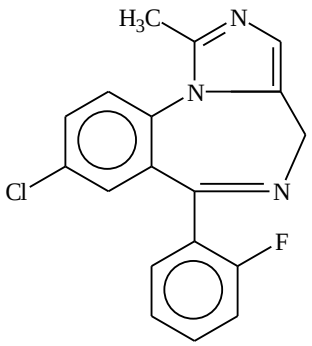
PRODUCT INFORMATION
MIDAZOLAM INJECTION

NAME OF DRUG

Midazolam.

DESCRIPTION

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



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

Molecular Weight: 325.8

CAS No: 59467-70-8

Midazolam Injection is a clear, colourless to pale yellow, isotonic solution containing midazolam 1mg/mL or 5 mg/mL (as hydrochloride), sodium chloride, hydrochloric acid (to produce hydrochloride) and sodium hydroxide in water for injections adjusted to pH 3.3.

PHARMACOLOGY

Class of drug: Benzodiazepine.

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

Pharmacodynamics

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 IM administration is 15 minutes. Peak sedation occurs 30 to 60 minutes following injection.

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

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

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

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

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

Pharmacokinetics

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

Pharmacokinetics in special clinical situations: In some intensive care and elderly patients given midazolam by IV infusion for prolonged sedation, the elimination half-life was found to increase by up to six times. Particular risk factors in the elderly include abdominal pathology,

sepsis and poor renal function. In these patients infusion at an unchanged rate resulted in higher plasma levels at steady state. Consequently, the infusion rate should be reduced once a satisfactory clinical response has been obtained.

Bioavailability: The mean absolute bioavailability of midazolam following IM administration is greater than 90%. The mean time of maximum midazolam plasma concentrations following IM dosing occurs within 45 minutes 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.

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

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

INDICATIONS

Intravenously as an agent for:

- conscious sedation prior to short surgical, diagnostic, therapeutic or endoscopic procedures such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography and cardiac catheterisation, either alone or in conjunction with an opioid.
- induction of anaesthesia preliminary to administration of other anaesthetic agents. With the use of an opioid premedicant, induction of anaesthesia can be obtained with a narrower dose range and in a shorter period of time.

Intermittent intravenous administration or continuous infusion for:

- sedation in intensive care units.

Intramuscularly for:

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

CONTRAINDICATIONS

- Patients with a hypersensitivity to benzodiazepines
- Myasthenia gravis
- Patients in shock, coma or in acute alcoholic intoxication with depression of vital signs

- Patients with acute narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma only if they are receiving appropriate therapy. Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with midazolam. Patients with glaucoma have not been studied.

PRECAUTIONS

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

- **Midazolam must never be used without individualisation of dosage. Midazolam should not be administered by rapid or single bolus intravenous administration (see DOSAGE AND ADMINISTRATION). Extravasation should also be avoided. The hazards of intra-arterial injection of midazolam into humans are unknown. Precautions against unintended intra-arterial injection should be taken.**

- **Patients should be continuously monitored for early signs of underventilation or apnoea. Vital signs should continue to be monitored during the recovery period. During intravenous application of midazolam respiratory depression, apnoea, respiratory and/or cardiac arrest have occurred. In some cases where this was not recognised promptly and treated, hypoxic encephalopathy or death has resulted. These life-threatening incidents may occur especially in elderly patients or patients with pre-existing respiratory insufficiency, especially if the injection is given too rapidly or with excessive doses. Particular care must be taken when administering the drug by IV route, in the elderly, to very ill patients, high-risk surgical patients and to those with significant hepatic impairment, chronic renal insufficiency, congestive heart failure or with limited pulmonary reserve because of the possibility of apnoea or respiratory depression. These patients require lower doses whether premedicated or not.**

- Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of midazolam.

- Elderly patients frequently have inefficient function of one or more organ systems and dosage requirements have been shown to be reduced with age. Patients with chronic renal failure or congestive heart failure eliminate midazolam more slowly.

- 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 six times. (See **Pharmacokinetics**).

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

- There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received midazolam.

Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with an opioid.

- A gradual dose reduction is recommended in patients on a prolonged IV dose of midazolam. Abrupt cessation of therapy may lead to withdrawal symptoms.

- 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. Should such reactions occur, the response to each dose of midazolam and all other drugs including local anaesthetics should be evaluated before proceeding.

- * The concomitant use of midazolam with alcohol or/and CNS depressants, including opioids, should be avoided. Such concomitant use has the potential to increase the clinical effects of midazolam possibly including severe sedation or clinically relevant respiratory depression, coma, and death. Limit dosages and durations to the minimum required. Concomitant use of barbiturates, alcohol or other central nervous system depressants increases the risk of underventilation or apnoea and/or cardio-ventricular depression* and may contribute to a profound and/or prolonged drug effect. When midazolam is used with a opioid analgesic, the dosage of both agents should be reduced. Opioid premedication also reduces the ventilatory response to carbon dioxide stimulation.

- Midazolam does not protect against the increase in intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anaesthesia.

- Since an increase in cough reflex and laryngospasm may occur with peroral endoscopic procedures, the use of a topical anaesthetic agent and the availability of necessary counter measures are recommended. The use of an opioid premedicant is recommended for bronchoscopies.

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

- As with other benzodiazepines midazolam may have the potential to cause dependence. Benzodiazepines should be avoided in patients with a history of alcohol or drug abuse. The risk of dependence increases with the duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse.

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.

Nonclinical research has shown that administration of anaesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate GABA activity can increase neuronal cell death in the brain and result in long-term cognitive deficits of juvenile animals

when administered at either high doses, or for prolonged periods, or both during the period of peak brain development. The mechanism of action of midazolam includes potentiation of GABA activity.

Use in the elderly

An increased risk for falls and fractures has been recorded in elderly benzodiazepine users.

Driving, operating machinery and other activities requiring mental alertness

After administration of midazolam, patients should not be discharged from hospital for at least three hours and then, if possible, only if accompanied by a responsible person. The decision as to when patients may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualised. Gross tests of recovery from the effects of midazolam cannot be relied upon to predict reaction time under stress. When midazolam is used with other drugs during anaesthesia, the contribution of these can vary and should be considered accordingly.

Patients should be warned to take extra care as a pedestrian and not to drive a vehicle or operate machinery until effects such as drowsiness, have subsided or until the day after anaesthesia and surgery, whichever is longer. The physician should decide when activities such as driving a vehicle or operating a machine may be resumed. The patient's attendants should be made aware that anterograde amnesia may persist longer than the sedation and therefore patients may not carry out instructions even though they appear to acknowledge them.

Carcinogenesis and mutagenesis

Midazolam maleate was administered with diet in mice and rats for two years at dosages of 1, 9 and 80mg/kg/day. In female mice in the highest dose group there was a marked increase in the incidence of hepatic tumours. In high dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumours. Dosages of 9 mg/kg/day of midazolam maleate do not increase the incidence of tumours. The pathogenesis of induction of these tumours is not known. These tumours were found after chronic administration, whereas human use will ordinarily be of single dose or of short duration. 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.

Effects on Fertility:

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

Use in pregnancy: Category C

Midazolam crosses the placenta and other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression can be expected to cause irregularities in the foetal heart rate, hypothermia, hypotonia, poor sucking and moderate respiratory

depression due to the pharmacological action of the product. Moreover, infants born to mothers who received benzodiazepines chronically during the latter stage of pregnancy may have developed physical dependence, and may be at some risk of developing withdrawal symptoms in the postnatal period. Midazolam is therefore not recommended for obstetric use.

Teratological studies with midazolam in a number of animal species have not shown association between administration of the drug and disturbances of fetal development, nor has clinical experience so far yielded any evidence of such an association. However, like any other drug, midazolam should not be used in the first three months of pregnancy unless considered absolutely necessary by the physician.

Use in lactation

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

INTERACTIONS WITH OTHER DRUGS

Midazolam can enhance the central sedative effect of neuroleptics, tranquillisers, antidepressants, sleep-inducing drugs, analgesics, anaesthetics, antipsychotics, anxiolytics, antiepileptic drugs and sedative antihistamines. This potentiation of effect can in certain cases be of advantage therapeutically.

There is potentially relevant interaction between midazolam and compounds which inhibit certain hepatic enzymes (particularly cytochrome CYP3A). Data clearly indicates that these compounds influence the pharmacokinetics of midazolam and may lead to prolonged sedation. At present this reaction is known to occur with rifampicin, carbamazepine, phenytoin, cimetidine, erythromycin, diltiazem, verapamil, ketoconazole, fluconazole, itraconazole, ritonavir and saquinavir.

Therefore patients receiving the above compounds or others which inhibit CYP3A together with midazolam should be monitored carefully for the first few hours after administration of midazolam. (Studies have shown that ranitidine has no influence on the pharmacokinetics of parenterally given midazolam).

In some patients the mutual potentiation of alcohol and midazolam can produce unforeseeable reactions (no alcoholic beverages for at least 12 hours after parenteral administration).

The sedative effect of intravenous midazolam is accentuated by premedication. Consequently, the dosage of midazolam should be adjusted according to the type and amount of premedication administered.

The plasma concentration of midazolam, following oral administration, has been shown to increase when used in combination with erythromycin and this results in a potentiation of midazolam's sedative effect. A much smaller change in plasma concentration with no observed potentiation of the sedative effects was observed following IV administration of midazolam, however, caution is advised.

A moderate reduction in induction dosage requirements of thiopentone (about 15%) has been noted following use of intramuscular midazolam for premedication. Simultaneous administration of cimetidine (but not ranitidine) has been reported to reduce clearance of midazolam. Displacement of midazolam from its plasma protein binding sites by sodium valproate may increase the response to midazolam and, therefore, care should be taken to adjust the midazolam dosage in patients with epilepsy.

The intravenous administration of midazolam decreases the minimum alveolar concentration (MAC) of halothane required for general anaesthesia. This decrease correlates with the dose of midazolam administered. The effects of midazolam can be reversed by the benzodiazepine antagonist flumazenil.

Pharmacokinetic Drug-Drug Interaction (DDI))

Inhibitors and inducers of CYP3A have the potential to increase and decrease the plasma concentrations and, subsequently, the pharmacodynamic effects of midazolam. Therefore, it is recommended to carefully monitor the clinical effects and vital signs during the use of midazolam when co-administered with a CYP3A inhibiting or inducing drug.

Drugs that inhibit CYP3A

Patients receiving compounds which inhibit CYP3A should not be administered midazolam whenever possible. Otherwise, the dose of midazolam should be adjusted and the patient kept under careful surveillance. There is a potential interaction with the following:

Azole antifungals: ketoconazole, fluconazole, itraconazole, posaconazole.

Macrolide antibiotics: erythromycin, clarithromycin.

HIV protease inhibitors: saquinavir.

Histamine receptor 2 antagonists: cimetidine.

Calcium-channel blockers: diltiazem.

HMG-CoA reductase inhibitor: atorvastatin.

Drugs that induce CYP3A

Rifampicin.

Herbs and Food

Echinacea purpurea root extract, St John’s Wort.

Acute protein displacement

Valproic acid: due to the high therapeutic plasma concentration of valproic acid, the protein displacement of midazolam in the acute dose setting, resulting in more apparent clinical effect of midazolam, cannot be excluded when used concurrently.

Pharmacodynamic Drug-Drug Interactions (DDI)

The co-administration of midazolam with other sedative/hypnotic agents, including alcohol, is likely to result in increased sedative/hypnotic effects. Examples include opiates/opioids (when they are used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines (used as anxiolytics or hypnotics), barbiturates, propofol, ketamine, etomidate, sedative antidepressants, antihistaminics and centrally acting antihypertensive drugs.

Enhanced effects on sedation, respiration and haemodynamics may occur when midazolam is co-administered with any centrally acting depressants including alcohol. Therefore, adequate monitoring of vital signs should be established. Alcohol should be avoided in patients receiving midazolam (**see PRECAUTIONS and OVERDOSAGE** for warning of other CNS depressants, including alcohol).

The sedative effect of IV midazolam is likely to be potentiated when either lignocaine or bupivacaine are administered IM,

Physostigmine: may reverse the hypnotic effects of midazolam.

Caffeine: may reverse the sedative effect of midazolam.

Effects on Laboratory Tests

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

ADVERSE EFFECTS

Fluctuations in vital signs that have been noted following parenteral administration of midazolam include:

- respiratory depression (22.9% following IV administration and 10.8% of patients following IM administration)
- apnoea (19% following IV administration)
- variations in blood pressure and pulse rate.

These common occurrences during anaesthesia and surgery are affected by the lightening or deepening of anaesthesia, instrumentation, intubation and use of concomitant drugs. Administration of 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 opioid analgesics (see also **DOSAGE AND ADMINISTRATION**).

The following additional adverse effects were reported after intramuscular administration:

- local effects at intramuscular injection site: pain (3.7%)
- headache (1.3%)
- induration (0.5%)
- redness (0.5%)
- muscle stiffness (0.3%)

The following additional adverse effects were reported subsequent to intravenous administration:

- local effects at the IV site: tenderness (7%)
- pain during injection (6.2%)
- hiccough (5.5%)
- redness (3.8%)
- nausea (3%)
- vomiting (2.9%)
- coughing (1.9%)
- induration (1.9%)
- drowsiness (1.3%)
- oversedation (1%)
- phlebitis (0.5%)

Other adverse experiences, observed mainly following IV injection and occurring at an incidence of less than 1%, are as follows:

- **respiratory:** larynogspasm, bronchospasm, dyspnoea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnoea.
- **cardiovascular:** bigeminy, premature ventricular contractions, tachycardia, nodal rhythm, cardiovascular collapse, vasovagal episode, cardiac arrest.
- **gastrointestinal:** acid taste, excessive salivation, retching.

- **CNS/neuromuscular:** anterograde amnesia, headache, euphoria, confusion, argumentativeness, nervousness, agitation, anxiety, grogginess, irritability, restlessness, emergence delirium or agitation, prolonged emergence from anaesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, tonic/clonic movements, muscle tremor, involuntary movements, athetoid movements, dizziness, ataxia, dysphoria, slurred speech, dysphonia, paresthesia.

- **ophthalmic:** blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, difficulty in focusing.

- **integumentary:** hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, erythema, rash, pruritus.

- **hypersensitivity:** in isolated cases, generalised hypersensitivity - including anaphylactic reactions and skin reactions - has been reported.

- **miscellaneous:** yawning, lethargy, chills, weakness, continued phonation, ears blocked, loss of balance, light-headedness, toothache, faint feeling, haematoma.

Post-marketing experience

The following adverse effects have been reported and are not listed above.

Psychiatric disorders: hallucinations.

Paradoxical reactions: hyperactivity, hostility, rage reaction, aggressiveness, tension, mood changes, 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.

Nervous system disorder: decreased alertness. Convulsions have been reported in premature infants and neonates.

Cardiac disorders: hypotension, bradycardia, vasodilating effects.

Respiratory disorders: respiratory depression, apnoea, respiratory arrest.

Gastrointestinal System Disorders: constipation, dry mouth.

Skin and Appendages Disorders: urticaria.

General and Application Site Disorders: thrombophlebitis, thrombosis.

Injury, Poisoning and Procedural Complications: An increased risk for falls and fractures has been recorded in elderly benzodiazepine users.

DOSAGE AND ADMINISTRATION

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

Dosage should be individualised and drug should be administered slowly.

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

Intravenous administration

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

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

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

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

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

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

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

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

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

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

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

Intramuscular administration

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

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

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

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

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

Dilution and admixture

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

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

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

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

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

OVERDOSAGE

Symptoms of overdosage

The manifestations of midazolam overdosage are similar to those observed with other benzodiazepines, ranging from drowsiness to coma. Overdose of midazolam is seldom life-threatening if the medicine is taken alone, but in mild cases, may lead to symptoms including drowsiness, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, areflexia, apnoea, hypotonia, hypotension, respiratory depression, coma, cerebrovascular perfusion and very rarely death. Coma may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other central nervous system depressants, including alcohol. When combined with other CNS depressants, the effects of overdosage are likely to be severe and may prove fatal.

Treatment of overdosage

Treatment of midazolam overdosage is the same as that followed for overdosage with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. In adults or children who have taken an overdose of benzodiazepines within 1 - 2 hours, consider activated charcoal with airway protection if indicated.

Flumazenil can be used to reverse the effects of midazolam (refer to Flumazenil Product Information leaflet) if CNS depression is severe. Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be combated by the judicious use of other accepted antihypotensive measures. There is no information as to whether peritoneal dialysis, forced diuresis or haemodialysis are of any value in the treatment of overdosage. Hepatic function should be monitored.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

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

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

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

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

±Not available in Australia.

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

Unopened ampoules will be suitable for use for up to 8 months after the foil sachet has been opened, if protected from light.

The expiry date (month/year) is stated on the package after EXP.

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine –S4 (Australia)**.**

NAME AND ADDRESS OF THE SPONSOR

Sponsor in Australia

Pfizer Australia Pty Ltd

A.B.N. 50 008 422 348

38-42 Wharf Road

West Ryde NSW 2114 Australia.

Manufacturer

Pfizer (Perth) Pty Limited

ABN 32 051 824 956

15 Brodie Hall Drive

Bentley WA 6102 Australia.

®Registered trademark

Steriluer® is a plastic ampoule produced by Pfizer.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

24 December 1999.

DATE OF MOST RECENT AMENDMENT:

19 February 2018

*Please note changes to product information.