

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Midazolam-Baxter 1mg/mL solution for injection.

Midazolam-Baxter 5mg/mL solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient

Midazolam hydrochloride.

Midazolam-Baxter 1mg/mL solution for injection

Each 5mL ampoule contains 5mg of midazolam (as hydrochloride).

Midazolam-Baxter 5mg/mL solution for injection

Each 1mL ampoule contains 5mg of midazolam (as hydrochloride).

Each 3mL ampoule contains 15mg of midazolam (as hydrochloride).

Each 10mL ampoule contains 50mg of midazolam (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear, colourless to pale yellow, sterile solution, free from particles, with a pH between 2.9 - 3.7.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Midazolam is a short-acting sleep-inducing agent for sedation for short procedures, induction of anaesthesia, and for prolonged sedation in intensive care units.

Intravenous

Midazolam is 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 a narcotic.

For induction of anaesthesia, preliminary to administration of other anaesthetic agents. With the use of a narcotic premedicant, induction of anaesthesia can be attained with a narrower dose range and in a shorter period of time.

For sedation in intensive care units, intermittent administration or continuous infusion.

Intramuscular

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

Dose

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 cardio-respiratory adverse events have been reported, provision for monitoring, detection and correction of these reactions must be made for every patient to whom Midazolam-Baxter injection is administered, regardless of age or health status.

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The dosage of Midazolam-Baxter administered should be adjusted according to the type and amount of premedication used.

Intravenously (IV)

Midazolam-Baxter should be administered slowly.

Conscious sedation

Endoscopic or cardiovascular procedures

For conscious sedation, Midazolam-Baxter can be used either alone or together with a narcotic immediately before the procedure, with supplemental doses to maintain the desired level of sedation throughout the procedure. For per oral procedures, the use of an appropriate topical anaesthetic is recommended. For bronchoscopic procedures, the use of a narcotic 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 min. Wait an additional 2 or more min to fully evaluate the sedative effect. When titrating the dose, 2 or more mins should be allowed after each increment.

In healthy adults the initial dose is approximately 2.5mg. Some patients may respond to as little as 1mg. Further doses of 1mg may be given if necessary. A total dose greater than 5mg 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 1.5mg. Total doses greater than 3.5mg are not usually necessary. Special caution is required for the indication of conscious sedation in patients with impaired respiratory function (see section 4.4).

If a narcotic premedicant or other CNS depressant is used the dose of Midazolam-Baxter should be lowered by 25 - 30%.

Induction of anaesthesia

The dosage of Midazolam-Baxter should be determined by the response of the individual patient.

Administration should be by slow IV injection until consciousness is lost using approximately 0.15 - 0.2mg/kg (10 - 15mg) administered at a rate of approximately 2.5mg/10sec. Maximum sedation is usually reached after 2 - 3 min but if required a further dose up to a total of 0.35mg/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-Baxter should be used with narcotic analgesics as it does not have analgesic properties and narcotic analgesics enhance its anaesthetic-inducing properties. When midazolam is given with narcotic 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.

Intravenous sedation in Intensive Care Units (ICU)

For sedation in ICU, the recommended infusion rate is 0.03 - 0.2mg/kg/hour. The dosage should be individualised and Midazolam-Baxter 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.

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After prolonged IV administration of Midazolam-Baxter, abrupt discontinuation of the product may be accompanied by withdrawal symptoms. Therefore, a gradual reduction of Midazolam-Baxter is recommended.

Midazolam-Baxter can be used in neurosurgical patients with increased intracranial pressure.

Intramuscularly (IM)

Preoperative sedation

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

For IM use, Midazolam-Baxter should be injected deep in a large muscle mass.

The recommended premedication dose of Midazolam-Baxter for low-risk adult patients below the age of 60 years is 0.07 - 0.08 mg/kg IM (~5 mg IM) administered approximately 1 h before surgery.

The dose must be individualised and reduced when IM Midazolam-Baxter 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 narcotics 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 narcotics, 2 - 3 mg (0.02 - 0.05 mg/kg) of Midazolam-Baxter 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 IM Midazolam-Baxter.

Onset is within 15 min, peaking at 30 - 60 min. It can be administered concomitantly with atropine sulfate or scopolamine hydrochloride and reduced doses of narcotics.

Special dosage instructions

Patients with renal impairment

In patients with severe renal impairment, Midazolam-Baxter may be accompanied by more pronounced and prolonged sedation, possibly including clinically relevant respiratory and cardiovascular depression. Midazolam-Baxter 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-Baxter may have to be reduced and vital signs should be monitored (see sections 4.4 and 5.2).

Dilution and admixture

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

To avoid potential incompatibility with other solutions, Midazolam-Baxter must not be mixed with any solutions except those listed above.

Midazolam-Baxter may be diluted to facilitate slow injection.

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Midazolam-Baxter ampoules are for single use in one patient only. Discard any unused solution. The solution should be visually inspected prior to use. Only clear solutions without particles should be used.

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

To reduce microbiological hazard, it is recommended that the infusion commence as soon as possible after preparation. Prepared infusion solution should be used within 24 hours when stored under refrigeration (2 - 8°C) or within 6 hours if stored at room temperature.

4.3 Contraindications

Midazolam-Baxter should not be used in patients with Myasthenia gravis, or those with hypersensitivity to benzodiazepines or any of their formulation excipients.

Midazolam-Baxter should not be administered to patients in shock or coma, or in acute alcoholic intoxication with depression of vital signs.

Benzodiazepines are contraindicated in 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 considerations

Midazolam must never be used without individualisation of dosage. Midazolam should not be administered by rapid or single bolus IV administration (see section 4.2). IV midazolam should only be used in settings with equipment and skilled personnel for continuous monitoring of cardio-respiratory function and resuscitation procedures. 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 IV 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 if the injection is given too rapidly or with excessive doses.

Particular care must be used in administering the drug, by the IV route, to 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 that 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 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

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organ systems and dosage requirements have 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 IV 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 IV 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. In conscious sedation studies, hypotension occurred more frequently in patients premedicated with a narcotic.

Withdrawal symptoms

After prolonged IV administration of midazolam, abrupt discontinuation of the product may be accompanied by withdrawal symptoms. Therefore, a gradual reduction of midazolam is recommended.

Paradoxical reactions

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness 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. If midazolam is the suspected cause, the use of the drug should be discontinued and all other drugs, including local anaesthetics, should be evaluated before proceeding.

Concomitant use of alcohol/CNS depressants

Concomitant use of barbiturates, alcohol or other central nervous system depressants increases the risk of under-ventilation or apnoea and/or cardio-ventricular depression and may contribute to a profound and/or prolonged drug effect. When midazolam is used with a narcotic analgesic, the dosage of both agents should be reduced. Narcotic premedication also reduces the ventilatory response to carbon dioxide stimulation.

Intra-arterial injection

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.

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.

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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 a narcotic premedicant is recommended for bronchoscopies. Administration of a muscle relaxant may sometimes be necessary to overcome midazolam-associated hiccoughs.

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.

Concomitant use with opioids

Concomitant use of benzodiazepines, including Midazolam-Baxter, 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-Baxter 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-Baxter is used with opioids (see section 4.5).

Use in renal impairment

There is a greater likelihood of adverse drug reactions in patients with severe renal impairment (see sections 4.2 and 5.2).

Use in hepatic impairment

Hepatic impairment reduces the clearance of IV 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).

Use in the elderly

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.

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.

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Paediatric neurotoxicity

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 the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive defects. 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.

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.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic Drug-Drug Interaction (DDI)

Midazolam is almost exclusively metabolized by CYP3A. Inhibitors and inducers of CYP3A have the potential to increase and decrease the plasma concentrations and, subsequently, the effects of midazolam. 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 hypothesized for valproic acid.

When co-administered with a CYP3A4 inhibitor, the clinical effects of midazolam may be stronger and 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.

Midazolam is not known to change the pharmacokinetics of other drugs.

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

Medicinal product	Interaction with intravenous midazolam ^a
Azole antifungals	
ketoconazole, voriconazole	<p>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 4-fold.</p> <p>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.</p> <p>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.</p>
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 upto 2.5-fold and was associated with a 2.7-fold increase in terminal half-life.
roxithromycin	<p><u>Information from oral midazolam</u></p> <p>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.</p>
Intravenous anaesthetics	
propofol	IV propofol increased the AUC and half-life of IV midazolam by 1.6-fold.

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Protease inhibitors	
saquinavir and other HIV protease inhibitors	<p>Co-administration with protease inhibitors may cause a large increase in the concentration of midazolam.</p> <p>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.</p> <p>If parenteral midazolam is co-administered with HIV protease inhibitors, the advice given above for the azole antifungals, ketoconazole and voriconazole should be followed.</p>
Hepatitis C virus protease inhibitors	Boceprevir and telaprevir reduce midazolam clearance. This effect resulted in a 3.4-fold increase of IV midazolam AUC and prolonged its elimination half-life 4-fold.
Histamine receptor 2 antagonists	
cimetidine	Cimetidine increased the steady-state plasma concentration of midazolam by 26%.
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	<p>Information from oral midazolam</p> <p>Verapamil increased the plasma concentrations of oral midazolam by 3-fold. The terminal half-life of midazolam was increased by 41%.</p>
Various medicines/herbs	
atorvastatin	Atorvastatin increased the plasma concentrations of IV midazolam by approximately 1.4-fold compared with the control group.
fluvoxamine	<p><u>Information from oral midazolam</u></p> <p>Fluvoxamine increased the plasma concentrations of oral midazolam by 40% and doubled the terminal half-life.</p>
tyrosine kinase inhibitors	<p><u>Information from oral midazolam</u></p> <p>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.</p>
aprepitant	<p><u>Information from oral midazolam</u></p> <p>Dose-dependently increased the AUC of oral midazolam with an increase of approximately 3.3-fold after 80 mg/day and an approximately 2-fold increase in terminal half-life.</p>

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bicalutamide	<u>Information from oral midazolam</u> Minor effects on oral midazolam with 27% increase in AUC and 13% on C _{max} .
Goldenseal	<u>Information from oral midazolam</u> Decreased the ratio of the CYP3A4-generated metabolite α -hydroxymidazolam to midazolam approximately 40% indicating CYP3A inhibitory effect.

^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%.
carbamazepine, phenytoin	<u>Information from oral midazolam</u> 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%.
efavirenz, clobazam	<u>Information from oral midazolam</u> 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 (1'-hydroxymidazolam) to the parent compound but the clinical significance of this is unknown.
vemurafenib	<u>Information from oral midazolam</u> 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%.

^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.

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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, antihistamines and centrally acting antihypertensive medicines. 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, 250mg 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 categorisation) 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 the administration of midazolam 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

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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.

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 foetal development, nor has clinical experience so far yielded any evidence of such an association. Midazolam should not be used in the first three months of pregnancy.

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 results in widespread 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.

In primates, exposure to anaesthetic agents has resulted in increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory.

In a published study conducted on rhesus monkeys, administration of an anaesthetic dose of ketamine increased neuronal apoptosis in the developing brain of the foetus. In other published studies, administration of either isoflurane or propofol resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring of rhesus macaques. Studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits. Healthcare providers should balance the benefits of appropriate anaesthesia in pregnant women who require procedures with the potential risks suggested by the nonclinical data.

Breast-feeding

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. Infants exposed to midazolam through breast milk should be monitored for sedation, poor feeding and poor weight gain.

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 0.35mg/kg.

4.7 Effects on ability to drive and use machines

Patients should be warned to take extra care as a pedestrian and not to drive a vehicle or operate a machine until the patient has completely recovered from the effects of the drug, such as drowsiness. The physician should decide when activities such as driving a vehicle or operating a machine may be resumed. The patients' attendants should be made aware that the patients' anterograde amnesia may persist longer than the sedation and therefore, patients may not carry out instructions even

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though they appear to acknowledge them. If sleep duration is insufficient or alcohol is consumed, the likelihood of impaired alertness may be increased (see section 4.5).

4.8 Undesirable effects

Summary of the safety profile

Fluctuations in vital signs have been noted following parenteral administration of midazolam and include respiratory depression (22.9% following IV administration and 10.8% of patients following IM administration) and apnoea (19% following IV administration), as well as 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 IM 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 narcotics (see section 4.2).

The following additional adverse reactions were reported after intramuscular administration: headache (1.3%), local effects at intramuscular injection site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%).

Post-marketing experience

The following additional adverse effects were reported subsequent to IV administration of midazolam.

Immune system disorders

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

Psychiatric disorders

Confusional state, euphoric mood, hallucinations, dysphoria, abuse.

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

Dependence

Use of midazolam - even in therapeutic doses - may lead to the development of physical dependence. After prolonged IV administration, discontinuation, especially abrupt discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions (see section 4.4).

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 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.

Convulsions have been reported in premature infants and neonates.

Cardiorespiratory adverse events

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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).

Respiratory disorders

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, tachypnoea. 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, 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, fatigue.

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

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 and very rarely death. Coma may be more

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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 CNS 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 overdose is symptomatic; institute supportive measures 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.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and sedatives (benzodiazepine derivatives).

ATC code: N05CD08.

Midazolam is a short-acting central nervous system depressant which induces sedation, hypnosis, amnesia and anaesthesia. Pharmacokinetic and pharmacodynamic data in chronic intravenous (IV) usage are not available beyond 15 days.

Pharmacodynamic effects

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 (IM) administration is 15 min, with peak sedation occurring 30 - 60 min following injection.

When used IV as a sedative for endoscopic or other short therapeutic or diagnostic procedures, the end point of slurred speech can be attained within 2.8 - 4.8 min, depending on the total dose administered and whether or not preceded by narcotic premedication. The time to induction of anaesthesia for surgical procedures is variable, occurring in approximately 1.5 min (0.3 - 8 min) when an opioid premedicant has been administered and in 2 - 2.5 min without premedication or with a sedative premedication. Approximately 2h are required for full recovery from midazolam-induced anaesthesia; however 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, IV midazolam decreases the sensitivity of the ventilatory response to elevated carbon dioxide tension in normal subjects and in those with chronic obstructive

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lung disease, who are at 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.

Although midazolam may cause modest decreases in mean arterial pressure, baroreceptor response is not affected and decreases in arterial pressure are accompanied by increases in heart rate. IV midazolam at doses of 0.15 - 0.2mg/kg did not have deleterious effects on cardiac haemodynamics.

IV 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.

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.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Absorption after IM injection

Absorption of midazolam from the muscle tissue is rapid and virtually complete.

The mean absolute bioavailability of midazolam following IM administration is >90%. The mean time of maximum midazolam plasma concentrations following IM dosing occurs within 45 min post-administration. Peak concentrations of midazolam as well as 1-hydroxymethyl midazolam after IM administration are about one-half of those achieved after equivalent IV 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%).

Distribution

The pharmacokinetic profile of midazolam in man is linear over the 0.05 - 0.4mg/kg dose range. The volume of distribution of midazolam at steady state is 0.6 - 1.9L/kg.

Midazolam is 97% plasma protein bound.

Metabolism

Less than 0.03% is excreted in the urine as intact midazolam. The drug is rapidly metabolised to the active metabolite, 1-hydroxymethyl midazolam, which is conjugated with subsequent excretion in the urine. The concentration of midazolam is 10- to 30-fold greater than that of 1-hydroxymethyl midazolam.

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Excretion

In normal subjects the mean elimination half-life of midazolam is between 1.4 - 2.4h and the clearance is in the range of 220 - 470mL/min. Midazolam is mainly excreted by renal route: 60 - 80% of the administered dose of midazolam is excreted in urine as glucoconjugated α -hydroxymidazolam. The elimination half-life of this metabolite is < 1h.

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 populations

Elderly

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

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 and 4.4)

Critically ill

Midazolam elimination half-life is prolonged in critically ill patients.

Cardiac insufficiency

Midazolam elimination half-life is prolonged in patients with congestive heart failure.

Obese

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

In patient populations with prolonged elimination half-life, midazolam 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 2 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 9mg/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 is ordinarily single dose or of short duration.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride, Hydrochloric Acid and Sodium Hydroxide in Water for injections (adjusted to pH 3.3).

6.2 Incompatibilities

Midazolam-Baxter is compatible with normal saline, glucose 5% and 10% in water, fructose IV infusion (levulose 5%), potassium chloride, sodium chloride and calcium chloride IV infusion (Ringer's solution) and compound sodium lactate IV infusion (Hartmann's solution).

To avoid potential incompatibility with other solutions, Midazolam-Baxter must not be mixed with any solutions except those listed above (see section 4.2/Dilution and Admixture).

6.3 Shelf life

24 months. The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

Midazolam-Baxter 1mg/mL solution for injection

Midazolam-Baxter 5mg/5mL is supplied in 5mL glass ampoules, in packs of 5, 10 or 25 ampoules.

Midazolam-Baxter 5mg/mL solution for injection

Midazolam-Baxter 5mg/1mL is supplied in 1mL glass ampoules, in packs of 5, 10 or 25 ampoules.

Midazolam-Baxter 15mg/3mL is supplied in 3mL glass ampoules, in packs of 5, 10 or 25 ampoules.

Midazolam-Baxter 50mg/10mL is supplied in 10mL glass ampoules, in packs of 5 or 10 ampoules.

Ampoules

Clear glass type I.

6.6 Special precautions for disposal and other handling

Midazolam-Baxter does not contain any anti-microbial agent. Midazolam-Baxter ampoules are for single use in one patient only.

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

7. MEDICINE SCHEDULE

Class C5 Controlled Drug.

8. SPONSOR

Midazolam-Baxter is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

9. DATE OF FIRST APPROVAL

17 March 2016

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10. DATE OF REVISION OF THE TEXT

20 November 2024.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections	Editorial changes i.e. formatting, headings, spacing.
4.1	Indications brought into alignment with innovator.
4.2	Dosage and Administration brought into alignment with innovator. Clarifying indications for IV and IM use.
4.3	Included reference to excipients.
4.4	Warnings and Precautions brought into alignment with innovator.
4.5	Interactions with other medicines section tabulated and expanded to bring into alignment with innovator. Including specific interaction studies, PK drug interaction data, and expanded on drug specific interactions.
4.6	Fertility section moved. Use in Pregnancy section updated in alignment with innovator. Breastfeeding section expanded.
4.7	Effects on ability to drive section updated.
4.8	Undesirable effects section updated in alignment with innovator, including expansion of post-marketing experience.
4.9	Overdose section brought into alignment with innovator.
5.1	Pharmacodynamic properties section updated to include mechanism of action.
5.2	Pharmacokinetic section updated subsections: Absorption, Distribution, Metabolism, Excretion and PK in special populations in alignment with innovator.
5.3	Pre-clinical safety data updated in alignment with innovator.
6.4	Special precautions for storage updated to store in outer carton.
6.6	Special precautions for disposal and other handling updated with relevant information; and Dilution and Admixture information moved to section 4.2.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.