# NEW ZEALAND DATA SHEET

## 1. MIDAZOLAM-BAXTER

**MIDAZOLAM-BAXTER** 1mg/mL solution for injection.
**MIDAZOLAM-BAXTER** 5mg/mL solution for injection.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

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

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

Ataralgesia in combination with ketamine in children (I.M. administration).

### 4.2 Dose and method of administration

#### Method of administration

For intramuscular, intravenous, rectal, intranasal or oral administration (see instructions in section 4.2, 'Dose').

#### Dose

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

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

#### 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 - 0.10mg per kg bodyweight I.M. according to age and general condition of the patient. Usual dosage about 5mg.

*Children:* proportionately higher doses are required than in adults in relation to bodyweight (0.15 - 0.20mg per kg bodyweight I.M.).

*Elderly and debilitated patients:* 0.025 - 0.05mg/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 - 0.45mg/kg bodyweight 20 - 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 10mL.

*Intranasal administration*
*Children:* 0.2mg/kg, 10 - 15 minutes prior to anaesthesia.

*Oral administration*
*Children:* 0.5mg/kg, 15 - 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 2.5mg I.V. 5 - 10 minutes before the beginning of the operation. Further doses of 1mg may be given as necessary. A total dose greater than 5mg 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 - 1.5mg. Total doses greater than 3.5mg are not usually necessary.

*Intranasal conscious sedation*
*Children:* 0.2mg/kg, 10 - 15 minutes before the intervention.

*Oral conscious sedation*
*Children:* 0.2 - 0.5mg/kg, 15 - 30 minutes before the intervention.

### Sedation in Intensive Care Units (ICU)

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

*Adults*

*Loading dose:* 0.03 - 0.3mg/kg.
*Maintenance dose:* 0.03 - 0.2mg/kg/hr. The dosage should be reduced or the loading dose should even be omitted in hypovolemic, vaso-constricted and hypothermic patients.

Induction and maintenance of anaesthesia

*Intravenous injection*

*Adults*

*Induction:* the dose is 10 - 15mg I.V. in combination with analgesics. A sufficiently deep level of sleep is generally achieved after 2 - 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-BAXTER** can be administered by continuous infusion.

*Intravenous continuous infusion*

*Adults:* for intravenous anaesthesia combined with ketamine, 0.03 - 0.1mg/kg/hr; narcotics, 0.03 - 0.3mg/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-BAXTER** with ketamine (ataralgesia) is recommended. **MIDAZOLAM-BAXTER** I.M. (0.15 - 0.20mg per kg bodyweight) in combination with 50 - 100mg ketamine I.M. (4 - 8mg per kg bodyweight). A sufficiently deep level of sleep is generally achieved after 2 - 3 minutes.

*Rectal administration*

*Children:* see 'Premedication before an Operation'.

*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.

For information on compatibility with infusion solutions, see section 6.6.

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

## 4.3 Contraindications

MIDAZOLAM-BAXTER should not be used in patients with Myasthenia gravis, or those with hypersensitivity to benzodiazepines.

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

MIDAZOLAM-BAXTER should be used only when age- and size-appropriate resuscitation facilities are available, as I.V. administration 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.

### 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. It is also greater in patients with a medical history of alcohol and/or drug abuse.

### Withdrawal symptoms

During prolonged treatment with midazolam in ICU, physical dependence may develop. Therefore, abrupt termination of the treatment will be accompanied by withdrawal symptoms. The following symptoms may occur: 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.

### Concomitant use of alcohol/CNS depressants

The concomitant use of midazolam with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of midazolam possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression.

### Medical history of alcohol or drug abuse

Midazolam should be avoided in patients with a medical history of alcohol or drug abuse.

### 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.

### Discharging criteria

After receiving midazolam parenterally, patients should be discharged from hospital or consulting room only if accompanied by an attendant. It is recommended that the patient is accompanied when returning home after discharge.

"Paradoxical" reactions
Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, have been reported to occur with midazolam. These reactions may occur with higher doses and/or when the injection is given rapidly. The rare incidence of susceptibility to such reactions has been reported among children and at higher I.V. doses in the elderly. Should such symptoms suggestive of a paradoxical reaction occur, the response to midazolam should be evaluated before proceeding.

Altered elimination of midazolam
Elimination of midazolam may be delayed in patients receiving compounds that inhibit or induce certain hepatic enzymes (particularly cytochrome P450 3A4) and the dose of midazolam may need to be adjusted accordingly (see section 4.5).

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

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

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

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

Risks from 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).

Other
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.

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.

The neonate also has reduced and/or immature organ function and is also vulnerable to profound and/or prolonged respiratory effects of midazolam. Careful monitoring of respiratory rate and oxygen saturation is required.

### Paediatric population

Paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful respiratory rate and oxygen saturation monitoring are essential (see 'Pre-term infants and neonates' above).

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

*Paediatric neurotoxicity*

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 when used for longer than 3 hours. The clinical significance of these findings is not clear. However, based on the available data across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately three years of age in humans.

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

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

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

Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines 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 (see also section 4.6).

## 4.5 Interaction with other medicines and other forms of interaction

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*

- Ketoconazole increased the plasma concentration of intravenous midazolam by 5-fold while the terminal half-life increased by about 3-fold. If parenteral midazolam is co-administered with the strong CYP3A inhibitor ketoconazole, it should be done in an intensive care unit (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 dosage adjustment should be considered, especially if more than a single I.V. dose of midazolam is administered.

- Fluconazole and itraconazole both increased the plasma concentrations of intravenous midazolam by 2 – 3-folds associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole, respectively.
- Posaconazole increased the plasma concentrations of I.V. midazolam by about 2-fold.

*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.

*HIV protease inhibitors*
Saquinavir and other HIV protease inhibitors: 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. If parenteral midazolam is co-administered with HIV protease inhibitors, treatment setting should follow the description in the section above for ketoconazole within azole antifungals (see section 4.4).

*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 with epilepsy (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 I.V. administration of midazolam decreases the minimum alveolar concentration (MAC) of halothane required for general anaesthesia.

*Opioids*
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. 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.

## 4.6 Fertility, pregnancy and lactation

### Pregnancy
Category C.
Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. 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 developed physical dependence, and may be at some risk of developing withdrawal symptoms in the postnatal period. Midazolam is therefore not recommended for obstetric use.

Teratological studies with midazolam in a number of animal species have not shown association between administration of the drug and disturbances of 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 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.

*Risk summary statement*
Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines 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.

*Preclinical data*
Published studies in pregnant primates demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (see also section 5.3).

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

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

## 4.8 Undesirable effects
### Tabulated summary of adverse reactions
The following undesirable effects have been reported to occur when midazolam is injected.

Frequency categories are as follows:
Very common: ≥1/10;
Common: ≥1/100 to <1/10;
Uncommon: ≥1/1,000 to <1/100
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000
Not known: cannot be estimated from the available data.

| | |
|---|---|
| *Immune system disorders* | |
| Frequency not known | Hypersensitivity, angioedema, anaphylactic shock |
| *Psychiatric disorders* | |
| Frequency not known | Confusional state, euphoric mood, hallucinations<br>Agitation*, hostility*, rage*, aggressiveness*, excitement*<br>Physical drug dependence and withdrawal syndrome<br>Abuse |
| *Nervous system disorders* | |
| Frequency not known | Involuntary movements (including tonic/clonic movements and muscle tremor)*, hyperactivity*<br>Sedation (prolonged and postoperative), alertness decreased, somnolence, headache, dizziness, ataxia, anterograde amnesia**, the duration of which is directly related to the administered dose<br>Convulsions have been reported in premature infants and neonates<br>Drug withdrawal convulsions |

| | |
|---|---|
| *Cardiac disorders* | |
| Frequency not known | Cardiac arrest, bradycardia |
| *Vascular disorders* | |
| Frequency not known | Hypotension, vasodilation, thrombophlebitis, thrombosis |
| *Respiratory, thoracic and mediastinal disorders* | |
| Frequency not known | Respiratory depression, apnoea, respiratory arrest, dyspnea, laryngospasm, hiccups |
| *Gastrointestinal disorders* | |
| Frequency not known | Nausea, vomiting, constipation, dry mouth |
| *Skin and subcutaneous tissue disorders* | |
| Frequency not known | Rash, urticaria, pruritis |
| *General disorders and administration site conditions* | |
| Frequency not known | Fatigue, injection site erythema, injection site pain |
| *Injury, poisoning and procedural complications* | |
| Frequency not known | Falls, fractures*** |
| *Social circumstances* | |
| Frequency not known | Assault* |

*Such paradoxical drug reactions have been reported, particularly among children and the elderly (see section 4.4)

**Anterograde amnesia may still be present at the end of the procedure and in few cases prolonged amnesia has been reported (see section 4.4).

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

### Description of selected adverse reactions

*Dependence*

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 (see section 4.4). Cases of abuse have been reported.

*Cardiorespiratory adverse events*

Severe cardiorespiratory adverse events have occurred. 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).

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

### 4.9 Overdose

#### Symptoms

The symptoms of overdose are mainly an intensification of the pharmacological effects; 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. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical especially 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.

#### Treatment

In most cases only observation of vital functions is required. Supportive measures should be initiated as indicated by the patient's clinical state. In the management of overdose special attention should be paid to the respiratory and cardiovascular functions in intensive care.

If CNS depression is severe use of flumazenil should be considered. Flumazenil should only be administered under closely monitored conditions as flumazenil has only a short half-life (approximately 1 hour) and patients will require monitoring after its effects have worn off. Extreme caution should be observed in the use of flumazenil in the presence of drugs that reduce seizure threshold e.g. tricyclic antidepressants.

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.

#### Mechanism of action

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

#### Pharmacodynamic effects

The mechanism of action of the benzodiazepines is under continuous investigation. Benzodiazepines appear to intensify the physiological inhibitory mechanisms mediated by gamma-aminobutyric acid (GABA), the most common inhibitory neurotransmitter in the brain.

The effects of midazolam on the CNS are dependent on the dose administered, the route of administration and the presence or absence of other premedications. Onset time of sedative effects after intramuscular (IM) administration is 15 min, with peak sedation occurring 30 - 60 min following injection.

When used I.V. 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 2 h 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, I.V. midazolam decreases the sensitivity of the ventilatory response to elevated carbon dioxide tension in normal subjects and in those with chronic obstructive 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. I.V. midazolam at doses of 0.15 - 0.2mg/kg did not have deleterious effects on cardiac haemodynamics.

I.V. 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.

## 5.2 Pharmacokinetic properties

### Absorption

*Absorption after I.M. injection:* Absorption of midazolam from the muscle tissue is rapid and virtually complete.

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

### Distribution

When midazolam is administered I.V. the plasma concentration-time curve shows one or two distinct phases of distribution. The volume of distribution of midazolam at steady state is 0.7 – 1.2L/kg. Midazolam is 97% plasma protein bound. The major fraction of plasma binding is due to albumin. There is a slow and insignificant passage of midazolam into the cerebrospinal fluid. Midazolam crosses the placenta and enters the foetal circulation. Small quantities of midazolam are found in breast milk.

### Metabolism

Midazolam is almost entirely eliminated by biotransformation. Midazolam is hydroxylated by the cytochrome P450 3A4 isozyme. α-hydroxymidazolam is the major urinary and plasma metabolite. The plasma concentrations of α-hydroxymidazolam are 12% of those of the parent compound. The

fraction of the dose extracted by the liver has been estimated to be 30 - 60%. α-hydroxymidazolam is pharmacologically active but contributes only minimally (about 10%) to the effects of I.V. midazolam. There is no evidence of a genetic polymorphism in the oxidative metabolism of midazolam (see section 4.5).

### Elimination

In healthy subjects the mean elimination half-life of midazolam is between 1.5 - 2.5h and the plasma clearance is in the range of 300–5000mL/min. Midazolam is mainly excreted by renal route with 60–80% of the administered dose of midazolam being excreted in urine as glucoconjugated α–hydroxymidazolam. Less than 1% is recovered as unchanged drug. The elimination half-life of this metabolite is <1 h. 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 populations

*Elderly*

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

*Hepatic impairment*

The elimination half-life in cirrhotic patients may be longer and the clearance smaller when compared to those in healthy volunteers (see section 4.4).

*Renal impairment*

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

*Critically ill*

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

*ardiac 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.

*Paediatric population*

*Children:* The rate of rectal absorption in children is similar to that in adults. However the elimination half-life (t½) after I.V. and rectal administration is shorter in children 3 - 10 years when compared to 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 - 12 hours, probably due to liver immaturity and the clearance is reduced (see section 4.4).

### 5.3 Preclinical safety data

#### Animal toxicology and/or pharmacology

Published studies in animals demonstrate that the use of anaesthetic and sedative agents 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. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer 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 for 24 hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the foetus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring of rhesus macaques. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits. Healthcare providers should balance the benefits of appropriate anaesthesia in pregnant women, neonates and young children who require procedures with the potential risks suggested by the nonclinical data.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Water for injections.

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

24 months.

**MIDAZOLAM-BAXTER** does not contain any anti-microbial agent. **MIDAZOLAM-BAXTER** ampoules are for single use in one patient only. Discard any unused solution.

Preparations for infusion: 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.

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

### 6.4 Special precautions for storage

Store below 30°C. 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.

### 6.6 Special precautions for disposal and other handling

**MIDAZOLAM-BAXTER** may be mixed in the same syringe with frequently used premedicants: morphine sulphate, pethidine, atropine sulphate or scopolamine.

**MIDAZOLAM-BAXTER** may be diluted to facilitate slow injection.

**MIDAZOLAM-BAXTER** 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 15mg midazolam per 100 - 1000mL infusion solution.

For single use only. Discard any unused solution.

## 7. MEDICINE SCHEDULE

Class C5 Controlled Drug.

## 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

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## 9. DATE OF FIRST APPROVAL

17 March 2016

## 10. DATE OF REVISION OF THE TEXT

4 March 2019.

## SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|---|---|
| ALL | Trade name changed to MIDAZOLAM-BAXTER |
| 4.4 | Paediatric population, Paediatric neurotoxicity: New warnings on the use of general anaesthetic agents and sedative medicines in pregnant women and young children added. |
| 4.6 | Pregnancy: New warnings on the use of general anaesthetic agents and sedative medicines in pregnant women and young children added. |

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