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

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

The solution should be visually inspected prior to use. Only clear solutions without particles should be used.

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. Special caution is required for the indication of conscious sedation in patients with impaired respiratory function (see section 4.4 Special warnings and precautions for use).

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 intensive care units (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 hypovolaemic, 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 perioperative events.

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

The recommended premedication dose of midazolam for low- 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

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).

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 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

General

Intravenous midazolam should only be used where immediate availability of oxygen, resuscitative drugs, appropriate equipment and skilled personnel are available for continuous monitoring of cardiorespiratory function and for resuscitation procedures. Patients should be continuously monitored for early signs of underventilation airway obstruction or apnoea. Vital signs should continue to be monitored during the recovery period.

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. There have been limited reports of intra-arterial injection of midazolam. Adverse events have included local reactions, as well as isolated reports of seizure activity in which no clear causal relationship was established. Precautions against unintended intra-arterial injection should be taken.

During intravenous application of midazolam respiratory depression, airway obstruction, oxygen desaturation, 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, 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.

Comorbidities

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.

Prolonged sedation

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 four times (see section 5.2).

Acute illness

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

Hypotension

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 behaviour, aggression, 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.

Concomitant use with alcohol, CNS depressants, opioids

Concomitant use of benzodiazepines, including midazolam, alcohol or/and other CNS 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.

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

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

Dependence

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.

Discharging criteria

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.

Endotracheal intubation

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.

Endoscopic procedures

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 premedication is recommended for bronchoscopies.

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

Sleep apnoea syndrome

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

Dependence

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.

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

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.

Paediatric neurotoxicity

Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anaesthetic agents early in life and may result in adverse cognitive or behavioural effects. 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. Anaesthetic and sedation drugs are a necessary part of the care of children needing surgery, other procedures, or tests that cannot be delayed, and no specific medications have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

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.

Published juvenile animal studies demonstrate 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.

With inhalation or infusion of anaesthetic and sedation 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.

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 sections 4.2 and 5.2).

Effects on laboratory tests

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

4.5 Interaction with Other Medicines and Other Forms of Interaction

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 with medicines that have high therapeutic serum concentrations, as has been hypothesised for sodium valproate.

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. Notably, administration of high doses or long-term infusions of midazolam to patients receiving strong CYP3A4 inhibitors, e.g. during intensive care, may result in long-lasting hypnotic effects, delayed recovery and respiratory depression, thus requiring dose adjustments. Carefully monitor the clinical effects and vital signs during the use of midazolam with a CYP3A4 inhibitor. Interactions between midazolam and medicinal products that inhibit CYP3A4 are listed in Table 1.

The effect of midazolam may be weaker and shorter lasting when co-administered with a CYP3A inducer and a higher dose may be required. Interactions between midazolam and medicinal products that induce CYP3A4 are listed in Table 2.

The inducing process needs several days to reach its maximum effect and also several days to dissipate. Contrary to a treatment of several days with an inducer, a short-term treatment is expected to result in less apparent DDI with midazolam. However, for strong inducers a relevant induction even after short-term treatment cannot be excluded.

Table 1: Interactions between midazolam and medicinal products that inhibit CYP3A4

Medicinal product	**Interaction with intravenous midazolam[a]**
Azole antifungals	
ketoconazole, voriconazole	Ketoconazole and voriconazole increased the plasma concentrations of intravenous midazolam by 5-fold and 3-4-fold, respectively, while the terminal half-life increased by about 3-fold. If parenteral midazolam is co-administered with these strong CYP3A inhibitors, it should be in an ICU or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Staggered dosing and dose adjustment should be considered, especially if more than a single IV dose of midazolam is administered. The same recommendation may apply to other azole antifungals, since increased sedative effects of IV midazolam, although lesser, have been reported.
fluconazole, itraconazole	Fluconazole and itraconazole both increased the plasma concentrations of IV midazolam by 2.4-fold and an increase in terminal half-life by 2.4-fold and 1.5-fold for itraconazole and fluconazole, respectively.

posaconazole	Posaconazole increased the plasma concentrations of IV midazolam by 1.8-fold.
Macrolide antibiotics	
erythromycin	Erythromycin increased the plasma concentrations of IV midazolam by 1.6-2-fold and increase in terminal half-life of midazolam by 1.4-1.8-fold.
clarithromycin	Clarithromycin increased the plasma concentrations of IV midazolam by up to 2.5-fold and was associated with a 2.7-fold increase in terminal half-life.
roxithromycin	Information from oral midazolam Roxithromycin has less of an effect on the pharmacokinetics of midazolam than erythromycin or clarithromycin. While no information on roxithromycin with IV midazolam is available, the mild effect on the terminal half-life of oral midazolam tablet increasing by 30% indicates that the effects of roxithromycin on IV midazolam may be minor.
Intravenous anaesthetics	
propofol	IV propofol increased the AUC and half-life of IV midazolam by 1.6-fold.
Protease inhibitors	
HIV protease inhibitors	Co-administration with protease inhibitors may cause a large increase in the concentration of midazolam. Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of IV midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life. If parenteral midazolam is co-administered with HIV protease inhibitors, the advice given above for the azole antifungals, ketoconazole and voriconazole should be followed.
Histamine receptor 2 antagonists	
ranitidine	Ranitidine had no effect on the steady-state plasma concentration of midazolam. Co-administration 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 ranitidine and dosage adjustment is not required.
Calcium-channel blockers	
diltiazem	A single dose of diltiazem given to patients undergoing coronary artery bypass grafting increased the plasma concentrations of IV

	midazolam by about 25% and the terminal half-life was prolonged by approximately 43%.
verapamil	Information from oral midazolam Verapamil increased the plasma concentrations of oral midazolam by 3-fold. The terminal half-life of midazolam was increased by 41%.
Various medicines/herbs	
atorvastatin	Atorvastatin increased the plasma concentrations of IV midazolam by approximately 1.4-fold compared with the control group.
intravenous fentanyl	A weak inhibitor of midazolam's elimination. AUC and half-life of intravenous midazolam were increased by 1.5-fold.
fluvoxamine	Information from oral midazolam Fluvoxamine increased the plasma concentrations of oral midazolam by 40% and doubled the terminal half-life.
tyrosine kinase inhibitors	Information from oral midazolam Tyrosine kinase inhibitors have been shown to be potent inhibitors of CYP3A4 in vitro (imatinib, lapatinib) or in vivo (idelalisib). After concomitant administration of idelalisib, oral midazolam exposure was increased on average 5.4-fold.
NK1 receptor agonists (aprepitant, netupitant)	Information from oral midazolam Dose-dependently increased the AUC of oral midazolam with an increase up to approximately 2.5-3.5-fold after 80 mg/day and increased terminal half-life by approximately 1.5-2-fold.
other medicines or herbal products	Information from oral midazolam A weak interaction with midazolam's elimination was observed (<2-fold change in AUC) when coadministered with bicalutamide, everolimus, or berberine contained in goldenseal. These weak interactions are expected to be further attenuated after intravenous administration.
ciclosporin	No clinically relevant pharmacokinetic and pharmacodynamic interaction. Therefore, the dose of midazolam needs no adjustment.

[a] For some interactions, additional information using orally administered midazolam is provided. Interactions with CYP3A inhibitors are more pronounced for oral as compared to IV midazolam. Midazolam ampoules are not indicated for oral administration.

Table 2: Interactions between midazolam and medicinal products that induce CYP3A4

Medicinal product	**Interaction with intravenous midazolam[a]**

rifampicin	Rifampicin (600 mg once daily) decreased the plasma concentrations of IV midazolam by about 60% after 7 days. The terminal half-life decreased by about 50-60%.
ticagrelor	A weak CYP3A activator in vitro but has only small effects on intravenously administered midazolam (-12%).
carbamazepine, phenytoin	Information from oral midazolam Repeat doses of carbamazepine or phenytoin resulted in a decrease in plasma concentrations of oral midazolam by over 90% and a shortening of the terminal half-life by almost 60%.
mitotane, enzalutamide	Information from oral midazolam 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.
efavirenz, clobazam	Information from oral midazolam 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-hydroxymidazolam) to the parent compound but the clinical significance of this is unknown.
vemurafenib	Information from oral midazolam Vemurafenib modulates CYP isozymes and induces CYP3A4 mildly: Repeat-dose administration resulted in a mean decrease of oral midazolam exposure of 39% (up to 80% in individuals).
Herbs and food	
echinacea purpurea root extract	Decreased the AUC of IV midazolam by 20% and decreased half-life by about 42%.
St John's wort	Decreased the AUC of IV midazolam by about 20% associated with a decrease in terminal half-life by about 16-19%.
quercetin, ginseng	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%.

[a] For some interactions, additional information using orally administered midazolam is provided. Interactions with CYP3A inhibitors are more pronounced for oral as compared to IV midazolam. Midazolam ampoules are not indicated for oral administration.

Pharmacodynamic drug-drug interactions (DDI)

Sedative/hypnotic agents and CNS depressants

The co-administration of midazolam with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced effects on sedation, respiration and haemodynamics. Examples include opiates/opioids (be they 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 medicines. Therefore, adequate monitoring of vital signs should be established. Alcohol should be avoided in patients receiving midazolam (see sections 4.4 and 4.9 for warning of other CNS depressants, including alcohol).

Benzodiazepines

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 GABAA sites, and opioids interact primarily at mu receptors. Concomitant use of benzodiazepines and opioids may result in profound respiratory depression. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Anaesthetics

Midazolam decreased the minimum alveolar concentration (MAC) of inhalational anaesthetics, including halothane.
It has been shown that high spinal anaesthesia can increase the sedative effect of IV midazolam. The midazolam dose may therefore be reduced. Also, when either lignocaine or bupivacaine were administered IM, the dose of IV midazolam required for sedation was reduced.

Medicines that increase alertness or memory

Medicines increasing alertness/memory such as the acetylcholinesterase inhibitor physostigmine, reversed the hypnotic effects of midazolam. Similarly, 250 mg of caffeine partly reversed the sedative effects of midazolam.

4.6 Fertility, Pregnancy and Lactation

Women of childbearing potential

Data from observational studies suggest that there is an increased risk of miscarriage from benzodiazepine exposure during pregnancy. When treating women of childbearing potential, the benefits of treatment should be weighed against the risks and the patient should be informed of the increased risk of miscarriage.

Use in pregnancy – Australian Pregnancy Category C

Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. Data from observational studies suggest that there is an increased risk of miscarriage from benzodiazepine exposure during pregnancy. 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 (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in the postnatal period. Monitor neonates exposed to midazolam during pregnancy or labour for signs of sedation and monitor neonates exposed to midazolam during pregnancy for signs of withdrawal; manage these neonates accordingly.

Data from animal studies

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

Midazolam is excreted in human breast milk, and may cause drowsiness, feeding difficulties and poor weight gain in the infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for midazolam and any potential adverse effects on the breastfed infant from midazolam or from the underlying maternal condition.

A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk during treatment for a range of at least 4 to 8 hours after midazolam administration in order to minimize drug exposure to a breastfed infant.

Breastfeeding patients receiving midazolam should be instructed to monitor infants for excessive sedation, poor feeding, and poor weight gain, and to seek medical attention if they notice these signs.

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. For paediatric patients, particular care should be taken to assure safe ambulation. 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

The majority of serious adverse effects, particularly those associated with oxygenation and ventilation, have been reported when midazolam is administered with other medications capable of depressing the central nervous system. The incidence of such events is higher in patients undergoing procedures involving the airway without the protective effect of an endotracheal tube, (e.g., upper endoscopy and dental procedures).

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%)

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).

The following additional adverse effects were reported subsequent to intravenous administration as a single sedative/anxiolytic/amnestic agent in adult patients:

- 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 reactions (cardiovascular reactions, bronchospasm and skin reactions), angioedema, anaphylactic shock.

Psychiatric disorders: Euphoria, grogginess, emergence delirium, prolonged emergence from anaesthesia, dreaming during emergence, 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, psychoses, inappropriate behaviour and other adverse behavioural effects, argumentativeness, tension, mood changes, 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, paraesthesia, 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.

Cardiovascular 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: Laryngospasm, bronchospasm, tachypnoea, severe cardiorespiratory 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, tachypnoea. 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).Coughing, hiccoughs.

Gastrointestinal system disorders: Nausea, vomiting, 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, generalised 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://pophealth.my.site.com/carmreportnz/s/.

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, hypnotic state, diminished reflexes, muscle relaxation and lethargy. Rarely, paradoxical or disinhibitory reactions (including agitation, irritability, impulsivity, violent behaviour, confusion, restlessness, excitement, and talkativeness) may occur. In more serious cases, symptoms may include dysarthria, 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 risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic 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 characterised 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 virtually complete. The mean absolute bioavailability after i.m. injection is over 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 i.m. injection are about one-half of those achieved after equivalent intravenous doses.

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% (range 40 – 65%).

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

The pharmacokinetic profile of midazolam in man is linear over the 0.05 – 0.4 mg/kg dose range. 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 0.6 to 1.9 L/kg. 96% to 98% of midazolam is bound to plasma proteins. The major fraction of plasma protein binding is due to albumin. The extent of protein binding does not vary in renal failure. 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. 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%. 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 mean elimination half-life is between 1.4 to 2.4 hours. Plasma clearance is in the range of 220 to 470 mL/min. Midazolam is mainly excreted by renal route: 60-80% of the dose is excreted in urine as glucoconjugated α-hydroxymidazolam The elimination half-life of the metabolite is shorter than 1 hour. When midazolam is given by i.v. infusion, its elimination kinetics do not differ from those following bolus injection.

Compounds that inhibit or induce cytochrome P450 3A4 (CYP3A) may alter patients' elimination of midazolam, and the dose may need to be adjusted accordingly (see section 4.5).

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).

Obese

The elimination half-life of midazolam is prolonged in obese patients. The clearance is not altered.

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. To avoid potential incompatibility with other solutions, midazolam must not be mixed with any solutions except those mentioned in section 4.2.

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.
www.pfizermedicalinformation.co.nz

9. DATE OF FIRST APPROVAL

05 October 2000

10. DATE OF REVISION OF THE TEXT

08 September 2025

Summary table of changes

Section changed	Summary of new information
All	Editorial revision throughout

Section changed	Summary of new information
4.2	Added precautionary step to inspect solution prior to use. Conscious Sedation: Special caution is required for the indication of conscious sedation in patients with impaired respiratory function Section amended to align with AU PI.
4.4	Added information on availability of oxygen, resuscitative drugs when administering IV midazolam. Added information on intra-arterial injection of midazolam. Included addition information on Paediatric neurotoxicity. Added cross referencing to Section 5.2 for Use in hepatic impairment. Deletion of paragraph Amnesia and Altered elimination as the information is already mentioned at section 4.7 and 4.5.
4.5	Deletion on information on medicines that have been withdrawn or are not registered in NZ. Addition of drug interaction information with high spinal anaesthesia and acetylcholinesterase inhibitor. Deletion of the information due to the duplicated intent of information in the Pharmacokinetic DDI paragraph. Editorial revision into tabular format
4.6	Added examples of withdrawal symptoms, and precautionary monitoring for neonates exposed to pregnancy and labour. Updated safety information on use in lactation. Added increased risk of miscarriage at Medsafe request
4.7	Added cautionary statement for paediatric patients.
4.8	Added information on serious adverse effects. Relocated AEs to appropriate SOC and remove duplicated AEs.
4.9	Include additional symptoms of overdose, and also updated standard statement per NZ DS template.
5.2	Added PK information on absorption, elimination and in obesity.

Section changed	Summary of new information
6.2	Added “To avoid potential incompatibility with other solutions, midazolam must not be mixed with any solutions except those mentioned in section 4.2”. to align with AU PI.
8	Addition of sponsor website address