activated charcoal with airway protection if indicated.

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 may precipitate seizures and is contraindicated in the presence of medicines that reduce seizure threshold (e.g. tricyclic antidepressants) and epileptic patients who have been treated with benzodiazepines.

In most cases only observation of vital functions is required. In the management of overdose special attention should be paid to the respiratory and cardiovascular functions in intensive care. The effects of overdosage can be controlled with the benzodiazepine antagonist flumazenil. Caution should be observed in the use of flumazenil in cases of mixed drug overdosage and in patients with epilepsy treated with benzodiazepines.

Refer to the prescribing information for flumazenil, for further information on the correct use of this medicine.

Hypotension may be combated by the judicious use of other accepted antihypotensive measures.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication.

Hepatic function should be monitored.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

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.

Pharmacotherapeutic Group: Central nervous system depressant.

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 i.m. or i.v. 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

The effects of midazolam on the CNS are dependent on the dose administered, the route of administration and the presence or absence of other premedications.

Absorption

Absorption after i.m. injection

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

Absorption after rectal administration

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

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

Metabolism

Midazolam is almost entirely eliminated by biotransformation. Less than 1% of the dose is recovered in urine as the unchanged substance. 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. The fraction of the dose extracted by the liver has been estimated to be 30 to 60%. The elimination half-life of the metabolite is shorter than 1 hour. 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 to 2.5 hours. Plasma clearance is in the range of 300 to 500 mL/min. When midazolam is given by i.v. infusion, its elimination kinetics do not differ from those following bolus injection.

Pharmacokinetics in special clinical situations

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 i.v. and rectal administration is shorter in children 3 to 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 to 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 may be reduced when compared to those in healthy volunteers (see section 4.2 and 4.4).

Patients with renal impairment

The elimination half-life in patients with chronic renal failure is similar to that in healthy volunteers. The free fraction of midazolam in chronic renal failure may be significantly higher than normal. After correcting for protein binding the pharmacokinetics of unbound midazolam is similar to that reported 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

Carcinogenicity

Midazolam maleate was administered with diet in mice and rats for two years at dosages of 1, 9 and 80 mg/kg/day. In female mice in the highest dose group there was a marked increase in the incidence of hepatic tumours. In high dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumours. Dosages of 9 mg/kg/day of midazolam maleate

do not increase the incidence of tumours. The pathogenesis of induction of these tumours is not known. These tumours were found after chronic administration, whereas human use will ordinarily be of single dose or of short duration. Midazolam did not have mutagenic activity in *Salmonella typhimurium* (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes, or in the micronucleus test in mice.

Animal Pharmacology and Toxicology

Nonclinical research and published studies of ketamine, isoflurane and propofol in pregnant primates demonstrate that the administration of anaesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate GABA activity can increase neuronal cell death in the brain and result in long-term cognitive deficits of juvenile animals when administered at either high doses, or for prolonged periods, or both during the period of peak brain development. The mechanism of action of midazolam includes potentiation of GABA activity. The relevance of these nonclinical findings to human use is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Midazolam Injection contains sodium chloride, hydrochloric acid and Water for Injections. Sodium hydroxide may be present if used for the adjustment of pH. It does not contain preservatives.

Composition of Midazolam Injection

Ingredient *1	Quantity		Function	Reference to Standards
	1mg/mL	5mg/mL		
Midazolam *Midazolamum*	1mg	5mg	active	*Ph. Eur.*
Sodium Chloride *Natrii Chloridum*	8.0mg	8.0mg	to adjust tonicity	*Ph. Eur.*
Hydrochloric Acid *Acidum Hydrochloridum Concentratum*	0.3µL	1.6µL	to produce the 'hydrochloride' of midazolam and to adjust pH	*Ph. Eur.*
Sodium Hydroxide*2 *Natrii Hydroxidum*	qs*2	qs*2	to adjust pH	*Ph. Eur.*
Water for Injections *Aqua ad Injectabilia*	qs to 1mL	qs to 1mL	diluent	*Ph. Eur.*

*1 All ingredients used in the formulation are of non-animal origin.

*2 Sodium Hydroxide is only needed if the pH is over adjusted with hydrochloride acid.

6.2 Incompatibilities

Do not dilute Midazolam ampoule solutions with macrodex 6% in dextrose.

Do not mix Midazolam ampoule solutions in alkaline injections. Midazolam precipitates in sodium bicarbonate.

6.3 Shelf Life

36 months

Midazolam Injection does not contain a preservative or bacteriostatic agent, hence, vials are for single use only and any unused portion should be discarded.

6.4 Special Precautions for Storage

Store below 25°C. Protect from light. Use once only and discard any remaining portion.

Unopened ampoules will be suitable for use for up to 8 months after the foil sachet has been opened, if protected from light.

6.5 Nature and Contents of Container

Midazolam Injection is presented in ampoules manufactured from medical grade, low density polyethylene which conforms to the specification of the European Pharmacopoeia 3.1.4 "Polyethylene - Low Density for Containers for Preparations for Parenteral Use and Ophthalmic Preparations" (1997).

5 mg in 1 mL and 5 mg in 5 mL - 10s.

15 mg in 3 mL and 50 mg in 10 mL - 5s.

6.6 Special Precautions for Disposal and Other Handling

Spill Procedures: Where possible, dam the spill. Cover with absorbent towels or pads or other absorbent material. Place in closed containers for disposal. Wash affected area with copious quantities of water. Dispose of in an approved facility for controlled incineration.

7. MEDICINE SCHEDULE

Controlled Drug C5.

8. SPONSOR

Pfizer New Zealand Ltd

P O Box 3998

Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363.

9. DATE OF FIRST APPROVAL

05 October 2000

10. DATE OF REVISION OF THE TEXT

11 April 2019

Summary table of changes

Section changed	Summary of new information
1, 2, 3, 5.3	Minor editorial modification per reformat guide.
4.4 & 4.6	Addition of TGA requested text to "Paediatric use" and "Use in Pregnancy" sections.
4.2 - 4.9 & 5.2	Update the safety information per latest approved Australian label which was updated per local innovator label.
6.1	Move Composition of Midazolam Injection from section 5.3 to section 6.1
6.2 & 6.3	Update related information per Medsafe.