

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

MIDAZOLAM INJECTION

Midazolam 1 mg/mL and 5 mg/mL Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Strength: 1mg/mL and 5mg/mL

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection

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

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

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

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

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

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

4.2 Dose and method of administration

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

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

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

Premedication before an Operation

Intramuscular administration

In patients suffering from pain before an intervention.

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

Adults: 0.07 to 0.10 mg per kg bodyweight i.m. according to age and general condition of the patient. Usual dosage about 5 mg.

Children: proportionately higher doses are required than in adults in relation to bodyweight (0.15 to 0.20 mg per kg bodyweight i.m.).

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

Rectal administration

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

Intranasal administration

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

Oral administration

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

Conscious Sedation

Intravenous conscious sedation

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

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

Intranasal conscious sedation

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

Oral conscious sedation

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

Sedation in Intensive Care Units

Intravenous sedation

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

Adults

Loading dose: 0.03 to 0.3 mg/kg.

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

Induction and Maintenance of Anaesthesia

Intravenous injection

Adults

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

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

Intravenous continuous infusion

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

Intramuscular administration

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

Rectal administration

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

Special Dosage Instructions

When midazolam is given with potent analgesics, the latter should be administered first so that the sedative effects of midazolam can be safely titrated on top of any sedation caused by the analgesic.

Compatibility with infusion solutions. The midazolam ampoule solution can be diluted with sodium chloride 0.9%, dextrose 5% and 10%, levulose 5%, Ringer's solution and Hartmann's solution in a mixing ratio of 15 mg midazolam per 100 to 1,000 mL infusion solution. These solutions remain physically and chemically stable for 24 hours at room temperature (or three days at 5°C).

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

4.3 Contraindications

Patients with a hypersensitivity to benzodiazepines or any other component of the product.

4.4 Special Warnings and Precautions For Use

Risks from Concomitant Use with Opioids

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

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

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

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

- adults over 60 years of age
- debilitated or chronically ill patients

- patients with chronic respiratory insufficiency
- patients with chronic renal failure, impaired hepatic function or with congestive heart failure
- paediatric patients with cardiovascular instability.

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

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

As with any substance with CNS depressant and/or muscle-relaxant properties, particular care should be taken when administering midazolam to a patient with myasthenia gravis, owing to pre-existing muscle weakness.

Tolerance

Some loss of efficacy has been reported when midazolam has been used as long-term sedation in intensive care units (ICU).

Dependence

When midazolam is used in long-term sedation in ICU, it should be borne in mind that physical dependence may develop. The risk of dependence increases with dose and duration of treatment.

Withdrawal symptoms

During prolonged treatment with midazolam in ICU, physical dependence may develop. Abrupt cessation of therapy may lead to withdrawal symptoms such as headaches, muscle pain, anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood changes, hallucinations and convulsions. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, it is recommended that the dose is decreased gradually.

Amnesia

Midazolam causes anterograde amnesia (frequently this effect is very desirable in situations such as before and during surgical and diagnostic procedures), the duration of which is directly related to the administered dose. Prolonged amnesia can present problems in outpatients, who are scheduled for discharge following intervention. After receiving midazolam parenterally, patients should be discharged from hospital or consulting room only if accompanied by an attendant.

“Paradoxical” reactions

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, hostility, rage reaction, aggression, paroxysmal excitement and assault have been reported. The highest incidence of susceptibility to such reactions has been reported among children and the elderly. Should such reactions occur, the response to each dose of midazolam and all other drugs including local anaesthetics should be evaluated before proceeding.

Altered elimination

Elimination of midazolam may be delayed in patients receiving compounds that inhibit certain hepatic enzymes (particularly cytochrome P450 3A4) (see section 4.5).

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

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

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

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

Paediatric use

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

Pre-term infants and neonates

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

Rapid injection should be avoided in the neonatal population.

Neonates have reduced and/or immature organ function and are vulnerable to profound and/or prolonged respiratory effects of midazolam.

4.5 Interactions With Other Medicines and Other Forms of Interaction

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

The metabolism of midazolam is predominantly mediated by cytochrome P450 3A4 (CYP3A4) isozyme. Approximately 25 % of the total cytochrome P450 system in the adult liver is from the CYP3A4 subfamily. Inhibitors (see section 4.4) and inducers of this isozyme may lead to interaction with midazolam.

CYP3A4 inhibitors

Azole antifungals: Co-administration with azole antifungals increases the plasma concentrations of intravenous midazolam by 5-fold for ketoconazole, by 3-fold for voriconazole and by 2 to 3-

fold for both fluconazole and itraconazole. The associated elimination half-life of intravenous midazolam was increased by 3-fold for ketoconazole and voriconazole, by 2.4-fold for itraconazole and by 1.5-fold for fluconazole.

When bolus doses of midazolam (given for short-term sedation) were administered to patients receiving itraconazole or fluconazole the effect of midazolam was not enhanced to a clinically significant degree, and dosage reduction is not required. However, administration of high doses of midazolam may require dosage adjustments.

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

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

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

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

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

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

Saquinavir and other HIV-protease inhibitors: Co-administration of a single intravenous dose of 0.05 mg/kg midazolam after 3 or 5 days of saquinavir dosing (1200 mg t.i.d.) to 12 healthy volunteers decreased the midazolam clearance by 56% and increased the elimination half-life from 4.1 to 9.5 h. Only the subjective effects to midazolam (visual analogue scales with the item “overall drug effect”) were intensified by saquinavir.

Therefore, bolus doses of intravenous midazolam can be given in combination with saquinavir. During a prolonged midazolam infusion, an initial dose reduction of 50% is recommended (see section 4.4).

Co-administration with other protease inhibitors may cause a large increase in the concentration of midazolam. Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of intravenous midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life.

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

Other interactions

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

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

Alcohol may enhance the sedative effect of midazolam.

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

4.6 Fertility, Pregnancy and Lactation

Use in pregnancy

Insufficient data are available on midazolam to assess its safety during pregnancy. Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. The administration of midazolam in the last trimester of pregnancy or at high doses during labour has been reported to produce irregularities in the foetal heart rate, hypotonia, poor sucking and hypothermia and moderate respiratory depression in the neonate. Moreover, infants born to mothers who received benzodiazepines chronically during the latter stage of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Use in lactation

Since midazolam passes into breast milk, it should not be administered to breast-feeding mothers

4.7 Effects on Ability to Drive and Use Machines

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or use machines. Prior to receiving midazolam, the patient should be warned not to drive a vehicle or operate a machine until recovered.

4.8 Undesirable Effects

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

Central and peripheral nervous system and psychiatric disorders

Drowsiness and prolonged sedation, reduced alertness, confusion, euphoria, hallucinations, fatigue, headache, dizziness, ataxia, postoperative sedation, anterograde amnesia, the duration of which is directly related to the administered dose. Anterograde amnesia may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported.

Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, have been reported, particularly among children and the elderly.

Convulsions have been reported in premature infants and neonates.

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

Gastrointestinal system disorders

Nausea, vomiting, hiccough, constipation, dry mouth.

Cardiorespiratory disorders

Severe cardiorespiratory adverse events have occurred on rare occasions. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest. Such life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered (see section 4.4).

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

Skin and appendages disorders

Skin rash, urticarial reaction, pruritus.

Body-as-a-whole disorders

In isolated cases, generalized hypersensitivity, from skin reactions to anaphylactoid reactions, have been reported.

Local reactions

Erythema and pain on injection site, thrombophlebitis, thrombosis.

4.9 Overdose

Symptoms

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

Treatment

Treatment of midazolam overdosage is the same as that followed for overdosage with other 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 overdose and in patients with epilepsy treated with benzodiazepines.

Contact the Poisons Information Centre for advice on the management of an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Midazolam is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water. The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables midazolam to form water-soluble salts with acids. These produce a stable and well tolerated injection solution.

Pharmacotherapeutic Group: Central nervous system depressant.

Mechanism of Action: The pharmacological action of midazolam is characterized by rapid onset and, because of rapid metabolic transformation, short duration. Because of its low toxicity, midazolam has a wide therapeutic range.

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

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

5.2 Pharmacokinetic Properties

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

Absorption

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

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

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

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

Distribution

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

Metabolism

Midazolam is almost entirely eliminated by biotransformation. Less than 1% of the dose is recovered in urine as the unchanged substance. Midazolam is hydroxylated by the cytochrome P450 3A4 isozyme. α -hydroxymidazolam is the major urinary and plasma metabolite. 60-80% of the dose is excreted in urine as glucuroconjugated α -hydroxymidazolam. Plasma concentrations of α -hydroxymidazolam are 12% those of the parent compound. The fraction of the dose extracted by the liver has been estimated to be 30 to 60%. The elimination half-life of the metabolite is shorter than 1 hour. α -hydroxymidazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous midazolam. There is no evidence of a genetic polymorphism in the oxidative metabolism of midazolam (see section 4.5).

Elimination

In healthy volunteers, the elimination half-life is between 1.5 to 2.5 hours. Plasma clearance is in the range of 300 to 500 mL/min. When midazolam is given by i.v. infusion, its elimination kinetics do not differ from those following bolus injection.

Pharmacokinetics in special clinical situations

Elderly: In adults over 60 years of age, the elimination half-life may be prolonged up to four times.

Children: The rate of rectal absorption in children is similar to that in adults. However, the elimination half-life ($t_{1/2}$) 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 smaller as compared to those in healthy volunteers (see section 4.4).

Patients with renal impairment: The elimination half-life in patients with chronic renal failure is similar to that in healthy volunteers.

Critically ill patients: The elimination half-life of midazolam is prolonged in the critically ill.

Patients with cardiac insufficiency: The elimination half-life is longer in patients with congestive heart failure compared with that in healthy subjects (see section 4.4).

5.3 Preclinical Safety Data

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.

Impairment of Fertility

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

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.

Composition of Midazolam Injection

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

*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. 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.

6.2 Incompatibilities

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

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

6.3 Shelf Life

5mg in 5mL, 5mg in 1mL, 15mg in 3mL and 50mg in 10mL: 36 months from date of manufacture.

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.

6.5 Nature and Contents of Container

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

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

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

6.6 Special Precautions for Disposal and Other Handling

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

7. MEDICINE SCHEDULE

Controlled Drug C5.

8. SPONSOR

Pfizer New Zealand Ltd

P O Box 3998
Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363.

9. DATE OF FIRST APPROVAL

5 October 2000

10. DATE OF REVISION OF THE TEXT

02 February 2018

SUMMARY TABLE OF CHANGES	
Section 5.3	Addition of the text ‘and result in long-term cognitive deficits’ under the sub-heading Animal Pharmacology and Toxicology
Section 5.3	Illustrated the acronym NMDA as ‘N-methyl-D-aspartate (NMDA)’ under the sub-heading Animal Pharmacology and Toxicology
Section 5.3	Added the text ‘Nonclinical research and’ at the beginning of the paragraph under the sub-heading Animal Pharmacology and Toxicology