AUSTRALIAN PRODUCT INFORMATION – MIDAZOLAM INJECTION (Midazolam)

1. NAME OF THE MEDICINE

Midazolam

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Midazolam Injection contains 1 mg/mL or 5 mg/mL midazolam (as hydrochloride)

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Midazolam Injection is a clear, colourless to pale yellow solution for injection. Midazolam Injection is adjusted to pH 3.3.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intravenously as an agent for:

- conscious sedation prior to short surgical, diagnostic, therapeutic or endoscopic procedures such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography and cardiac catheterisation, either alone or in conjunction with an opioid.

- induction of anaesthesia preliminary to administration of other anaesthetic agents. With the use of an opioid premedicant, induction of anaesthesia can be obtained with a narrower dose range and in a shorter period of time.

Intermittent intravenous administration or continuous infusion for:

- sedation in intensive care units.

Intramuscularly for:

- preoperative sedation (induction of sleepiness or drowsiness and relief of apprehension) and to impair memory of perioperative events.

4.2 Dose and method of administration

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

Dosage should be individualised and drug should be administered slowly.

Lower doses may be required in elderly or debilitated patients or in patients with hepatic or renal insufficiency. Because serious and life-threatening cardiorespiratory adverse events have been reported, provision for monitoring, detection and correction of these reactions must be made for every patient to whom midazolam is administered, regardless of age or health status. The dosage of midazolam administered should be adjusted according to the type and amount of premedication used.

Intravenous administration

Endoscopic or cardiovascular procedures: For conscious sedation, midazolam can be used either alone or together with an opioid immediately before the procedure with supplemental doses to maintain the desired level of sedation throughout the procedure**.**

For peroral procedures: the use of an appropriate topical anaesthetic is recommended. For bronchoscopic procedures, the use of an opioid premedicant is recommended. Individual response will vary with age, physical status and concomitant medications, but may also vary independent of these factors.

Titrate dosage to desired sedative end point, such as slurring of speech, with slow administration immediately prior to the procedure. The initial dose should be given over a period of at least 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. When titrating the dose 2 or more minutes should be allowed after each increment.

In healthy adults the initial dose is approximately 2.5 mg. Some patients may respond to as little as 1 mg. Further doses of 1 mg may be given if necessary. A total dose greater than 5 mg is not usually necessary to reach the desired end point.

In cases of severe illness and in elderly patients the initial dose must be reduced to 1 to 1.5 mg. Total doses greater than 3.5 mg are not usually necessary.

If an opioid premedicant or other CNS depressant is used the dose of midazolam should be lowered by 25% to 30%.

Induction of anaesthesia**:** The dosage of midazolam should be determined by the response of the individual patient. Administration should be by slow intravenous injection until consciousness is lost using approximately 0.15-0.2 mg/kg (10-15 mg) administered at a rate of approximately 2.5 mg per 10 seconds. Maximum sedation is usually reached after 2-3 minutes but if required a further dose up to a total of 0.35 mg/kg may be administered. The onset of sedation has not been found to be dose-dependent but the time to recovery is related to the amount of drug administered.

Midazolam should be used with opioid analgesics as it does not have analgesic properties and opioid analgesics enhance its anaesthetic-inducing properties.

Intravenous sedation in ICU: For sedation in ICU, the recommended infusion rate is 0.03-0.2 mg/kg/hour. The dosage should be individualised and midazolam titrated to the desired state of sedation according to the clinical need, physical status, age and concomitant medication. It may be possible to reduce the dose (infusion rate) once the therapeutic effect has been obtained.

The dosage should be reduced in hypovolemic, vasoconstricted and hypothermic patients.

After prolonged intravenous administration of midazolam, abrupt discontinuation of the product may be accompanied by withdrawal symptoms. Therefore, a gradual reduction of midazolam is recommended. Midazolam can be used in neurosurgical patients with increased intracranial pressure.

Intramuscular administration

***For preoperative sedation*:** induction of sleepiness or drowsiness and relief of apprehension and to impair memory of preoperative events.

For intramuscular use, midazolam should be injected deep in a large muscle mass.

The recommended premedication dose of midazolam for good risk adult patients below the age of 60 years is 0.07 to 0.08 mg/kg intramuscular (approximately 5 mg intramuscular) administered approximately one hour before surgery.

The dose must be individualised and reduced when intramuscular midazolam is administered to patients with chronic obstructive pulmonary disease, other higher risk surgical patients, patients 60 or more years of age, and patients who have received concomitant opioids or other CNS depressants (see Section 4.8 Adverse effects (undesirable effects)). In a study of patients 60 years or older who did not receive concomitant administration of opioids, 2 to 3 mg (0.02 to 0.05 mg/kg) of midazolam produced adequate sedation during the preoperative period. In approximately 25% of patients, 1 mg provided satisfactory sedation. As with any potential respiratory depressant, these patients require special observation for signs of cardio-respiratory depression after receiving intramuscular midazolam.

Onset is within 15 minutes, peaking at 30 to 60 minutes. It can be administered concomitantly with atropine sulfate or hyoscine hydrobromide and reduced doses of opioids.

Special Dosage Instructions

Rrenal 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 Special warnings and precautions for use, Use in renal impairment).

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 Section 4.4 Special warnings and precautions for use, Use in hepatic impairment and 5.2 Pharmacokinetic properties).

Dilution and admixture

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).

The 15 mg/3 mL, 5 mg/mL and 5 mg/5 mL formulations may be diluted to facilitate slow injection.

The 50 mg/10 mL ampoules may be added to the infusion solutions in a mixing ratio of 15 mg midazolam per 100-1000 mL infusion solution.

The product and its admixtures contain no antimicrobial agent. In order to reduce microbiological hazards it is recommended that further dilution be effected immediately prior to use and infusion commenced as soon as practicable after preparation of the admixture.

Infusion should be completed within 24 hours of preparation and the residue discarded, however infusion with calcium chloride intravenous infusion (Ringer's solution) and compound sodium lactate intravenous infusion (Hartmann's solution) should be completed within 4 hours as the potency of midazolam is known to decrease. Any storage of diluted solution should be at 2°C to 8°C.

4.3 Contraindications

- Patients with hypersensitivity to benzodiazepines or any of their formulation excipients
- 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

Intravenous midazolam should only be used where appropriate equipment and personnel are available for continuous monitoring of cardiorespiratory function and for resuscitation procedures.

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 Dose and method of administration). 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. Particular care must be taken when administering the drug by intravenous route, in the elderly, to very ill patients, high-risk surgical patients and to those with significant hepatic impairment, (benzodiazepines may precipitate or exacerbate encephalopathy in patients with severe hepatic impairment), chronic renal insufficiency, congestive heart failure, or with limited pulmonary reserve because of the possibility of apnoea or respiratory depression may occur. These patients require lower doses whether premedicated or not.

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

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 Pharmacokinetic properties).

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.

A gradual dose reduction is recommended in patients on a prolonged intravenous dose of midazolam. 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, mood changes, hallucinations and convulsions. In severe cases, the following symptoms may occur: depersonalisation, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact.

Reactions such as restlessness, agitation, irritability, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, combativeness, delusion, anger, aggressiveness, anxiety, nightmares, hallucinations, psychoses, inappropriate behaviour or other adverse behavioural effects have been reported. 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 concomitant use of midazolam with alcohol or/and CNS depressants, including opioids, should be avoided. Such concomitant use has the potential to increase the clinical effects of midazolam possibly including severe sedation or clinically relevant respiratory depression, coma, and death. Limit dosages and durations to the minimum required. Concomitant use of

barbiturates, alcohol or other central nervous system depressants increases the risk of underventilation or apnoea and/or cardio-ventricular depression* and may contribute to a profound and/or prolonged drug effect that could result in coma or death. When midazolam is used with an opioid analgesic, the dosage of both agents should be reduced. Opioid premedication also reduces the ventilatory response to carbon dioxide stimulation.

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.

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.

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

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

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 Dose and method of administration, Special dosage instructions and 5.2 Pharmacokinetic properties, Pharmacokinetics in special populations).

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 Dose and method of administration, Special dosage instructions and 5.2 Pharmacokinetic properties, Pharmacokinetics in special populations).

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 interactions

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.

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.

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.

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.

- *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.

- *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.

- *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.

<u>Histamine receptor 2 antagonists</u>

- *Cimetidine* increased the steady state plasma concentration of midazolam by 26%.

<u>Calcium-channel blockers</u>

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

<u>Various drugs/Herbs</u>

- *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 i.v. midazolam were increased by 1.5-fold in presence of fentanyl.

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.

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.

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 Section 4.4 Special warnings and precautions for use and Section 4.9 Overdose for warning of other CNS depressants, including alcohol).

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

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 0.35mg/kg.

Use in pregnancy

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.

4.7 Effects on ability to drive and use machines

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 Interactions with other medicines and other forms of interactions).

4.8 Adverse effects (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 effects have been reported.

Immune System Disorders: Generalised hypersensitivity: 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: Prolonged sedation, decreased alertness, 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 cardio-respiratory adverse effects have occurred on rare occasions. These have included cardiac arrest, hypotension, bradycardia, vasodilating effects, bigeminy, premature ventricular contractions, tachycardia, nodal rhythm, cardiovascular collapse, and vasovagal episode. 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 Special warnings and precautions for use).

Respiratory disorders: Larynogspasm, bronchospasm, tachypnoea, severe cardio-respiratory adverse effects have occurred on rare occasions. These have included respiratory depression, apnoea, respiratory arrest, dyspnoea, laryngospasm, hyperventilation, wheezing, shallow respirations, airway obstruction, tachyponea. 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 Special warnings and precautions for use). Coughing, hiccoughs.

Gastrointestinal System Disorders: Nausea, vomiting, constipation, dry mouth, acid taste, retching, excessive salivation.

Skin and Appendages Disorders: Skin rash, urticaria, 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.

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 suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Signs and symptoms

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 and lethargy. In more serious cases, symptoms may include ataxia, areflexia, apnoea, hypotonia, hypotension, respiratory depression, 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.

Recommended 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. 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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of drug: Benzodiazepine.

Midazolam is a short-acting central nervous system depressant which induces sedation, hypnosis, amnesia and anaesthesia. As with all benzodiazepines, Midazolam will also induce muscle relaxation. Pharmacokinetic and pharmacodynamic data in chronic intravenous usage are not available beyond 15 days.

Mechanism of action

The mechanism of action of the benzodiazepines is under continuous investigation. Benzodiazepines appear to intensify the physiological inhibitory mechanisms mediated by gamma-aminobutyric acid (GABA), the most common inhibitory neurotransmitter in the brain. 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. Onset time of sedative effects after intramuscular administration is 15 minutes. Peak sedation occurs 30 to 60 minutes following injection.

When used intravenously (as a sedative for endoscopic or other short therapeutic or diagnostic procedures) the end point of slurred speech can be attained within 2.8 to 4.8 minutes, depending on the total dose administered and whether or not preceded by opioid premedication. The time to induction of anaesthesia for surgical procedures is variable occurring in approximately 1.5 minutes (0.3-8 minutes) when an opioid premedicant has been administered and in 2 to 2.5 minutes without premedication or with a sedative premedication.

Approximately two hours are required for full recovery from midazolam-induced anaesthesia. Duration of effect is dependent on the dose and other drugs used. Induction of anaesthesia is unsuccessful in approximately 14% of patients with midazolam alone but in only about 1% when given with an opioid.

At doses sufficient to induce sedation, intravenous midazolam decreases the sensitivity of the ventilatory response to elevated CO_2 tension in normal subjects and in those with chronic obstructive lung disease, who are at special risk of hypoxia. Sedation with midazolam has no adverse effects on pulmonary compliance and does not cause bronchoconstriction or significantly affect functional residual capacity or residual volume. Midazolam may cause a modest decrease in mean arterial pressure. Baroreceptor response is not affected and decreases in arterial pressure are accompanied by increases in heart rate. Intravenous midazolam at doses of 0.15 to 0.2 mg/kg did not have a deleterious effect on cardiac haemodynamics.

Intravenous administration of midazolam does not alter intracranial pressure unless the patient is intubated. As with thiopentone, the intracranial pressure rises during intubation. Cerebral blood flow may be reduced by up to 35%, which is of the same order as caused by equivalent doses of diazepam. The effect on cerebral metabolism is not clearly established.

Midazolam reduces the intraocular pressure to the same degree as thiopentone and diazepam. However, the increase in intraocular pressure after succinylcholine administration or endotracheal intubation is not prevented by midazolam, thiopentone or diazepam.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Bioavailability: The mean absolute bioavailability of midazolam following intramuscular administration is greater than 90%. The mean time of maximum midazolam plasma concentrations following intramuscular dosing occurs within 45 minutes post-administration. Peak concentrations of midazolam as well as 1-hydroxymethyl midazolam after intramuscular administration are about one-half of those achieved after equivalent intravenous doses.

Distribution

Protein binding: 97% of midazolam becomes bound to plasma proteins. The extent of protein binding does not vary in renal failure.

Metabolism

Less than 0.03% is excreted in the urine unchanged. The drug is rapidly metabolised to 1-hydroxymethyl midazolam which is conjugated with subsequent excretion in the urine. The elimination half-life of the active metabolite is similar to that of parent drug. The concentration of midazolam is 10 to 30 times greater than that of 1-hydroxymethyl midazolam.

Excretion

The pharmacokinetic profile of midazolam in man is linear over the 0.05 to 0.4 mg/kg dose range. In normal subjects the drug exhibited a short elimination half-life (1 to 2.8 hours) with a large volume of distribution (0.8 to 1.86 L/kg) and a rapid plasma clearance (0.24 to 0.73 L/hr/kg).

Pharmacokinetics in Special Populations

Renal impairment

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.

Hepatic impairment

The clearance in cirrhotic patients may be reduced and the elimination half-life may be longer when compared to those in healthy volunteers (see Sections 4.2 Dose and method of administration, Special dosage instructions and 4.4 Special warnings and precautions for use).

Pharmacokinetics in special clinical situations

In some intensive care and elderly patients given midazolam by intravenous infusion for prolonged sedation, the elimination half-life was found to increase by up to six times. Particular risk factors in the elderly include abdominal pathology, sepsis and poor renal function. In these patients infusion at an unchanged rate resulted in higher plasma levels at steady state. Consequently, the infusion rate should be reduced once a satisfactory clinical response has been obtained.

5.3 Preclinical safety data

Genotoxicity

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.

Carcinogenicity

Midazolam maleate was administered with diet in mice and rats for two years at dosages of 1, 9 and 80mg/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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride

Hydrochloric acid (to produce hydrochloride)

Sodium Hydroxide

Water for injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Protect from light. Protect packaging against any physical damage.

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 5mg in 1mL (sterile) Steriluer® Plastic Ampoule (2 x 5 pack)

Midazolam Injection 15mg in 3mL (sterile) Steriluer® Plastic Ampoule (5 pack) ±

Midazolam Injection 5mg in 5mL (sterile) Steriluer® Plastic Ampoule (2 x 5 pack)

Midazolam Injection 50mg in 10mL (sterile) Steriluer® Plastic Ampoule (5 pack)

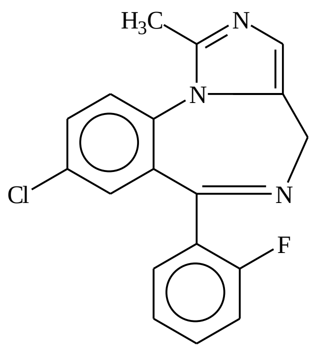
±Not available in Australia.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Midazolam is a benzodiazepine from the imidazobenzodiazepine group. Its chemical name is 8-chloro-6- (2-fluorophenyl)-1-methyl-4H-imidazo [1,5-a][1,4] benzodiazepine. It is a white or yellowish crystalline powder, practically insoluble in water, freely soluble in acetone and alcohol, soluble in methanol.

Molecular Formula: $C_{18}H_{13}ClFN_3$

Molecular Weight: 325.8

CAS number

59467-70-8

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine –S4 (Australia)

8. SPONSOR

Pfizer Australia Pty Ltd

Level 17, 151 Clarence Street

Sydney NSW 2000

Toll Free Number: 1800 675 229

www.pfizer.com.au

Manufacturer

Pfizer (Perth) Pty Limited

ABN 32 051 824 956

15 Brodie Hall Drive

Bentley WA 6102 Australia.

9. DATE OF FIRST APPROVAL

24 December 1999

10. DATE OF REVISION

21 December 2018

®Registered trademark

Steriluer® is a plastic ampoule produced by Pfizer.

Summary Table of Changes

Section changed	Summary of new information
All	Reformatted to TGA PI standard
4.4 & 4.6	Addition of TGA requested text to "Paediatric use" and "Use in Pregnancy" sections
4.4 & 4.6 & 4.7 & 4.8 & 4.9	Update the safety information per local innovator label
5.3	Update the information per TGA request
8	Sponsor address change