PRODUCT MONOGRAPH

MIDAZOLAM INJECTION
5 mg/mL
15 mg/3 mL
5 mg/5mL
50 mg/10 mL

Pfizer Standard

Benzodiazepine
Premedicant-Sedative-Anesthetic Agent

Pfizer Canada Inc.
Kirkland, Quebec, H9J 2M5

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Midazolam Injection

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THERAPEUTIC CLASSIFICATION

Premedicant-Sedative-Anesthetic Agent

GENERAL

Adult and Pediatric

Intravenous midazolam injection has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous midazolam should be used only in hospital or ambulatory care settings that provide for continuous monitoring of respiratory and cardiac function i.e. pulse oximetry. Immediate availability of resuscitative drugs and age and size-appropriate equipment for bag/valve/mask ventilation and intubation, and personnel trained in their use and skilled in airway management should be assured (see **WARNINGS**). For deeply sedated patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

The initial intravenous dose for sedation in adult patients may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant opioids or other central nervous system depressants. The initial dose and all subsequent doses should always be titrated slowly; administered over 2-3 minutes and allow about 2 minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Doses of sedative medications in pediatric patients must be calculated on a mg/kg basis, and initial doses and all subsequent doses should always be titrated slowly. The initial pediatric dose of midazolam for sedation/anxiolysis/amnesia is age, procedure, and route dependent (see **DOSAGE AND ADMINISTRATION** for complete dosing information).

Neonates
Midazolam should not be administered by rapid injection in the neonatal population. Severe hypotension and seizures have been reported following rapid intravenous administration, particularly with concomitant use of fentanyl (see **DOSAGE AND ADMINISTRATION** for complete information).

ACTION AND CLINICAL PHARMACOLOGY

Midazolam is a short-acting, water-soluble benzodiazepine which has central nervous system (CNS) depressant effects. Depending on the route of administration and dose used, midazolam can produce sedative-hypnotic effects or induce anesthesia. The administration of midazolam may often be followed by anterograde amnesia.

Onset of sedative effects after intramuscular administration is about 15 minutes, with peak sedation occurring 30 to 60 minutes following injection. Sedation (defined as drowsiness with ability to respond to verbal commands) after intravenous injection is usually achieved within 3 to 6 minutes; the time of onset is affected by the dose administered, the concurrent administration of opioid premedications and the condition of the patient. When midazolam is used intravenously, induction of anesthesia can usually be achieved in 1.5 minutes when opioid premedication has been administered and in 2 to 2.5 minutes without opioid premedication. When used as directed, recovery after awakening from general anesthesia usually occurs within 2 hours, but recovery may take up to 6 hours in some cases. Recovery in patients receiving midazolam may be slightly slower than in patients who receive thiopental.

Intravenous doses of midazolam depress the ventilatory response to CO_2 stimulation for 15 minutes or more beyond the duration of ventilator depression following administration of thiopental. **The ventilatory response to CO_2 is markedly impaired in patients with chronic obstructive pulmonary disease.** Intravenous sedation with midazolam in healthy volunteers does not adversely affect the mechanics of respiration (pulmonary resistance, static recoil, functional residual capacity or residual volume). However, total lung capacity (TLC) and peak expiratory flow decrease significantly, but static compliance and maximum expiratory flow at 50% of awake TLC (V_{max}) increase. In healthy volunteers an intramuscular premedicating dose of 0.07 mg/kg did not depress the ventilator response to CO_2 stimulation to a clinically significant extent. The intravenous administration of midazolam decreases in a dose dependent manner the minimum alveolar concentration (MAC) of halothane required for general anesthesia.

In cardiac hemodynamic studies, induction with midazolam was associated with a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume and systemic vascular resistance. When used in intravenous sedation midazolam produces a higher incidence of fall in mean arterial pressure than diazepam. Slow heart rates (less than 65/minute), particularly in

patients taking propranolol for angina, tended to rise slightly while faster heart rates (e.g. 85/minute) tended to slow slightly.

In patients without any previous history of cerebrospinal diseases scheduled for elective surgery under lumbar spinal anesthesia, intravenous administration of midazolam at a dose of 0.15 mg/kg tended to reduce the cerebrospinal fluid pressure during induction of anesthesia to an extent similar to 3.9 mg/kg of intravenous thiopental. Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with midazolam. Patients with glaucoma have not been studied. The increase in intraocular pressure after succinylcholine administration or endotracheal intubation is not prevented by midazolam, diazepam or thiopental.

Pharmacokinetics in Adults

Midazolam dosing should not be based on pharmacokinetic values; it should always be titrated to achieve a given clinical effect. This is especially important when used for long-term sedation in the Intensive Care Unit (ICU). The elimination half-life of midazolam is increased in congestive heart failure, hepatic cirrhosis and chronic renal failure. It is markedly and unpredictably increased in critically ill patients with multiorgan failure. The following table summarizes the available data.

Patient Type	Dose Range (mg/kg)	Elimination $t_{1/2}$ [a] (hr)	Volume of Distribution Vd (L/kg)	Total Body Clearance: TBC (L/hr/kg)
Normal Subjects 21-50 years	0.07-0.25	1.0 [b]-2.8	0.80-1.64	0.24-0.43
Surgical (Elective) 30-54 years	0.15-0.45	3.0-3.9	1.67-3.21	0.37-0.51
Congestive Heart Failure 33-67 years	0.1	6.5	2.50	0.27
Hepatic Dysfunction 21-59 years	0.07	2.4	1.77	0.50
Severe Alcoholic Cirrhosis 39-54 years	0.075	3.9	1.49	0.32
Chronic Renal Failure[c] 24-68 years	0.20	3.3	3.40	0.60
Volunteers:				
Male 24-33 years 60-74 years	5 mg [d] 5 mg [d]	1.9 4.0	1.34 1.64	0.47 0.26
Female 23-37 years 64-79 years	5 mg [d] 5 mg [d]	2.3 3.0	2.00 2.11	0.56 0.45
Patients:				
Male 30 years[e] 82 years[e]	0.2 0.2	2.3 8.5	1.44 3.63	0.49 0.34
Female 31 years[e] 86 years[e]	0.2 0.2	2.9 3.0	1.36 2.30	0.36 0.55
Obese volunteers 22-62 years	5 mg [d]	6.5	2.66	0.25

a Harmonic mean (hr)

b Lower value of the range in the study (mean not reported)

c In two critically ill patients with impaired renal function and renal failure with impaired hepatic function t½ values of 18 hours and 21 hours, respectively, were reported (Shelly MP, et al. Anesthesia 1987;42:619-26).

d Absolute dose

e Mean age

Following intravenous administration, midazolam is rapidly metabolized to 1-hydroxymethyl midazolam, which is the major metabolite, and to 4-hydroxy and 1,4-dihydroxy midazolam, which are minor metabolites. Mean peak plasma concentration of midazolam is several fold greater than that of 1-hydroxymethyl midazolam. The half-life of elimination of this metabolite is similar to that of the parent compound. Less than 0.03% of the dose is excreted in the urine as intact midazolam, 45% to 81% of the dose is excreted in urine as the conjugates of the metabolites. Midazolam is approximately 97% plasma protein-bound in normal subjects. In patients with chronic renal failure, the free fraction of drug in plasma can be significantly higher than in healthy subjects.

The mean relative bioavailability of midazolam following intramuscular administration is greater than 90%. Following intramuscular administration, the mean time to peak midazolam plasma concentrations is one half hour. Peak concentrations of midazolam, as well as 1-hydroxymethyl midazolam, after intramuscular administration are about one-half of those achieved after equivalent intravenous doses. There is, however, no direct correlation between clinical effects and blood levels of midazolam. The elimination half-life of intramuscular administered midazolam is comparable to that observed following intravenous administration.

In animals and humans, midazolam has been shown to cross the placenta and to enter the fetal circulation. Clinical data indicate that midazolam is excreted in human milk. Following oral intake, low concentrations of midazolam could be detected for short periods of time.

Pharmacokinetics in Adult Intensive Care Unit (ICU) Patients
The pharmacokinetics of midazolam following continuous intravenous infusion was determined in intubated, mechanically ventilated patients although not critically ill. The kinetics in critically ill patients with multisystem dysfunction is unpredictable and it is recommended that midazolam be titrated to the desired effect.

Patient type	**Dosing**		**Pharmacokinetic values**		
	Bolus* Doses (mg/kg)	Maintenance Infusion Rate (mg/kg/hr)	Css (ng/mL)	$T_{1/2}$ (h)	Total Body Clearance (l/kg/hr)
Coronary artery bypass graft surgery (n=30) 45-71 years	0.015 0.03 0.05	0.014 to 0.017	66	9.3	0.26
Abdominal aortic surgery (n=30) 50-76 years	0.03 0.06 0.10	0.036 0.054 0.080	76 132 205	6.2 6.2 6.5	0.52 0.40 0.41

*Bolus doses of 0.05, 0.06 and 0.10 mg/kg administered in these studies are not recommended in clinical practice (see **DOSAGE AND ADMINISTRATION**)

The elimination half-life of midazolam was longer following continuous infusion in ICU patients than following the injection of single intravenous doses. The data were derived from studies in which midazolam was infused for less than 24 hours. Steady-state plasma levels increased with increasing rates of infusion.

In patients with acute renal failure (n=6, mean age 48 years), total body clearance was lower (132 mL/min *versus* 198 mL/min) and the elimination half-life of midazolam longer (13.2 hours versus 7.6 hours) than in patients with normal kidney function (n=33, mean age 62 years). In patients with impaired kidney function, the excretion of 1-hydroxymethyl midazolam glucuronide, the major metabolite of midazolam, is impaired. The de-glucuronidation of this metabolite may increase its plasma concentration which in turn may interfere with the hydroxylation of midazolam itself.

Pharmacokinetics in the Pediatric Population

In healthy children aged one year and older, the pharmacokinetic properties of midazolam are similar to those in adults. Weight-normalized clearance is similar to or higher than adult and elimination half-life is similar to or shorter than adult. As with adults, absolute bioavailability of intramuscular midazolam is greater than 80%.

In seriously ill neonates and children the half-life of midazolam is substantially prolonged and the clearance reduced compared to healthy adults or other groups of children (see **REFERENCES**; reference no. 41). It cannot be determined if these differences are due to age, immature organ function or immature metabolic pathways, underlying illness or debility.

In the literature, midazolam is reported to be administered orally and rectally in pediatric patients as well as *via* the recommended parenteral routes, intravenously and intramuscularly. When administered *via* the nonparenteral routes, the elimination half-life is similar to that of the parenteral administration; however, the bioavailability is less than 50% *versus* greater than 80% when administered intramuscularly.

The following tables display pharmacokinetic data on midazolam in pediatric patients. This information was collected from published scientific literature (see **REFERENCES**, references no. 40-51):

Table I: Kinetics of Intravenous Midazolam in Pediatric Patients After Single Intravenous Doses or Short Intravenous Infusions

Number of Patients	Age (years)	Dose (mg/kg)	Vd, area method (L/kg)	Elimination $T_{1/2}$ (hours)	Clearance (ml/min/kg)
18	12.8[a]	0.08	-	1.45	8.0
20	8-17[b]	up to 0.1	0.6	0.78	10.0
21	3.8-7.3[c]	0.075-0.6	1.4-1.7[c]	1.4-1.7[c]	4.8-11.2[c]
6	2.5[a]	0.2	2.4	2.4	13.3
8	1-10[b]	0.15	-	1.2	9.1
12	5-9[b]	0.5	2.2	1.8	15.4
17	1.3-5.2[c]	0.3	2.4-2.7[c]	2.8-3.3 [c]	8.5-12.0 [c]
9	2-9[b]	0.2	-	0.6	7.6
6	5-7	0.1	-	1.8	3.2
10	2-5 days	0.2	-	6.5	2.0

a. Mean value
b. Actual Range
c. Range of Mean Values for Subgroups

Table II. Kinetics of Intravenous Midazolam in Pediatric Patients During and After Prolonged Intravenous Infusion

Number of Patients	Age (years)	Infusion Rate Mcg/kg/min)	Infusion Duration (hr)	Elimination $T_{1/2}$ (hours)	Clearance (ml/min/kg)
10	0.5-8.8[b]	2-5	21-114	4.0 (n=5)	-
10	4.9[a]	0.8	16	3.1	9.6
15	1-5 days [b]	1.0	60	12.0	1.7
187	0-10 days [b]	1.15[b]	62[a]	-	1.17[a]

a. Mean value
b. Actual Mean

INDICATIONS AND CLINICAL USE

Adult Population

Midazolam Injection has been found useful:

- As intramuscular premedication prior to surgical or diagnostic procedures.
- As an intravenous agent for patients requiring sedation/anxiolysis/amnesia prior to and during short endoscopic or short diagnostic procedures and direct-current cardioversion.
- As an alternative intravenous agent for the induction of anesthesia.

Midazolam may also be administered as a continuous intravenous infusion in intubated, mechanically ventilated patients requiring sedation in the Intensive Care Unit (ICU).

When used intravenously as an agent for sedation/anxiolysis/amnesia for short endoscopic or other short diagnostic procedures, the desired psycho-sedation can usually be attained within 3 to 6 minutes, depending on the dose administered and whether or not opioid premedication is used concomitantly.

Induction of anesthesia with midazolam occurs in approximately 1.5 minutes when an opioid premedicant has been administered and in 2 or more minutes with or without a nonopioid premedicant. Duration of effect when used for induction of anesthesia is generally dose-dependent.

Pediatric Patients

Midazolam has been clinically used for intravenous (including continuous infusion) or intramuscular sedation of pediatric patients. Sedation, anxiolysis, and/or amnesia may be necessary for diagnostic or therapeutic procedures, preanesthesia, as a component of anesthesia during surgical procedures, or during treatment in critical care settings.

CONTRAINDICATIONS

Midazolam injection is contraindicated in patients with a known hypersensitivity to benzodiazepines or any component of the product, and acute pulmonary insufficiency, and also in patients with severe chronic obstructive pulmonary disease (see **WARNINGS**). Careful monitoring and slow administration is essential if the drug is used in elderly or debilitated patients. Marked hypoventilation is common if the patient is not responsive to verbal commands.

Outside the ICU setting, marked intravenous sedation must be avoided in elderly or debilitated patients. All patients receiving midazolam for intravenous sedation should, of course, remain sufficiently alert to respond appropriately to verbal requests.

Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma. Midazolam lowered the intraocular pressure in subjects without eye disease, but did not prevent the increases elicited by succinylcholine or endotracheal intubation. Patients with glaucoma have not been studied.

WARNINGS

Midazolam Injection must never be used without individualization of dose. The immediate availability of oxygen and other appropriate medication, and the equipment necessary for resuscitation, the maintenance of a patent airway, support of ventilation and cardiac function, should be ensured prior to the use of intravenous midazolam in any dose.

Because intravenous midazolam depresses respiration and because opioid agonists and other sedatives can add to this depression, midazolam should be administered as an induction agent only by a person trained in general anesthesia and should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintenance of a patent airway and support of ventilation.

Patients should be continuously monitored for early signs of hypoventilation or apnea which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken. Vital signs should continue to be monitored during the recovery period. Opioid agonists and other sedatives add to the respiratory depression produced by midazolam.

Midazolam should be used for intravenous sedation only with caution and must not be administered by single bolus or rapid intravenous administration. Doses used for intravenous sedation should be always restricted to the special low levels recommended (see **DOSAGE AND ADMINISTRATION**) and careful attention should be given in the selection and exclusion of patients that might be especially susceptible to adverse cardiac and respiratory reactions. Older chronically ill patients and those with concomitant use of other cardiorespiratory depressant agents are also especially susceptible to adverse reactions. It should be borne in mind that a fall in oxygen saturation will increase the probability of arrhythmias and other potentially fatal events in susceptible patients. Oxygen supplementation should be used in elderly patients

with chronic respiratory or cardiac disease and patients who are seriously ill. Experience in the administration of drugs for intravenous sedation, continuous monitoring of patients to detect reversible adverse effects which may occur in individual patients and the means and setting required for immediate management of these patients are essential prior to the administration of midazolam for intravenous sedation.

Serious cardiorespiratory events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. Strict adherence to the cautions and warnings recommended in the use of this drug is therefore required in order to minimize the incidence of these reactions.

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported. These reactions may be due to inadequate or excessive dosing or improper administration of midazolam; however, consideration should be given to the possibility of cerebral hypoxia or true paradoxical reactions. Should such reactions occur, the response to each dose of midazolam and all other drugs, including local anesthetics, should be evaluated before proceeding.

Outside the ICU setting, midazolam should not be administered to patients in shock, coma, acute alcoholic intoxication, renal failure, or with severe depression of vital signs. Extreme care must be used in administering Midazolam Injection particularly by the intravenous route to the elderly, to very ill patients and to those with limited pulmonary reserve due to the possible occurrence of excessive sedation and/or of apnea or respiratory depression. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of midazolam (see **CONTRAINDICATIONS)**.

Myasthenic patients have the potential for respiratory decompensation if a substance with CNS-depressant and/or muscle-relaxant properties is administered. However, those myasthenic patients with established respiratory failure will need mechanical ventilation and for this sedation will be necessary. Careful monitoring of the patients is recommended should midazolam be used for sedation.

Concomitant use of barbiturates, alcohol, opioids or other CNS depressants increases the risk of apnea and may contribute to excessive and/or prolonged drug effect.

Midazolam should not be given with an opioid as an intramuscular combination for premedication due to the risk of apnea. If opioid premedication is given, the subsequent intravenous dose of midazolam should be reduced.

The safety and efficacy of midazolam following non-intravenous and non-intramuscular routes of administration have not been established. Midazolam should only be administered intramuscularly or intravenously. The hazards of intra-arterial injection of midazolam solutions in humans are unknown; therefore, precautions against unintended intra-arterial injection should be taken. Extravasation should also be avoided.

Twenty-four months (life-time) toxicity studies in mice and rats indicate carcinogenic activity (see **TOXICOLOGY**). The significance of these findings relative to the infrequent use of midazolam in humans is, at present, unknown. The physician should therefore take these findings into consideration when using midazolam.

Occupational Hazards
Patients receiving midazolam injection on an outpatient basis should not engage in hazardous activities requiring complete mental alertness (i.e. operating machinery or driving a motor vehicle) until the effects of the drug, such as drowsiness, have subsided, or until one full day after anesthesia and surgery, whichever is longer. Patients should also be cautioned about the ingestion of alcohol or other CNS depressant drugs until the effects of midazolam have subsided.

PRECAUTIONS

General
Since an increase in cough reflex and laryngospasm may occur with peroral endoscopic procedures, the use of a topical anesthetic agent and the availability of necessary countermeasures are recommended. During routine diagnostic bronchoscopies, in patients with CO_2 retention, the use of opioid premedication is recommended.

ICU Sedation
When administering midazolam injection as a continuous infusion for ICU sedation, the changes in the rate of administration should be made slowly (at 30 minute intervals) in order to avoid hypotension and/or overdosage. The change in dose should be in increments of 25 to 50% of the original dose (see **DOSAGE AND ADMINISTRATION**). Dosage should be titrated to a desired level of sedation; reliance on predicted kinetics may result in significant overdosage.

As with other sedative medications, there is wide interpatient variability in midazolam dosage requirements, and these requirements may change with time.

The infusion rate should be adjusted to achieve the required level of sedation according to the patient's age and clinical status. In patients who are still sedated and/or who received large doses of opioids, a bolus dose may not be necessary and the initial infusion rate should be substantially decreased. The elimination half-life of midazolam is variable and may be considerably longer than seen during short-term administration (e.g. induction of aesthesia) (see **GENERAL**, Pharmacokinetics). Recovery may be dependent upon the duration of infusion and is more prolonged if the infusion exceeds 24 hours.

Physical and Psychological Dependence
Physical and psychological dependence may occur during benzodiazepine treatment. The risk is more pronounced in patients on long-term or high-dose treatment and in predisposed patients such as those with a history of alcoholism, drug abuse or marked psychiatric disorders.

In order to minimize the risk of dependence, midazolam should only be administered for the shortest possible duration. Should treatment need to be extended, a careful assessment of the risks and benefits should be made.

Withdrawal symptoms may occur from a few hours to over a week after discontinuing treatment. Symptoms may range from tremor, restlessness, insomnia, anxiety, headache and inability to concentrate to sweating, muscular/abdominal spasms and perceptual changes in more severe cases. In rare instances, delirium and convulsions may also occur. Consequently, abrupt discontinuation of midazolam should generally be avoided and a gradual tapering of dose followed.

Use in Geriatrics and Debilitated Patients
Doses of midazolam injection should be decreased for elderly and debilitated patients (see **DOSAGE AND ADMINISTRATION**). Complete recovery after midazolam administration in such patients may take longer.

Use in Children
Based upon published literature, pediatric patients generally require higher doses of midazolam than adults (see **DOSAGE AND ADMINISTRATION**). Convulsions have occurred in children, most frequently in premature infants and neonates (see **ADVERSE DRUG REACTIONS**).

Use in Pregnancy
Safety in pregnancy has not been established. Therefore, midazolam should not be used in women who may be pregnant. Several studies have suggested an increased risk of congenital malformations associated with the use of some of the benzodiazepines during the first trimester of pregnancy.

Use in Obstetrics
The use of midazolam has not been evaluated in obstetric studies; therefore, it is not recommended for obstetrical use. Measurable levels of midazolam were found in maternal venous serum, umbilical venous and arterial serum and amniotic fluid, indicating placental transfer of the drug in humans. Fifteen to 60 minutes following intramuscular administration of 0.05 mg/kg of midazolam, both the umbilical venous and the umbilical arterial serum concentrations were lower than maternal venous concentrations.

Pregnant women in active labour have significantly higher midazolam plasma levels, a smaller volume of distribution and a lower clearance than pregnant women undergoing Cæsarean section or nonpregnant gynecological patients. When given immediately before Cæsarean section, midazolam can cause depression of the infant.

Use in Nursing Mothers
Midazolam is excreted in human milk. Therefore, midazolam is not recommended for use in nursing mothers.

Patients with Special Conditions
Higher risk surgical patients or debilitated patients require lower dosages, whether as a premedicant or for intravenous sedation or induction of anesthesia.

Patients with chronic obstructive pulmonary disease may experience prolonged sedation and prolonged respiratory depression (see **CONTRAINDICATIONS**).

Patients with congestive heart failure and obese subjects have a substantially prolonged elimination half-life and an increased volume of distribution of midazolam. Patients with chronic renal failure or severe alcoholic cirrhosis exhibit changes in elimination half-life, volume of distribution and total body clearance (see **CLINICAL PHARMACOLOGY**). Caution should therefore be exercised in administering midazolam to these patients.

Drug Interactions
The hypnotic effect of intravenous midazolam and the risk of apnea is accentuated by premedication, particularly opioids (e.g. morphine, meperidine and fentanyl), secobarbital, and the droperidol-fentanyl combination. Consequently, the dosage of midazolam should be adjusted according to the type and amount of premedication administered.

A slight reduction in induction dosage requirements of thiopental (about 13%) has been noted following intramuscular use of midazolam for premedication.

The administration of midazolam has resulted in a dose dependent reduction of the minimum alveolar concentration of halothane required during maintenance of anesthesia.

Preliminary data, with a small number of subjects, reveal that midazolam appears to potentiate the effect of pancuronium.

Midazolam injection does not cause a clinically significant change in onset or duration of action of a single intubating dose of succinylcholine. Midazolam does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium.

Midazolam has been used as an induction agent in conjunction with commonly used premedicants or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, succinylcholine and *d*-tubocurarine and other nondepolarizing muscle relaxants) or topical anesthetic s (e.g. lidocaine).

The metabolism of midazolam is predominantly mediated by cytochrome P-450 3A4 (CYP3A4) isozyme. Approximately 25% of the total cytochrome P-450 system in the adult liver is from the CYP3A4 subfamily. Inhibitors and inducers of this isozyme may lead to drug interaction with midazolam. Data from spontaneous reports as well as kinetic studies in humans indicate that midazolam may interact with compounds which affect or are also metabolized by the cytochrome P-450 3A4 hepatic enzymes. Data indicate that these compounds (cimetidine, erythromycin, diltiazem, verapamil, ketoconazole, fluconazole and itraconazole) influence the pharmacokinetics of midazolam (increased C_{max} and AUC) and may lead to prolonged sedation

(azithromycin has little or no effect on the pharmacokinetics of midazolam). Therefore patients receiving the above compounds or others which inhibit P-450 3A4 enzymes (including saquinavir) together with midazolam should be monitored for the first few hours after administration of midazolam. For further information see **INTERACTION STUDIES CONDUCTED WITH MIDAZOLAM INJECTION**.

Interaction Studies Conducted with Midazolam Injection

CYP3A4 Inhibitors
Itraconazole and Fluconazole
Coadministration of midazolam and itraconazole or fluconazole prolonged the elimination half-life of midazolam from 2.9 to 7.0 hours (itraconazole) or 2.9 to 4.4 hours (fluconazole). Bolus doses of midazolam given for short-term sedation did not enhance the effect of midazolam to a clinically significant degree by itraconazole and fluconazole, and dosage reduction is not required. However, administration of high doses of midazolam may require dosage adjustments. Long-term infusions of midazolam to patients receiving antimycotics, e.g. during intensive care treatment, may result in long-lasting hypnotic effects if the dose is not titrated according to the effect.

Erythromycin
Coadministration 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.

Cimetidine and Ranitidine
Cimetidine increased the steady-state plasma concentration of midazolam by 26%, whereas ranitidine had no effect. Coadministration 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 drugs can be given concomitantly and no dosage adjustment of midazolam is required.

Saquinavir
Coadministration of a single intravenous dose of 0.05 mg/kg midazolam after 3 or 5 days of saquinavir dosing (1 200 mg t.i.d.) to 12 healthy volunteers decreased the midazolam clearance by 56 % and increased the elimination half-life from 4.1 to 9.5 hours. Only the subjective effects

to midazolam (visual analogue scales with the item "overall drug effect") were intensified by saquinavir. Therefore, bolus doses of intravenous midazolam can be given in combination with saquinavir. During a prolonged midazolam infusion, an initial dose reduction of 50% is recommended.

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

Other Interactions
Sodium Valproate
Displacement of midazolam from its plasma 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.

Lidocaine
Midazolam had no effect on the plasma protein binding of lidocaine in patients undergoing antiarrhythmic therapy or regional anesthesia with lidocaine.

ADVERSE REACTIONS

See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions.

Adverse Reactions in Adults
Sedative effects and fluctuations in vital signs were the most frequent findings following parenteral administration of midazolam injection. These are affected by the lightening or deepening of anesthesia, instrumentation, intubation and use of concomitant drugs. The more frequently encountered fluctuations in vital signs included decreased tidal volume and/or decreased respiratory rate and apnea, as well as variations in blood pressure and pulse rate. When used in intravenous sedation, midazolam tends to produce a higher incidence of fall in mean arterial pressure than diazepam.

The most frequently reported adverse reactions observed in association with the use of midazolam in clinical research programs are reported in Table III. Although adverse reactions may not have been observed in all clinical research programs, the possibility of their occurrence with the different clinical uses of midazolam cannot be excluded.

Table III: Most Frequently Reported Adverse Reactions

Organ System	Adverse Effect	%			
		IM Premed N=380	**IV Sedation N=512**	**IV Induction N=1073**	**IV ICU Sedation N=115**
Cardiovascular	Increased Mean Arterial Pressure	2.6	8.0	16.7	6.9
	Decreased Mean Arterial Pressure	6.3	29.9	30.8	17.0
	Hypotension				26.0*
	Increased Pulse Rate	7.1	29.9	36.0	
	Decreased Pulse Rate	9.5	16.8	12.6	
Respiratory	Increased Respiratory Rate / Tachypnea	11.5[a]			
	Decreased Respiratory Rate	10.8 [a]	36.9	0.1	
	Apnea		25.6	0.1	
	Coughing		1.0	22.9	
	Respiratory Depression		0.2	2.0	
	Airway Obstruction		0.2	25.0	
			0.2	1.0	
Central Nervous System	Headache	1.3	0.8	2.0	
	Drowsiness		0.5	1.7	
	Excessive Sedation		0.6	1.6	
	Dizziness		0.2	1.2	
	Hallucination				2.8
	Agitation				1.8
	Confusion	0.3	0.6	0.9	2.8
Gastro-intestinal	Hiccoughs	0.3	0.4[b]	6.0	0.9
	Nausea	0.5	0.8 [b]	4.0	
	Emesis/Vomiting	0.5	0.6 [b]	3.5	

a: N=130
b: N=500

* Hypotension during ICU Sedation was defined as systolic blood pressure ≤90 mmHg or diastolic blood pressure ≤50 mmHg or a clinically significant fall in blood pressure.

Other adverse reactions occurring at a lower incidence, usually less than 1% are:

Cardiovascular
Premature ventricular contractions, bigeminy, vasovagal episode, bradycardia, tachycardia, and nodal rhythm.

Respiratory
Laryngospasm, bronchospasm, dyspnea, shallow respiration, hyperventilation and wheezing.

CNS/Neuromuscular
Nervousness, restlessness, anxiety, argumentativeness, aggression, insomnia, nightmares; deep sedation, prolonged sedation, oversedation, disorientation, slurred speech, emergence delirium, agitation during emergence, prolonged emergence from anesthesia, dreaming during emergence; dysphoria, euphoria, anterograde amnesia, lightheadedness, feeling faint; tremors, muscle contractions, twitches and abnormal spontaneous muscular activity, tonic/clonic movements, athetoid movements; ataxia.

Gastrointestinal
Acid taste, excessive salivation and retching.

Special Senses
Blurred vision, diplopia, nystagmus, visual disturbance, difficulty focusing eyes, pinpoint pupils, cyclic movement of eyelids, ears blocked and loss of balance.

Dermatological
Erythema, rash, pruritus and hives.

Hypersensitivity
Allergic reactions, including anaphylactic shock.

Miscellaneous
Muscle stiffness, toothache, yawning, cold feeling when drug injected and cool sensation in arm during infusion.

Adverse Reactions in Pediatric Patients
Limited information is available from published literature regarding the use of midazolam in pediatric patients. However, based on information obtained from published literature and spontaneous adverse reaction reporting, the safety profile in children more than one month of age appears to be very similar to that observed in adults.

The most frequent acute events were airway compromise and hypoventilation. This most often occurred when used in conjunction with opioids or other anesthetic agents. The next most common adverse event with long-term use was withdrawal syndrome. The following list shows the other reported side effects. This list is not exhaustive.

Respiratory System: Respiratory arrest, respiratory failure, apnea, hypoxia, oxygen desaturation. Danger of respiratory disorders may increase when midazolam is administered with opioids. Therefore the dosage of both agents should be reduced (see **WARNINGS AND DOSAGE AND ADMINISTRATION**).

Psychiatric
Withdrawal syndrome, combative reaction, agitation, hallucination.

Central and Peripheral Nervous System
Convulsions, excessive sedation, tonic/clonic convulsions, cerebral convulsion, lethargy. Convulsions occurred primarily in neonates (under 4 months old) and/or children with history of seizures.

Cardiovascular
Hypotension, bradycardia, cardiac/cardiopulmonary arrest.

Miscellaneous
Lack of efficacy, paradoxical response, therapeutic response decreased.

Local and Vein Tolerance
The incidence of local and vein tolerance observed in the early experience with midazolam is listed in Table IV.

Table IV: Incidence of local and vein tolerance

	% Incidence		
Adverse Effects on Local and Vein Tolerance	**IM Premed**	**IV Sedation**	**IV Induction**
	N = 380	**N = 512**	**N = 1073**
LOCAL			
Pain at injection site	3.7	-	-
Pain during injection of drug	0.0	0.4	7.5
Induration at injection site	0,5	-	-
Swelling at injection site	0.0	0.0	0.2
Erythema at injection site	0.5	-	-
Hive-like elevation at injection site	-	-	0.2
Warmth at injection site	-	-	01
Burning at injection site	-	-	0.1
Hematoma at IV site	-	-	0.3
VEIN			
Tenderness of vein	0.0	1.4	8.0
Induration of vein	-	1.6	2.1
Redness of vein	0.0	1.4	3.4
Red wheal/flare along vein	-	-	0.1
Pain in vein after injection	-	-	0.1
Phlebitis	-	-	0.6
Thrombophlebitis	-	-	0.1

In pediatric patients similar observations as in adults have been made. Some of the most frequently reported findings include: rash, urticaria, erythema, hives, skin necrosis and wheals.

Laboratory Abnormalities

Isolated elevations in certain parameters of liver function, e.g. AST(SGOT), ALT(SGPT), alkaline phosphatase and total bilirubin, as well as isolated changes in total protein and albumin, have been reported.

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701 E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms
The manifestations of midazolam overdosage are: sedation, somnolence, confusion, impaired coordination, diminished reflexes, untoward effects on vital signs, coma and possible cardiorespiratory arrest.

Treatment
Treatment of overdosage is the same as that followed for overdosage with other benzodiazepines. Continuous monitoring of vital signs including EKG should be immediately instituted and general supportive measures should be employed. Immediate attention should be given to the maintenance of an adequate airway and support of ventilation. If not already present, an intravenous infusion line should be established and further measures should be taken to provide critical care. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, and other appropriate countermeasures. Cardiopulmonary resuscitation may be required. At present, there is no information as to whether peritoneal dialysis, forced diuresis or hemodialysis are of value in the treatment of midazolam overdosage.

The benzodiazepine antagonist, flumazenil is a specific antidote in known or suspected overdose. (For conditions of use refer to flumazenil Product Monograph). Caution should be observed with the use of flumazenil in cases of mixed drug overdosage and in patients with epilepsy treated with benzodiazepines.

DOSAGE AND ADMINISTRATION

General
Midazolam Injection should only be administered intramuscularly or intravenously (see **WARNINGS**). The dosage of midazolam must be carefully individualized. In elderly and debilitated patients, lower doses are required. The dosage of midazolam should further be adjusted according to the type and amount of premedication used. **Excess doses or rapid or single bolus IV administration may result in respiratory depression and/or arrest, particularly in elderly or debilitated patients** (see **WARNINGS**). Clinical experience has shown midazolam to be more potent than diazepam on a mg per kg basis.

Midazolam injection has been shown to cause dose-related anterograde amnesia, an impairment or a lack of recall of events following administration of the drug.

Midazolam does not protect against the circulatory effects of succinylcholine administration or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

For intramuscular use, Midazolam Injection should be injected deep in a large muscle mass. Intravenous midazolam should be administered as an induction agent only by a person trained in

general anesthesia and should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintenance of a patent airway and support of ventilation. The necessary equipment and the appropriate medications must be immediately available to ensure the safety of the procedures involved and the maintenance of respiratory and cardiovascular functions (see **WARNINGS**).

Midazolam Injection for intravenous sedation prior to and during short endoscopic or short diagnostic procedures and direct current cardioversion, should always be administered slowly (see WARNINGS and Intravenous Sedation). Rapid intravenous injection may cause respiratory depression or apnea requiring respiratory assistance or controlled ventilation.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. Should such reactions occur, the response to each dose of midazolam and all other drugs, including local anesthetics, should be evaluated before proceeding with the administration of the drug (see **WARNINGS**).

For induction of general anesthesia in healthy patients, the initial dose should be administered over 20 to 30 seconds for optimal effect. About 2 minutes must pass to see the effect of the dose. Extreme care should be taken to avoid intra-arterial injection or extravasation.

Midazolam is compatible with 5% Dextrose Injection and 0.9% Sodium Chloride Injection. Both the 1 mg/mL and 5 mg/mL formulations may be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection.

Usual Recommended Adult Dosage
Intramuscular Premedication
For preoperative sedation and to impair memory of perioperative events
For premedication, the recommended dose of Midazolam Injection is 0.07 to 0.08 mg/kg IM (usual IM dose is about 5 mg for an average adult) administered 30 to 60 minutes preoperatively. Lower doses should be used in elderly or debilitated patients. In a study of patients 60 years or older who did not receive concomitant opioids, 2 to 3 mg of midazolam produced adequate sedation during the preoperative period. Some patients responded to doses as low as 1 mg. As with any potential respiratory depressant, these patients require observation for signs of cardiorespiratory depression after receiving IM midazolam. Onset of action is within 15 minutes, with peak effect occurring 30 to 60 minutes following injection. Midazolam can be administered concomitantly with atropine sulfate or scopolamine hydrobromide. When administered concomitantly with an opioid, the dose of midazolam should be reduced.

Intravenous Sedation (see **WARNINGS**)
For short endoscopic or short diagnostic procedures and direct current cardioversion: Midazolam Injection 1 mg/mL formulation is recommended for IV sedation to facilitate slow injection.

Midazolam can be used either alone or combined 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 anesthetic is recommended.

During routine diagnostic bronchoscopies, with no compromise of respiratory function, the use of opioid premedication is recommended.

Table V: Dosage Table for Intravenous Sedation (see Method of Administration)

	Unpremedicated Patients		Premedicated Patients (Opioids or CNS Depressants)
Patient Type	**Initial Dose**	**Total Dose**	
Patients below age 55	No more than 2 to 2.5 mg	-Some patients may respond to as little as a total dose of 1 mg. -More than a total dose of 5 mg is not usually necessary. -Do not exceed 0.1 mg/kg	Reduce dosage by about 30%
Patients age 55 or older; Debilitated patients; Chronically ill patients; Patients with limited pulmonary reserve	No more than 1 to 1.5 mg	-Patients may respond to as little as a total dose of 1 mg. -More than a total dose of 3.5 mg is not usually necessary. -Do not exceed 0.07 mg/kg	Reduce dosage by about 30% (i.e. 60% less than for healthy young un-premedicated patients)

Method of Administration
When used for intravenous sedation, midazolam should not be administered by rapid or single bolus intravenous administration (see **WARNINGS**).

Midazolam should be administered immediately prior to the procedure in small increments and titrated slowly until the desired sedative effect is achieved. An initial titration with a small dose, such as 2 to 2.5 mg (see Table V) **administered over a 2 to 3 minute period** is suggested for an average healthy adult. After waiting about 2 minutes, the dosage may be further titrated **in small increments of the initial dose** if necessary to the desired sedative effect. Wait about 2 minutes after each increment to fully evaluate the sedative effect. Additional maintenance doses may be given in increments of 25% of the initial dose to maintain the desired level of sedation, only by slow titration. The desired end point can usually be attained within 3 to 6 minutes, depending on the total dose administered and whether or not it is preceded by opioid premedication. Opioid premedication when indicated, results in less variability of patient response.

The dosage should be lowered in the elderly and debilitated, and in patients with limited pulmonary reserve (see Table V). Because the danger of underventilation or apnea is greatest in these patients and because peak effect may take longer, increments should be smaller and the rate of injections slower.

Intravenous Induction of Anaesthesia (see Table VI)
For induction of general anesthesia before administration of other anesthetic agents: Individual response to midazolam is variable, particularly when an opioid premedicant is not used. The dosage should be titrated according to the patient's age and clinical status.

Table VI: **Dosage Table for Intravenous Induction (**see **Method of Administration)**

Patient Type	Unpremedicated Patients		Premedicated Patients (Opioids or CNS Depressants)	
	Initial Dose	**Increments**	**Initial Dose**	**Increments**
Patients below age 55	0.3-0.35 mg/kg	**If needed** to complete induction, increments of approximately 25% of the initial dose may be used.	0.15-0.35 mg/kg 0.25 mg/kg will usually suffice	**If needed** to complete induction, increments of approximately 25% of the initial dose may be used.
Patients age 55 or older; (ASA I or II surgical patients)	0.3 mg/kg		0.2 mg/kg	
Patients with severe systemic disease or other debilitation	0.2-0.25 mg/kg In some cases as little as 0.15 mg/kg will suffice	The need for increment doses to complete induction must be evaluated by the anesthesiologist.	0.15-0,2 mg/kg In some cases as little as 0.15 mg/kg will suffice	The need for increment doses to complete induction must be evaluated by the anesthesiologist.

Method of Administration

Doses are administered over 20 to 30 seconds, allowing 2 minutes for effect.

ICU Sedation

For initiation and maintenance of ICU sedation in intubated, mechanically ventilated patients (see Table VII).

Table VII: Dosage Table for ICU Sedation

Patient Type	Bolus Dose	Initial infusion Dose	Max. Dose	Increments
No prior Opioids or CNS Depressants	0.015-0.03 mg/kg	0.01-0.03 mg/kg/hr	0.07-0.15 mg/kg/hr	For optimal sedation the maintenance infusion rate may be increased or decreased by increments of 25%-50% of the initial dose at intervals of 30 minutes
Prior/Concomitant Opioids or CNS Depressants	0.015-0.03 mg/kg	0.01-0.03 mg/kg/hr	0.07 mg/kg/hr	

Dosage and rate of infusion should be individualized to achieve the required level of sedation according to the patient's age and clinical status. In patients who are still sedated and/or who received large doses of opioids, a bolus dose may not be necessary and the initial infusion rate of midazolam should be substantially decreased.

Recommended Pediatric Dosage

As a group, pediatric patients generally require higher doses of midazolam than do adults and younger children may require higher doses than older children. In obese individuals, the dose should be calculated based on ideal body weight. When midazolam is given in conjunction with opioids or other sedatives, the potential for respiratory depression/airway obstruction is increased. For appropriate patient monitoring, see **WARNINGS** section. Midazolam should be administered as an induction agent only by a person trained in general anesthesia and should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintenance of a patent airway and support of ventilation (see **WARNINGS**).

Patients should be discharged in the care of a responsible individual.

Intramuscularly
Usual Pediatric Dose
For sedation prior to anesthesia or procedures (for longer and/or more stimulating procedures, intramuscular midazolam can be used to facilitate insertion of an intravenous catheter for titration of additional medication.):

Sedation with intramuscular midazolam is age and dose dependent: higher doses may result in deeper and more prolonged sedation. Doses of 0.1-0.15 mg/kg are usually effective and do not prolong emergence from general anesthesia. For more anxious patients, doses up to 0.5 mg/kg may be needed. Midazolam and an opioid should not be mixed as a premedication, however if required then constant monitoring is recommended. Should both be required the initial dose of each must be reduced and the second agent of the two should be administered intravenously on arrival at the procedure area.

Intravenously by Intermittent Injection
Usual Pediatric Dose
For sedation prior to and during procedures or prior to anesthesia:

For all patients titrate slowly to the desired effect. The initial dose should be administered over 2-3 minutes. Wait an additional 2-3 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments until the appropriate level of sedation is achieved. See Table VIII.

Table VIII: Dosage Table for Pediatric Intravenous Intermittent Injection

Age of Child	Initial Dose	Total Dose	Comments
6 months-5 years	0.015-0.1 mg/kg	0.6 mg/kg	The initial dose should be administered over 2-3 minutes, wait for an additional 2-3 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments, until the appropriate level of sedation is achieved.
6-12 years	0.025-0.05 mg/kg	0.4 mg/kg	
12-17 years	Dose as Adults		

The dose of Midazolam Injection must be reduced in patients premedicated with opioids or other sedative agents including midazolam.

Continuous Intravenous Infusion (For Sedation in Critical Care Settings)
Usual Pediatric Dose
To initiate sedation, an intravenous loading dose of 0.05 to 0.2 mg/kg administered over at least 2 to 3 minutes can be used to establish the desired clinical effect. **Intravenous loading doses should not be used in neonates** (Midazolam Injection should not be administered as a rapid intravenous dose to preterm and term neonates. See below for **Preterm and Neonatal Dosing Information**). This loading dose may be followed by a continuous intravenous infusion to

maintain the effect. Based on pharmacokinetic parameters and reported clinical experience, continuous intravenous infusions of Midazolam Injection should be initiated at a rate of 0.001-0.002 mg/kg/min (1-2 mcg/kg/min). The rate of infusion can be increased or decreased as required, or supplemental intravenous doses of Midazolam Injection can be administered to increase or maintain the desired effect. Frequent assessment using standard pain/sedation scales is recommended. Drug elimination may be delayed in patients receiving erythromycin and/or other P-450IIIa enzyme inhibitors (see **DRUG INTERACTIONS**) and in patients with liver dysfunction, renal dysfunction, low cardiac output (especially those requiring ionotropic support), and in neonates. Hypotension may be observed in patients who are critically ill, particularly those receiving opioids and/or when Midazolam Injection is rapidly administered.

When initiating an infusion with Midazolam Injection in hemodynamically compromised patients, the usual loading dose of Midazolam Injection should be titrated in small increments, separated by 2-3 minutes, and the patient monitored for hemodynamic instability, e.g. hypotension, respiratory rate and oxygen saturation.

The dose of Midazolam Injection must be reduced in patients premedicated with opioids or other sedative agents including midazolam.

Neonatal Dosage
Based on the pharmacokinetic parameters and reported clinical experience in preterm and term neonates, continuous intravenous infusion of Midazolam Injection should be initiated at a rate of 0.0005-0.001 mg/kg/min (0.5-1 mcg/kg/min). Intravenous loading doses should not be used in neonates, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. Hypotension may be observed in patients who are critically ill and in preterm and term infants, particularly those receiving fentanyl and/or when midazolam is administered rapidly. Due to an increased risk of apnea, extreme caution is advised when sedating preterm and former preterm patients in combination with regional anesthesia.

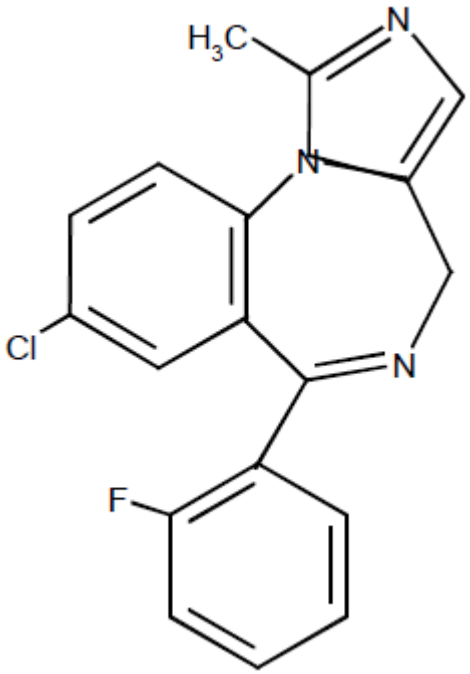
PHARMACEUTICAL INFORMATION

Drug Substance

Proper or Common Name: midazolam

Chemical Name: 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo [1,5-α][1,4] Benzodiazepine

Structural Formula:



Molecular Formula: $C_{18}H_{13}C1FN_3$

Molecular Weight: 325.8 g/mol

Description: White to yellow crystalline powder. Practically insoluble in water; freely soluble in acetone and in ethanol; soluble in methanol. The hydrochloride salt of midazolam, which is formed *in situ*, is soluble in aqueous solutions.
Melting range: 161-164°C.

COMPOSITION

Each mL of sterile aqueous solution contains: midazolam 1 mg or 5 mg (hydrochloric acid added for solubilization), sodium chloride 8 mg for tonicity, hydrochloric acid and, if necessary, sodium hydroxide to adjust pH and water for injection.

STORAGE AND STABILITY RECOMMENDATIONS

Store between 5°C-25°C. Protect from light. Protect packaging from any physical damage. Unopened ampoules will be suitable for use for up to 8 months after the foil sachet has been opened, if kept in carton in order to protect from light.

Midazolam Injection is compatible and stable for 24 hours when diluted to 0.03-0.5mg/mL with either 5% dextrose injection, or 0.9% sodium chloride injection.

The 15mg/3mL, 5mg/mL and 5mg/5mL formulations may be diluted to facilitate slow injection. The 50mg/10mL ampoules may be added to the infusion solutions in a mixing ratio of 15mg midazolam per 100-1000mL 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 the preparation of the admixture.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitation, discolouration and leakage prior to administration whenever solution and container permit.

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. Store diluted solution between 2°C - 8°C for up to 24 hrs.

AVAILABILITY OF DOSAGE FORMS

Midazolam Injection 5 mg in 1 mL (sterile) Steriluer® Plastic Ampoule (2 x 5 pack)
Midazolam Injection 15 mg in 3mL (sterile) Steriluer® Plastic Ampoule (5 pack)
Midazolam Injection 5 mg in 5mL (sterile) Steriluer® Plastic Ampoule (2 x 5 pack)
Midazolam Injection 50 mg in 10 mL (sterile) Steriluer® Plastic Ampoule (5 pack)

DETAILED PHARMACOLOGY

Midazolam possesses all the pharmacological effects of the benzodiazepines, namely it is a sedative, hypnotic, anticonvulsant, anxiolytic, muscle relaxant and amnestic agent. In addition, midazolam enhances GABAergic inhibition, decreases the firing rate of single neurons, decreases the cerebral metabolic rate for oxygen, decreases cerebral blood flow, enhances the survival time of mice in a hypoxic milieu and induces amnesia in the passive avoidance paradigm.

Midazolam binds in nanomolar concentrations to the high-affinity, stereospecific benzodiazepine receptor sites in the mammalian brain. These receptor sites are functionally coupled to GABA recognition sites and to sites related to chloride channels. Midazolam decreases the cyclic GMP level in the cerebellum.

The CNS pharmacological effects of midazolam can be reversed with flumazenil (Ro 15-1788), a specific benzodiazepine antagonist.

In most tests, the potency of midazolam is comparable to that of diazepam or somewhat greater. However, in tests predicting sedation, amnesia and attenuation of muscle tone and coordination, midazolam is considerably more potent than diazepam.

The onset of effect of midazolam is rapid and its duration of action short.

In conscious normotensive dogs, midazolam causes slight but significant changes in several cardiovascular parameters, namely it decreases mean arterial pressure and systemic vascular resistance and increases heart rate and cardiac output.

Rats given 2.5 mg/kg ^{14}C midazolam intravenously, excreted within 24 hours 81% of the radioactivity in the fæces and 10% in the urine. During the first day, the highest levels of radioactivity were found in the liver. Four phenolic derivatives of midazolam were identified in the rats' bile. These biliary metabolites were excreted as glucuronide and/or sulfate conjugates.

TOXICOLOGY

Acute Toxicity

LD_{50} Midazolam Hydrochloride

Species	Strain	Route	LD_{50} (mg/kg)	Observation Period
Mice	Charles River	IV	(M) 47 (F) 48	14 days
		IM	>50	
Rats	Charles River	IV	>50	14 days
		IM	>10[a]	

[a] Highest dose administered

Signs and Symptoms
Decreased motor activity, muscle relaxation, ataxia, loss of righting reflex, hypnosis, respiratory depression.

Long-Term Toxicology
1. Two-Week IM-Rats:
Midazolam base (5.0 mg/mL) was administered intramuscularly once a day for two weeks to rats (12/sex/group) at doses of 0 (saline control), 0 (vehicle control), 0.5, 1.6 or 5.0 mg/kg.

The 5.0 mg/kg/day dose produced a significant decrease in food consumption and a slight decrease in body weight gain, in male rats. Transient, dose-related signs of CNS depression were observed in all midazolam-treated groups within five minutes of the injections. The duration of these pharmacological effects was 2.0, 1.0 and 0.5 hr in the high, mid and low-dose groups, respectively. In rats from all midazolam treated groups, multifocal, extensive myositis, myodegeneration and myonecrosis were encountered at the injection sites. The lesions were characterized as chronic active myositis and were moderate to severe in all treatment groups. However, in the low-dose group, the lesions were less extensive with respect to the amount of tissue involved.

2. Five-Week IV-Rats:
Midazolam base (5.0 mg/mL) was administered intravenously once a day for five weeks to rats (12/sex/group) at doses of 1.0, 2.5 or 6.0 mg/kg. A control group received 1.2 mL/kg/day of saline. Local tolerance during the first four weeks was good in all treated groups, however, during the last week of treatment intraperitoneal injections were necessary in most members of the high-dose group because of swollen tails. All animals survived the five-week treatment period. Sedation and ataxia were noted in the high-dose group for several minutes after injection. Except for minimal decreases of 6-7% in body weight in males receiving the mid and high doses, no effects on this parameter were observed. The only clinical laboratory finding was a slight reduction in total serum protein in males of the high-dose group.

3. Two-Week IM-Dogs:
Midazolam base (5.0 mg/mL) was administered intramuscularly, once a day for two weeks to dogs (three/sex/group) at doses of 0 (saline control), 0 (vehicle control), 0.3, 1.0 or 3.0 mg/kg.

Administration of 3.0 and 1.0 mg/kg/day of midazolam was associated with dose-related and transient behavioural changes and central nervous system effects.

Mean serum total creatine phosphokinase (CPK), alanine aminotransferase (SGPT) and aspartate aminotransferase (SGOT) were significantly elevated in the group treated with 3.0 mg/kg/day compared to the control group. However, the SGOT value was within normal limits.

Mild focal scarring was seen at the sites of injection in both treated and control dogs.

4. Five-Week IV/IM-Dogs:
In a five-week toxicity study, midazolam base (5.0 mg/mL) was administered intravenously once daily for five weeks to dogs (three/sex/group) at doses of 1.0 or 6.0 mg/kg. Two additional groups of dogs (two/sex/group) received 2.5 mg/kg/day intravenously or intramuscularly. The control group received 1.2 mL/kg/day intravenous saline.

All animals survived the five-week treatment period. In the first week, dose-related sedation and ataxia were noted for up to three to five hours after intravenous or intramuscular injection. These effects became considerably less pronounced after one week. Alkaline phosphatase values were slightly increased in treated animals, although no clear dose-relationship was evident. Increased $alpha_1$-globulins and decreased $alpha_2$-globulins were noted in treated animals. Slight and nonsignificant dose-related increases in absolute pituitary and liver weights were observed, however, relative organ weights did not show similar trends. Postmortem evaluation showed that the frequency and severity of the inflammatory changes at the intravenous injection sites were similar in all groups except at the high dose where both parameters were somewhat greater than in the controls.

5. Two-Week IV-Rabbits:
In a two-week toxicity study, a saline solution of midazolam maleate (0.5%) or diazepam injectable formulation (0.5%) was administered intravenously into the marginal ear veins of rabbits (four/group) at doses of 1.5 or 5.0 mg/kg/day. A fifth group received a 0.25% solution of midazolam maleate, 1.5 mg/kg/day.

At the 5.0 mg/kg/day dose, two rabbits received midazolam for 14 days and the other two for ten consecutive days.

The diazepam injections could not be continued beyond seven days due to the necrotic condition of the ears. The other irritation parameters, swelling, erythema and hemorrhage, were severe after the injection of diazepam and moderate after midazolam.

At the 1.5 mg/kg/day dose, midazolam was injected for 14 days while diazepam could be administered for 11 to 13 consecutive days. Necrosis was slight in the midazolam-treated rabbits and severe in the diazepam-treated animals. Swelling, erythema and hemorrhage were slight to moderate after midazolam and moderate to severe after diazepam. Rabbits receiving 1.5 mg/kg/day of midazolam in the 0.25% solution showed less irritation than rabbits receiving the same dose of midazolam in the 0.5% solution.

Decreased motor activity, muscle relaxation and hypnosis (in some animals) were noted in the midazolam-treated animals while the diazepam-treated rabbits showed ataxia, decreased motor activity and muscle relaxation.

Serum alkaline phosphatase levels were elevated in a few midazolam-treated rabbits, although this was not a dose-related phenomenon. One high-dose midazolam-treated rabbit exhibited an elevated white blood cell count.

6. One-Year Oral-Dogs:
A one year toxicity study was conducted in beagle dogs (nine/sex/group) with midazolam maleate. The compound was administered orally in gelatin capsules at doses of 0 (control), 1.0, 7.0 or 45 mg/kg/day, seven days per week. The 53-week treatment period was followed by a 14-week recovery period.

Two dogs from the mid-dose group and one dog from the high-dose group died during the study after having received 280, 60 and 212 doses of midazolam, respectively. However, the gross and microscopic findings indicated that the deaths were not treatment related.

Female dogs receiving the high dose and male dogs receiving the mid and high doses of midazolam gained significantly less weight than the controls.

Treatment-related clinical effects included CNS depression and some behavioural changes, both of which declined after a few weeks of treatment. Abnormal stools and salivation, licking and emesis were observed in both treated and control groups, but the incidences were greater in the treated dogs and showed dose-dependency.

Serum alkaline phosphatase levels increased substantially in both male and female dogs in the 45 mg/kg/day groups; the increase was on the average eight-fold over pretreatment levels. The values were somewhat higher in female dogs. The abnormality was reversible and at the end of the 14-week recovery period, serum alkaline phosphatase levels were greatly decreased, although they did not reach pretreatment levels. Serum alkaline phosphatase levels were also increased in the mid-dose midazolam groups, although to a lesser extent and returned to normal during the recovery period.

Gamma glutamyl transpeptidase (GGTP) levels were significantly and dose-dependently elevated in male dogs and significantly elevated at the highest dose in female dogs at week 52. The values were within normal limits. Serum alanine amino-transferase (SGPT) levels were significantly elevated in male dogs in the high dose group, at week 52.

Liver weights were significantly increased, this change was both dose- and time-related. At week 26, the increase was statistically significant in the high dose group, while at week 52, it occurred in both the mid- and high-dose groups. At the end of the 14 week recovery period, the mean liver weights of treated and control dogs were statistically not different.

Microscopic evaluation of the liver revealed the following pathology: parenchymal cell hypertrophy, altered cytoplasmic staining, yellow-brown granules in parenchymal cells and whorls of eosinophilic material. These changes reverted to normal in ¾ dogs by the end of the 14 week recovery period.

Mutagenicity
In the Ames test, with and without metabolic activation, using five *Salmonella typhimurium* strains: TA 1535, TA 1537, TA 1538, TA 100 and TA 98, results were negative at concentrations

of 50, 100 and 500 mcg of midazolam per plate. A concentration of 750 mcg/plate was too toxic to the bacteria and could not be evaluated.

The fluctuation test (without metabolic activation) also revealed no mutagenicity of midazolam for *Salmonella typhimurium* strains TA 1535, TA 1537, and TA 1538 at concentrations up to 25 mcg/mL. Higher concentrations could not be evaluated because of toxicity of the bacteria.

Carcinogenicity

1. Twenty-four Month Oral- Mice:

A twenty-four month oral (dietary admix) carcinogenicity study with midazolam was conducted in mice (80 male and 80 female/group) at doses of 0 (control 1), 0 (control 2), 1, 9 or 80 mg/kg/day.

In male mice in the high-dose group, survival was decreased when compared to controls. Mean body weights were significantly increased in male and female mice in the high-dose group and in female mice in the mid-dose group.

The 24 months administration of midazolam, at the 80 mg/kg/day dose level, led in male mice to decreased white blood cell counts, ulceration/abrasion of the prepuce, inflammatory changes of the urinary tract and distention of the urinary bladder.

Mean absolute and relative liver weights were significantly increased in male and female mice in the high-dose group and in male mice in the mid-dose group.

Hepatocellular hypertrophy was a prominent histological finding in both male and female mice at the 80/mg/kg/day dose and in male mice at the 9 mg/kg/day dose. In female mice, the 80 mg/kg/day dose of midazolam markedly increased the incidence of hepatic neoplasms. The hepatic masses or nodules, seen at autopsy, were found to be primary adenomas and carcinomas upon histologic examination. Hepatic neoplasms were also seen in female mice in the mid and low-dose groups, at a frequency higher than in controls, however, the difference was not statistically significant.

In female mice in the high-dose group, there was an increase in the incidence of follicular hyperplasia, adenoma/carcinoma of the thyroid, and a significant increase in the incidence of adrenal cortical hypertrophy and adrenomedullary hyperplasia.

2. Twenty-four Month Oral-Rats:

A twenty-four month oral (dietary admix) carcinogenicity study with midazolam was conducted in rats (90 male and 90 female/group) at doses of 0 (control 1), 0 (control 2), 1, 9 or 80 mg/kg/day.

In female rats, midazolam administration was associated with a decrease of body weight at the high dose and an increase of body weight at the mid dose. In male animals, the 80 mg/kg/day dose caused an increase in body weight during the earlier part of the study.

The 80 mg/kg/day dose was associated with the following changes in clinical chemical parameters: a decrease of serum glucose in both male and female rats at 26 weeks, an increase of serum urea nitrogen in female rats at 26 weeks and albuminuria in male rats after 26 weeks persisting to 78 weeks. At later times, all parameters were similar to control.

Absolute and relative liver weights were increased in both male and female animals, treated with 80 and 9 mg/kg/day of midazolam. Absolute liver weights were also increased in low-dose treated female rats.

In addition, the following organ weight changes were observed in animals treated with the 80 mg/kg/day dose of midazolam and were considered treatment related: increase in absolute and relative kidney weights in both sexes, increase in absolute and relative thyroid weights in both sexes, increase in absolute and relative adrenal gland weights in male rats, decrease in absolute and relative pituitary gland weights in female rats and decreased weights of the testes.

Dose-related centrilobular hepatocytic hypertrophy and centrilobular fatty changes were observed in the livers of both sexes. In addition, there was a statistically nonsignificant increase in the incidence of hepatocellular adenomas/carcinomas in female rats at all three doses.

In male rats, treated with 80 mg/kg/day of midazolam, the incidence of thyroidal tumours (adenomas/carcinomas) was significantly increased. The increase was limited to follicular adenomas; there was no increase observed in the incidence of follicular carcinomas.

Reproduction and Teratology

1. Fertility and General Reproductive Performance:

In a reproduction study, rats were administered midazolam maleate injection at doses of 1.0, 4.0, or 16.0 mg/kg/day by oral intubation. The highest dose produced pronounced pharmacological effects, namely sedation and ataxia, which lasted up to 2 hours. Twenty-four male rats were treated for 62 days prior to mating and through the mating period and 24 female rats for 14 days prior to mating and through day 13 of gestation (Group A) or day 21 of lactation (Group B). Control rats received daily intubation of the vehicle. Approximately one-half of the rats were sacrificed on gestation day 13. The remaining dams were allowed to deliver for subsequent perinatal and postnatal evaluations and were sacrificed on lactation day 21.

Gonadal function, mating behaviour, conception rate, early and late stages of gestation, parturition, lactation, neonatal viability, and growth of the pups were not adversely affected when midazolam was administered orally at doses up to 16 mg/kg/day.

2. Teratology-Rats (IV):

A teratology study was performed with groups of 30 rats given midazolam maleate intravenously at doses of 0.2, 1.0 or 4.0 mg/kg/day from day 7 through 15 of gestation. One group of females was not injected and served as a nontreated control. A second control group was injected with the vehicle. Fetuses from 20 rats per group were delivered by Cæsarean section. An additional ten rats per group were allowed to deliver for subsequent postnatal evaluation of the pups.

In the Cæsarean section group, the average maternal body weight decreased significantly during gestation in dams receiving the 4.0 mg/kg/day dose.

There were no significant differences between control and treated animals in the average litter size, average fetal body weight, distribution of fetuses by sex, the number of fetuses born dead, resorption rate or percent litters showing resorptions. No increase in external soft tissue or skeletal abnormalities was noted and the incidence of skeletal variations was comparable in all groups.

In the 1.0 and 4.0 mg/kg/day group of rats, that were allowed to deliver, a small increase in postimplantation loss was noted. This is considered to be the result of resorbed fetuses and/or pup cannibalism. In the 4.0 mg/kg/day treatment group, two of 133 pups exhibited partial paralysis of fore and hind limbs and poor motor coordination.

3. Teratology-Rabbits (IV):
A teratology study was conducted in groups of 15 female white rabbits given midazolam maleate intravenously at doses of 0.2, 0.6, or 2.0 mg/kg/day from days 7 through 18 of gestation. A control group of 30 rabbits received injections of the vehicle. A second group of 15 rabbits served as a nontreated control.

Sedation was present in all midazolam-treated rabbits, its severity and duration being dose dependent. Pretreatment parameters (percentage of animals pregnant, average number of *corpora lutea* and implantation sites) were similar in treated and control groups. Furthermore, there were no significant differences between control and treated animals in the average litter size, the average fetal body weight, average crown-rump length, distribution of fetuses by sex and 24-hr viability index of the kits. The resorption rate and percentage of litters showing resorptions were slightly higher in those receiving the 2.0 mg/kg/day dose of midazolam. The frequency of external, visceral and skeletal abnormalities was similar in control animals and those treated with the mid and high dose of midazolam. However, in one dose receiving 0.2 mg/kg/day of midazolam, 9/10 and 6/10 fetuses had external (open eyelids) and skeletal (cleft palate) abnormalities, respectively.

4. Perinatal and Postnatal-Rats (IV):
A perinatal and postnatal study was performed in groups of 20 female rats given midazolam maleate intravenously at doses of 0.2, 1.0 or 4.0 mg/kg/day from day 15 of gestation through day 21 of lactation. A control group of 20 rats received injections of the vehicle. A second control group served as a nontreated control.

Intravenous midazolam induced ataxia in the dams, the severity and duration of which was dose-dependent.

Maternal weight gains were significantly reduced in the 4.0 mg/kg/day dose group on the day of delivery and in the 1.0 and 4.0 mg/kg/day dose groups on lactation day 7. The following slight but significant effects were observed in the 4.0 mg/kg/day dose group: prolonged gestation period, smaller average litter size and increased postimplantation loss.

Late fetal development, lactation, neonatal viability and growth of the pups were not affected by midazolam treatment. External, visceral and skeletal abnormalities were not seen in any of the treatment groups.

Dependence Liability
To date only animal data are available.

Physical Dependence
Physical dependence was studied in several species. In phenobarbital-dependent cynomolgus monkeys, midazolam, in oral doses up to 10 mg/kg, did not suppress the abstinence symptoms which appeared when phenobarbital was withdrawn. A 20 mg/kg dose of midazolam suppressed some of the minor signs (apprehension, hyperirritability, piloerection), but the effect was probably due to general sedation.

Midazolam, when administered at a maximal oral dose of 135 mg/kg/day, for 28 consecutive days, produced only mild symptoms of withdrawal in cynomolgus monkeys. An additional 28 days of drug administration did not intensify the withdrawal symptoms. In contrast, phenobarbital produced withdrawal of intermediate severity, and several benzodiazepines caused intensified withdrawal after the second, as compared to the first, 28-day period.

Signs indicative of withdrawal were not seen in either rats or dogs at the end of the 18 or 12 months toxicity study, respectively.

The intravenous administration of the benzodiazepine antagonist, flumazenil (Ro 15-1788), did not precipitate withdrawal symptoms in monkeys chronically treated with midazolam.

Self-Administration
In baboons trained to intravenously self-inject cocaine, both the barbiturates and the benzodiazepines were self-administered, but with different intensities. The barbiturates maintained high levels of self-injection in all the animals and over a wide dose range. Midazolam also produced high rates of self-injection, although not in all of the animals and only in a narrow dose range. Benzodiazepines, with a slow rate of elimination, maintained modest levels of self-administration. The rapid elimination of midazolam might contribute to the effect observed.

Drug Discrimination
In rats trained to discriminate between saline and diazepam, midazolam, like other benzodiazepines, produced a dose-dependent, diazepam-appropriate response.

Irritation Studies
I. Venous Irritation-Rabbits:
Midazolam base (2.0 and 5.0 mg/mL), administered intravenously into the ear veins of rabbits at a single dose of 0.7 mg/kg, produced minimal irritation to the ears.

II. Muscle Irritation-Rabbits:
The intramuscular irritation potential of midazolam base (5.0 mg/mL) and its vehicle was tested in rabbits in volumes of 1.0 and 0.1 mL. Single dose administration of 1.0 mL of midazolam produced moderate hemorrhage and necrosis while the vehicle produced slight hemorrhage and minimal necrosis. At 0.1 mL, midazolam produced very slight hemorrhage and well-defined necrosis; the vehicle also produced very slight hemorrhage but no necrosis. The study indicated that midazolam can cause slight muscle irritation following intramuscular administration.

III. Hemolysis Testing-Dogs:
Intravenous administration of midazolam base (1.0 mg/mL) to dogs did not produce hemolysis after a dose of 0.7 mg/kg (0.7 mL/kg) administered over approximately 30 seconds.

However, intravenous injection of a dose of 0.7 mg/kg (0.14 mL/kg) of the 5.0 mg/mL injectable midazolam base formulation produced a slight hemolysis in one post-treatment undiluted plasma sample.

No hemolysis occurred in the animals treated with normal saline at a volume of 0.7 or 0.14 mL/kg.

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