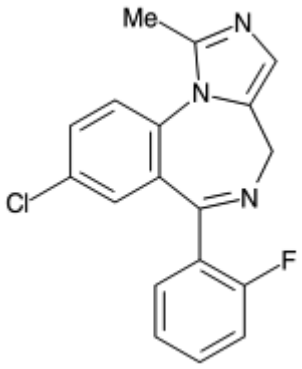
# PRODUCT INFORMATION
# MIDAZOLAM SANDOZ® INJECTION AMPOULE

## NAME OF THE MEDICINE

***Active*** Midazolam (as hydrochloride)

***Chemical name:***
8-chloro-6-(2-fluorophenyl)-1-methyl- 4*H*-imidazo[1,5-*a*][1,4] benzodiazepine

***Chemical structure of midazolam***




***Molecular formula*:** $C_{18}H_{13}ClFN_3$
***Molecular weight*:** 325.8
***CAS*:** 59467-70-8

## DESCRIPTION

Midazolam is a benzodiazepine from the imidazobenzodiazepine group. The free base of the active substance of midazolam is a lipophilic substance with low solubility in water. The basic nitrogen in position 2 of the imidazobenzodiazepine ring enables the active substance of midazolam to form water soluble salts with acids. These produce a stable injection. The solution is adjusted to a pH of 3.3.

***Inactive*** Sodium chloride, hydrochloric acid (to produce hydrochloride), sodium hydroxide and water for injections

## PHARMACOLOGY

Midazolam is a short acting central nervous system (CNS) depressant which induces sedation, hypnosis, amnesia and anaesthesia. Pharmacokinetic and pharmacodynamic data in chronic intravenous usage are not available beyond 15 days.
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 administration is 15 minutes, with peak sedation occurring 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 it is preceded by narcotic premedication. The time to induction of anaesthesia for surgical procedures is variable, occurring in approximately 1.5 minutes (0.3 to 8 minutes) when an opioid premedication has been administered, and in 2 to 2.5 minutes without premedication or with a sedative premedication. Approximately two hours is 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, 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. The latter are, of course, 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.

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. Intravenous midazolam at doses of 0.15 to 0.2 mg/kg did not have deleterious effects 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 suxamethonium administration or endotracheal intubation is not prevented by midazolam, thiopentone or diazepam.

### *Pharmacokinetics*

Elimination

In normal subjects the mean elimination half-life of midazolam is between 1.4 – 2.4 h and the clearance is in the range of 220 – 470 mL/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 < 1 h.
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 **Interactions with Other Medicines**).

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.

*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.

Absorption and Bioavailability

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

The mean absolute bioavailability of midazolam following intramuscular administration is greater than 90%. The mean time of maximum midazolam plasma concentrations following intramuscular dosing occurs within 45 minutes post-administration. Peak concentrations of midazolam, as well as 1-hydroxymethyl midazolam, after intramuscular administration, are about one-half of those achieved after equivalent intravenous doses.

*Absorption after rectal administration:* After rectal administration midazolam is absorbed quickly. Maximum plasma concentration is reached in about 30 min. The absolute bioavailability is about 50% (range 40 – 65%).

***Metabolism***

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

Distribution The pharmacokinetic profile of midazolam in humans is linear over the 0.05 to 0.4 mg/kg dose range. 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 a narcotic.

Intravenously 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.

Sedation in intensive care units by intermittent intravenous administration or continuous infusion.

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

## CONTRAINDICATIONS

Midazolam should not be given to patients with myasthenia gravis; hypersensitivity to benzodiazepines.

Midazolam should not be given 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, but 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

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**). Intravenous midazolam should only be used in settings with equipment and skilled personnel for continuous monitoring of cardiorespiratory 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 intravenous 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 intravenous route, to elderly patients, very ill patients, high risk surgical patients and 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.

*Preoperative sedation:* Adequate observation of the patient after preoperative sedation of midazolam is mandatory as individual sensitivity varies and symptoms of overdose may occur.

Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of midazolam. Elderly patients frequently have inefficient function of one or more organ systems and dosage requirements have been shown to be reduced with age. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly.

In some intensive care patients and in some elderly patients given midazolam by intravenous infusion for prolonged sedation, the elimination half-life was found to increase by up to four times (see ***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 a narcotic.

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

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 barbiturates, alcohol or other CNS depressants increases the risk of underventilation or apnoea and/or cardio-ventricular depression and may contribute to a profound and/or prolonged drug effect. 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.

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.

After parenteral administration of midazolam, patients should not be discharged from hospital for at least three 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.

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

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.

### *Effects on Fertility*
The effects of midazolam on fertility have not been established.

### *Use in 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 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 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.

### *Use in lactation*

There is evidence that midazolam is excreted in breast milk and its effects on the newborn infant are not known. Therefore midazolam is not recommended for use in breastfeeding mothers.

### *Paediatric Use*

Safety and effectiveness of midazolam in children below the age of eight years have not been established. Pharmacokinetics in children have not been established and may differ from adults.

### *Use in the elderly*

An increased risk for falls and fractures has been recorded in elderly benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

### *Carcinogenicity*

Midazolam maleate was administered with diet in mice and rats for two years at dosages of 1, 9 and 80 mg/kg/day. In female mice, in the highest dose group, there was a marked increase in the incidence of hepatic tumours. In high dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumours. Dosages of midazolam maleate 9 mg/kg/day 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.

### *Mutagenicity*

Midazolam did not have mutagenic activity in *Salmonella typhimurium* (five bacterial strains), Chinese hamster lung cells (V79), human lymphocytes or in the micronucleus test in mice.

### *Genotoxicity*

The effects of midazolam on genotoxicity have not been established.

### *Effect on ability to drive or operate machinery*

Patients should be warned to take extra care as a pedestrian and not to drive a vehicle or operate a machine until the effects of the drug, 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 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 though they appear to acknowledge them.

## INTERACTIONS WITH OTHER MEDICINES

### ***Specific interaction studies***

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 a potentially relevant interaction between midazolam and compounds that inhibit or induce certain hepatic enzymes (particularly CYP3A.). Data clearly indicate that these compounds influence the pharmacokinetics of midazolam and may lead to an altered degree and/or duration of

sedation. At present enzyme induction is known to occur *in vivo* with rifampicin, carbamazepine and phenytoin, and enzyme inhibition occurs with cimetidine, erythromycin, diltiazem, verapamil, ketoconazole, fluconazole, itraconazole, ritonavir and saquinavir.

Therefore patients receiving the above compounds or others that inhibit CYP3A. should not be administered midazolam whenever possible. Otherwise the dose of midazolam should be adjusted and the patient kept under careful surveillance. During long-term midazolam infusions, a reduction of up to 50% of the initial dose followed by careful titration is recommended. 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 these 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 intravenous administration of midazolam, however, caution is advised.

A moderate reduction in induction dosage requirements of thiopental (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)***

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 pharmacodynamic 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 of drug interaction with drugs that have high therapeutic serum concentrations, as has been hypothesized for valproic acid (see below). Midazolam is not known to change the pharmacokinetics of other drugs.

It is recommended to carefully monitor the clinical effects and vital signs during the use of midazolam; taking into account that the clinical effects of midazolam might be stronger and also last longer after co-administration of a CYP3A-inhibiting drug. Depending on the magnitude of the CYP3A-inhibiting effect, the dose of midazolam may be largely reduced. Conversely, administration of a CYP3A-inducing drug may require a higher dose of midazolam to achieve the desired effect.

In case of CYP3A induction and irreversible inhibition (so-called mechanism based inhibition), the effect on the pharmacokinetics of midazolam may persist for a period of several days up to few weeks after administration of the CYP3A inhibitor. Examples for mechanism based CYP3A inhibitors include antibacterials (e.g. clarithromycin, erythromycin, isoniazid); anti-HIV agents (e.g.

HIV protease inhibitors, delavirdine); antihypertensives (e.g. verapamil, diltiazem); sex steroids and their receptor modulators (e.g. gestodene, raloxifene), and several herbal constituents (e.g. bergamottin (grapefruit)). In contrast to the other mechanism based inhibitors (see listing below), ethinyloestradiol/norgestrel (used for oral contraception) and grapefruit juice (200 mL) did not significantly change the Area Under the plasma concentration / time Curve ($AUC_{0-\infty}$) of (or exposure to) IV midazolam.

The range of the inhibiting/inducing potency of drugs is wide. The antifungal ketoconazole, a very potent CYP3A inhibitor, increased the plasma concentration of intravenous midazolam by approximately 5-fold. The tuberculostatic drug, rifampicin, belongs to the strongest inducers of CYP3A and its co-administration resulted in a decrease in the $AUC_{0-\infty}$ of IV midazolam by approximately 60%.

The mode of midazolam use also determines the magnitude of change in its pharmacokinetics due to CYP3A modulation: (i) The change in plasma concentration is expected to be less for intravenous compared with oral administration of midazolam. This is because CYP3A modulation not only affects the systemic clearance, but also the bioavailability of oral midazolam. (ii) There are no studies available that have investigated the effect of CYP3A modulation on the pharmacokinetics of midazolam after either rectal or intramuscular administration. After rectal administration the drug partially bypasses the liver and the expression of CYP3A is lower in the colon compared with the upper gastrointestinal tract. Therefore, it is expected that the change in midazolam plasma concentration, due to CYP3A modulation, will be less for the rectal than for the oral route of administration. After intramuscular administration, the drug directly enters the systemic circulation. Therefore, it is expected that the effect of CYP3A modulation will be similar to that for intravenous administration of midazolam. (iii) In line with pharmacokinetic principles, clinical studies have shown that after a single intravenous dose of midazolam, in the presence of CYP3A inhibition, the change in maximal clinical effect due to CYP3A modulation will be minor, whereas the duration of effect may be prolonged. However, after prolonged dosing of midazolam, both the magnitude and duration of effect may be increased.

The following listing gives examples of clinical pharmacokinetic drug-drug interactions with midazolam after intravenous administration. Importantly, any drug shown to possess CYP3A-modulating effects, either *in vitro* or *in vivo*, has the potential to change the plasma concentration of midazolam, and therefore its effects. The listing includes information from clinical drug-drug interaction studies for oral midazolam. As outlined above, the change in plasma concentration is expected to be less for intravenous compared with oral midazolam.

## 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.

*Azole antifungals*

- Ketoconazole: Increased the $AUC_{0-\infty}$ of intravenous midazolam 5-fold while the terminal half-life increased by approximately 4-fold.

- Fluconazole and itraconazole: Both increased the $AUC_{0-\infty}$ of intravenous midazolam, which was associated with a 2.4-fold and 1.5-fold increase in terminal half-life for itraconazole and fluconazole, respectively. A 100–300% increase in plasma midazolam

at 48 hours after receiving fluconazole was commonly (3/10) seen in intensive care unit patients with a midazolam infusion. Orally, fluconazole increased $C_{max}$ 1.7-fold and $AUC_{0-\infty}$ 3.6-fold, while for itraconazole they increased 2.5- and 6.6-fold, respectively.

- Posaconazole: Increased the $AUC_{(tf)}$ (AUC zero to last measurable concentration) of intravenous midazolam by 1.8-fold.

*Macrolide antibiotics*

- Erythromycin: Resulted in an increase in the $AUC_{(tf)}$ of intravenous midazolam and was associated with a 1.4–1.8-fold increase in the terminal half-life of midazolam.

- Clarithromycin: Increased the AUC of intravenous midazolam by approximately 2.5-fold and was associated with a 2.7-fold increase in terminal half-life.

*Additional information from oral midazolam*

- Roxithromycin has less of an effect on the pharmacokinetics of midazolam than erythromycin or clarithromycin. After oral administration with roxithromycin the maximum plasma concentration ($C_{max}$) of midazolam increased approximately 40% compared with increases of 2.7-fold caused by erythromycin and 2.8-fold with clarithromycin, while the 40% increase in $AUC_{0-\infty}$ is matched by 4.4-fold and 7-fold increases, respectively. The mild effect on the terminal half-life of midazolam (~ 30%) indicates that the effects of roxithromycin on IV midazolam may be minor.

*HIV protease inhibitors*

- *Saquinavir and other HIV protease inhibitors*: 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.

*Histamine receptor 2 antagonists*

- Cimetidine increased the steady state plasma concentration of midazolam by 26%.

*Calcium-channel blockers*

- Diltiazem: After pretreatment with lorazepam and a single dose of diltiazem, on cessation of an intravenous infusion of midazolam, the AUC from cessation for 23 h increased approximately 25% and the terminal half-life was prolonged approximately 43%.

*Additional information from oral midazolam*

- Verapamil and diltiazem: Increased the $C_{max}$ of oral midazolam 2-fold, while $AUC_{0-\infty}$ increased 3- and 4-fold, respectively. The terminal-half-life of midazolam increased 41% and 49%, respectively.

*Various drugs/Herbs*

- Atorvastatin: Increased the AUC of intravenous midazolam by approximately 1.4-fold compared with control group.

*Additional information from oral midazolam*

- Fluvoxamine: Increased the $AUC_{0-\infty}$ and $C_{max}$ of oral midazolam 40% and doubled the terminal half-life.

- Nefazodone: Increased the $AUC_{0-\infty}$ of oral midazolam 4.6-fold with an increase in $C_{max}$ of 1.8-fold and in terminal half-life of 1.6-fold.

- Aprepitant: Dose-dependently increased the AUC of oral midazolam with an increase of approximately 3.3-fold after 80 mg/d, associated with an approximate 2-fold increase in terminal half-life.

- Chlorzoxazone: Decreased the ratio of the CYP3A-generated metabolite α-hydroxymidazolam to midazolam, indicating a CYP3A-inhibiting effect of chlorzoxazone.

- Bicalutamide: Showed only minor effects on oral midazolam, i.e. a 27% increase in $AUC_{0-\infty}$ and 13% on $C_{max}$.

- Goldenseal: Decreased the ratio of the CYP3A-generated metabolite α-hydroxymidazolam to midazolam approximately 40%, indicating CYP3A-inhibitory effect.

## Drugs that induce CYP3A

- Rifampicin (600mg o.d.) decreased the AUC of IV midazolam by approximately 60% after 7 days. The terminal half-life decreased by approximately 50 - 60%.

*Additional information from oral midazolam*

- Carbamazepine and phenytoin: Repeat dosages of carbamezepine or phenytoin resulted in a decrease in the AUC and $C_{max}$ of oral midazolam by over 90% and a shortening of the terminal half-life by almost 60%.

- Efavirenz: The 5-fold increase in the ratio of the CYP3A-generated metabolite α-hydroxy-midazolam to midazolam confirms its CYP3A-inducing effect.

## Herbs and food

- Echinacea purpurea root extract: Decreased the AUC of intravenous midazolam 20% and was associated with a decrease in half-life approximately 42%.

- St John's wort: Decreased the AUC of intravenous midazolam by approximately 20% and AUC of oral midazolam by 50% with $C_{max}$ decreased by 40–50%. It was associated with a decrease in terminal half-life by approximately 16-19%.

## Acute protein displacement

- Valproic acid: In one publication, protein displacement of midazolam by valproic acid was discussed as a potential mechanism of DDI. The clinical relevance of this study is considered very limited because of methodological concerns. However, 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.

## *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. Midazolam decreased the minimum alveolar concentration (MAC) of Halothane.

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).

It has been shown that high spinal anaesthesia can increase the sedative effect of intravenous midazolam. The midazolam dose may therefore be reduced. Also, when either lignocaine or bupivacaine were administered intramuscular, the dose of intravenous midazolam required for sedation was reduced.

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

## ADVERSE EFFECTS

Fluctuations in vital signs have been noted following parenteral administration of midazolam and include respiratory depression (22.9% following intravenous administration and 10.8% of patients following intramuscular administration) and apnoea (19% following intravenous 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 intramuscular midazolam to elderly and/or higher risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases the patients also received other CNS depressants capable of depressing respiration, especially narcotics (see **DOSAGE AND ADMINISTRATION**).

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

The following additional adverse reactions were reported subsequent to intravenous administration: hiccups (5.5%), nausea (3%), vomiting (2.9%), coughing (1.9%), oversedation (1%), drowsiness (1.3%); local effects at the intravenous site included tenderness (7%), pain during injection (6.2%), redness (3.8%), induration (1.9%), phlebitis (0.5%).

**Post-Marketing experience**: The following additional adverse reactions were reported subsequent to intravenous administration.

***Respiratory***. Severe cardio-respiratory adverse effects have occurred on rare occasions. These have included respiratory depression, apnoea, respiratory arrest, laryngospasm, bronchospasm, dyspnoea, 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 **PRECAUTIONS**). Coughing, hiccoughs.

***Cardiovascular.*** Severe cardio-respiratory adverse effects have occurred on rare occasions. These have included bigeminy, premature ventricular contractions, tachycardia, nodal rhythm, cardiovascular collapse, vasovagal episode, cardiac arrest, hypotension, bradycardia and vasodilating effects. 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 **PRECAUTIONS**).

***Gastrointestinal***. Acid taste, excessive salivation, retching, nausea, vomiting, constipation, dry mouth.

***Nervous system Disorder***. Anterograde amnesia, the duration of which is directly related to the administered dose, may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported. Headache, euphoria, confusion, decreased alertness, argumentativeness, nervousness, agitation, hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, anxiety, grogginess, irritability, restlessness, emergence delirium or agitation, prolonged sedation and postoperative sedation, dreaming during emergence, sleep disturbance, insomnia, nightmares, tonic/clonic movements, muscle tremor, involuntary movements, athetoid movements, dizziness, ataxia, dysphoria, slurred speech, dysphonia, paraesthesia. Convulsions have been reported in premature infants and neonates.

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

***Ophthalmic***. Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, difficulty in focusing.

***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.

***Immune System Disorders:*** In isolated cases, generalised hypersensitivity, including anaphylactic, cardiovascular and skin reactions and bronchospasms, has been reported.

***Miscellaneous***. Yawning, lethargy, chills, weakness, continued phonation, blocked ears, loss of balance, lightheadedness, toothache, faint feeling, haematoma.

***Injury, Poisoning and Procedural Complications:*** An increased risk for falls and fractures has been recorded in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

***Psychiatric Disorders:*** Confusional state, euphoric mood, hallucinations, dysphoria.
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.

***Other:*** urticarial reaction.

## DOSAGE AND ADMINISTRATION

Dosage should be individualised and the 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 injection 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***
Midazolam should be administered slowly.

Endoscopic or cardiovascular procedures
For conscious sedation midazolam 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 peroral 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 independently 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 two minutes. Wait an additional two or more minutes to fully evaluate the sedative effect. When titrating the dose two 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 1mg. Further doses of 1 mg 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 1.5 mg. Total doses greater than 3.5 mg are not usually necessary. Special caution is required for the indication of conscious sedation in patients with impaired respiratory function (see **PRECAUTIONS**).

If a narcotic 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 to 0.2 mg/kg (10 to 15 mg), administered at a rate of approximately 2.5 mg per ten seconds. Maximum sedation is usually reached after two to three 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 narcotic analgesics as it does not have analgesic properties and narcotic analgesics enhance its anaesthetic inducing properties.

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

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

After prolonged intravenous administration of midazolam, abrupt discontinuation 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***
For preoperative sedation. Induction of sleepiness or drowsiness and relief of apprehension and to impair memory of perioperative events.

Inject intramuscularly, 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 (approximately 5 mg) intramuscularly administered approximately one hour before surgery.

The dose must be individualised and reduced when intramuscular midazolam is administered to patients with chronic obstructive pulmonary disease, other higher risk surgical patients, patients 60 years or over, and patients who have received concomitant narcotics or other CNS depressants (see **ADVERSE EFFECTS**). In a study of patients 60 years or older, who did not receive concomitant administration of narcotics, 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, 1mg provided satisfactory sedation. As with any potential respiratory depressant, these patients require special observation for signs of cardiorespiratory depression after receiving intramuscular midazolam.

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

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

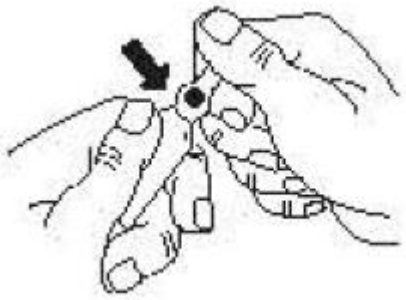
To avoid potential incompatibility with other solutions, midazolam must not be mixed with any solutions except those listed above.

The 15 mg/3 mL, 5 mg/1 mL and 5 mg/5 mL formulations may be diluted to facilitate slow injection.

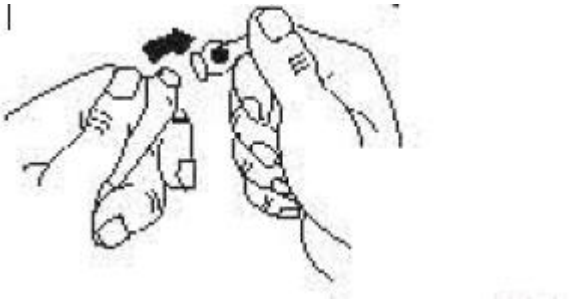
The 50 mg/10 mL ampoules may be added to the infusion solutions in a mixing ratio of midazolam 15 mg/100 mL to 1,000 mL infusion solution. To reduce microbiological hazard it is recommended that the infusion commence as soon as possible after preparation and in any case within 24 hours. Any storage should be at 2ºC to 8ºC.

Ampoules are intended for single patient use only. Discard any remaining contents.

Handling of the ampoules:
Allow the solution in the tip to run down by bumping and shaking the ampoule.



Colour point to the top.



Break the ampoule as shown in the picture above.

## OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of 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 protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

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

***Treatment***

Treatment of 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.

## PRESENTATION AND STORAGE CONDITIONS

Midazolam Sandoz 5 mg/5 mL; 5 mg/1 mL; 15 mg/3 mL; 50 mg/10 mL injection ampoules – clear glass ampoules containing a clear sterile solution of midazolam 'ready for injection'.

Pack Size: 5 & 10 ampoules

*Not all presentations may be marketed in Australia*

Store below 25°C. Do not freeze. Protect from light.

## NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park
NSW 2113
Tel: 1800 634 500

## POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

**Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):** 25/07/2003

**Date of most recent amendment:** 19/05/2016