WARNING

Adult and Pediatric: Intravenous midazolam hydrochloride 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 hydrochloride should be used only in hospital or ambulatory care settings, including physicians’ and dental offices, that provide for continuous monitoring of respiratory and cardiac function, ie, 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 pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedures.

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 narcotics or other central nervous system (CNS) depressants. The initial dose and all subsequent doses should always be titrated slowly; administer over at least 2 minutes and allow an additional 2 or more 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/amnesia/amnesia is age, procedure, and route dependent (see DOSAGE AND ADMINISTRATION for complete dosing information).

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

DESCRIPTION

Midazolam hydrochloride is a water-soluble benzodiazepine available as a sterile, nonpyrogenic parenteral dosage form for intravenous or intramuscular injection. Each mL contains midazolam hydrochloride equivalent to 1 mg or 5 mg midazolam USP compounded with 0.8% sodium chloride. The pH is approximately 3 (2.5 to 3.5) and is adjusted with hydrochloric acid and, if necessary, sodium hydroxide.

Midazolam is a white to light yellow crystalline compound, insoluble in water. The hydrochloride salt of midazolam, which is formed in situ, is soluble in aqueous solutions. Chemically, midazolam HCl is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine hydrochloride. Midazolam hydrochloride has the chemical formula C21H18ClFNN2·HCl, a calculated molecular weight of 362.25 and the following structural formula:

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\text{Midazolam Hydrochloride (Chemical Structure)}
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Under the acidic conditions required to solubilize midazolam in the product, midazolam is present as an equilibrium mixture (shown below) of the closed-ring form shown above and an open-ring structure formed by the acid-catalyzed ring opening of the 4,5-double bond of the diazepine ring. The amount of open-ring form is dependent upon the pH of the solution. At the specified pH of the product, the solution may contain up to about 25% of the open-ring compound. At the physiologic conditions under which the product is absorbed (pH of 5 to 8) into the systemic circulation, any open-ring form present reverts to the physiologically active, lipophilic, closed-ring form (midazolam) and is absorbed as such.

The following chart plots the percentage of midazolam present as the open-ring form as a function of pH in aqueous solution. As indicated in the graph, the amount of open-ring compound present in...
solution is sensitive to changes in pH over the pH range specified for the product: 3.0 to 4.0 for the 1 mg/mL concentration and 3.0 to 3.6 for the 5 mg/mL concentration. Above pH 5, at least 99% of the mixture is present in the closed-ring form.

**CLINICAL PHARMACOLOGY**

Midazolam is a short-acting benzodiazepine central nervous system (CNS) depressant. The effects of midazolam hydrochloride on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other medications. Onset time of sedative effects after IM administration in adults is 15 minutes, with peak sedation occurring 30 to 60 minutes following injection. In one adult study, when administered the following day, 78% of the patients who received midazolam hydrochloride intramuscularly had no recall of memory cards shown 30 minutes following drug administration; 40% had no recall of the memory cards shown 60 minutes following drug administration. Onset time of sedative effects in the pediatric population begins within 5 minutes and peaks at 15 to 30 minutes depending upon the dose administered. In pediatric patients, up to 85% had no recall of pictures shown after receiving intramuscular midazolam compared with 5% of the placebo controls.

Sedation in adult and pediatric patients is achieved within 3 to 5 minutes after intravenous (IV) injection; the time of onset is affected by total dose administered and the concurrent administration of narcotic premedication. Seventy-one percent of the adult patients in endoscopy studies had no recall of introduction of the endoscope; 82% of the patients had no recall of withdrawal of the endoscope. In one study of pediatric patients undergoing lumbar puncture or bone marrow aspiration, 88% of patients had impaired recall vs 5% of the placebo controls. In another pediatric oncology study, 91% of midazolam treated patients were amnestic compared with 35% of patients who had received fentanyl alone.

When midazolam hydrochloride is given IV as an anesthetic induction agent, induction of anesthesia occurs in approximately 1.5 minutes when narcotic premedication has been administered and in 2 to 2.5 minutes without narcotic premedication or other sedative premedication. Some impairment in test of memory was noted in 90% of the patients studied. A dose response study of pediatric patients premedicated with 1 mg/kg intramuscular (IM) meperidine found that only 4 out of 6 pediatric patients who received 600 mcg/kg IV midazolam lost consciousness, with eye closing at 108 ± 140 seconds. This group was compared with pediatric patients who were given thiopental 5 mg/kg IV; 6 out of 6 closed their eyes at 20 ± 3.2 seconds. Midazolam did not dependably induce anesthesia at this dose despite concomitant opioid administration in pediatric patients.

Midazolam, used as directed, does not delay awakening from general anesthesia in adults. Gross tests of recovery after awakening (orientation, ability to stand and walk, suitability for discharge from the recovery room, return to baseline Trieger compresis) usually indicate recovery within 2 hours but recovery may take up to 6 hours in some cases. When compared with patients who received thiopental, patients who received midazolam generally recovered at a slightly slower rate. Recovery from anesthesia or sedation for procedures in pediatric patients depends on the dose of midazolam administered, coadministration of other medications causing CNS depression and duration of the procedure.

In patients without intracranial lesions, induction of general anesthesia with IV midazolam hydrochloride is associated with a moderate decrease in cerebrospinal fluid pressure (lumbar puncture measurements), similar to that observed following IV thiopental. Preliminary data in neurosurgical patients with normal intracranial pressure but decreased compliance (subarachnoid screw measurements) show comparable elevations of intracranial pressure with midazolam and with thiopental during induction. No similar studies have been reported in pediatric patients.

The usual recommended intramuscular premedicating doses of midazolam hydrochloride do not depress the ventilatory response to carbon dioxide stimulation to a clinically significant extent in adults. Intravenous induction doses of midazolam hydrochloride depress the ventilatory response to carbon dioxide stimulation for 15 minutes or more beyond the duration of ventilatory depression following administration of thiopental in adults. Impairment of ventilatory response to carbon dioxide is more marked in adult patients with chronic obstructive pulmonary disease (COPD). Sedation with IV midazolam does not adversely affect the mechanics of respiration (resistance, static recoil, most lung volume measurements); total lung capacity and peak expiratory flow decrease significantly but static compliance and maximum expiratory flow at 50% of awake total lung capacity (Vmax) increase. In one study of pediatric patients under general anesthesia, intramuscular midazolam (100 or 200 mcg/kg) was shown to depress the response to carbon dioxide in a dose-related manner.

In cardiac hemodynamic studies in adults, IV induction of general anesthesia with midazolam hydrochloride was associated with a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume and systemic vascular resistance. Slow heart rates (less than 65/minute), particularly in patients taking propranolol for angina, tended to rise slightly; faster heart rates (e.g., 85/minute) tended to slow slightly. In pediatric patients, a comparison of IV midazolam hydrochloride (500 mcg/kg) with propofol (2.5 mg/kg) revealed a mean 15% decrease in systolic blood pressure in patients who had received IV midazolam vs a mean 25% decrease in systolic blood pressure following propofol.

**Pharmacokinetics**

Midazolam's activity is primarily due to the parent drug. Elimination of the parent drug takes place via hepatic metabolism of midazolam to hydroxylated metabolites that are conjugated and excreted in the urine. Six single-dose pharmacokinetic studies involving healthy adults yield pharmacokinetic parameters for midazolam in the following ranges: volume of distribution (Vd), 1.0 to 3.1 L/kg; elimination half-life, 1.8 to 6.4 hours (mean approximately 3 hours); total clearance (Cl), 0.25 to 0.54 L/hr/kg. In a parallel group study, there was no difference in the clearance, in subjects administered 0.15 mg/kg (n=4) and 0.3 mg/kg (n=4) IV doses indicating linear kinetics. The clearance was successively reduced by approximately 30% at doses of 0.45 mg/kg (n=4) and 0.6 mg/kg (n=5) indicating non-linear kinetics in this dose range.
Absorption: The absolute bioavailability of the intramuscular route was greater than 90% in a cross-over study in which healthy subjects (n=17) were administered a 7.5 mg IV or IM dose. The mean peak concentration (Cmax) and time to peak (Tmax) following the IM dose were 90 ng/ml (20% CV) and 0.5 hr (50% CV). Cmax for the 1-hydroxy metabolite following the IM dose was 8 ng/ml (Tmax=1.9 hr).

Following IM administration, Cmax for midazolam and its 1-hydroxy metabolite were approximately one-half of those achieved after intravenous injection.

Distribution: The volume of distribution (Vd) determined from six single-dose pharmacokinetic studies involving healthy adults ranged from 1.0-3.1 L/kg. Female gender, old age, and obesity are associated with increased values of midazolam Vd. In humans, midazolam has been shown to cross the placenta and enter into fetal circulation and has been detected in human milk and CSF (see CLINICAL PHARMACOLOGY, Special Populations).

In adults and children older than 1 year, midazolam is approximately 97% bound to plasma protein, principally albumin.

Metabolism: In vitro studies with human liver microsomes indicate that the biotransformation of midazolam is mediated by cytochrome P450-3A4. This cytochrome also appears to be present in gastrointestinal tract mucosa as well as liver. Sixty to seventy percent of the biotransformation products is 1-hydroxy-midazolam (also termed alpha-hydroxy-midazolam) while 4-hydroxy-midazolam constitutes 3% or less. Small amounts of dihydroxymidazolam have also been detected but not quantified. The principal urinary excretion products are glucuronide conjugates of the hydroxylated derivatives.

Drugs that inhibit the activity of cytochrome P450-3A4 may inhibit midazolam clearance and elevate steady-state midazolam concentrations.

Studies of the intravenous administration of 1-hydroxy-midazolam in humans suggest that 1-hydroxy-midazolam is at least as potent as the parent compound and may contribute to the net pharmacologic activity of midazolam. In vitro studies have demonstrated that the affinities of 1- and 4-hydroxymidazolam for the benzodiazepine receptor are approximately 20% and 7%, respectively, relative to midazolam.

Excretion: Clearance of midazolam is reduced in association with old age, congestive heart failure, liver disease (cirrhosis) or conditions which diminish cardiac output and hepatic blood flow.

The principal urinary excretion product is 1-hydroxy-midazolam in the form of a glucuronide conjugate; smaller amounts of the glucuronide conjugates of 4-hydroxy- and dihydroxy-midazolam are detected as well. The amount of midazolam-excreted unchanged in the urine after a single IV dose is less than 0.5% (n=3). Following a single IV infusion in 5 healthy volunteers, 45% to 57% of the dose was excreted in the urine as 1-hydroxymethyl midazolam conjugate.

Pharmacokinetics—continuous infusion: The pharmacokinetic profile of midazolam following continuous infusion, based on 282 adult subjects, has been shown to be similar to that following single-dose administration for subjects of comparable age, gender, body habitus and health status. However, midazolam can accumulate in peripheral tissues with continuous infusion. The effects of accumulation are greater after long-term infusions than after short-term infusions. The effects of accumulation can be reduced by maintaining the lowest midazolam infusion rate that produces satisfactory sedation.

Infrequent hypotensive episodes have occurred during continuous infusion; however, neither the time to onset nor the duration of the episode appeared to be related to plasma concentrations of midazolam or alpha-hydroxy-midazolam. Further, there does not appear to be an increased chance of occurrence of a hypotensive episode with increased loading doses.

Patients with renal impairment may have longer elimination half-lives for midazolam (see CLINICAL PHARMACOLOGY, Special Populations: Renal Failure).

Special Populations:

Changes in the pharmacokinetic profile of midazolam due to drug interactions, physiological variables, etc., may result in changes in the plasma concentration-time profile and pharmacological response to midazolam in these patients. For example, patients with acute renal failure appear to have a longer elimination half-life for midazolam and may experience delayed recovery (see CLINICAL PHARMACOLOGY, Special Populations: Renal Failure). In other groups, the relationship between prolonged half-life and duration of effect has not been established.

Pediatrics and Neonates: In pediatric patients aged 1 year and older, the pharmacokinetic properties following a single dose of midazolam reported in 10 separate studies of midazolam are similar to those in adults. Weight-normalized clearance is similar or higher (0.19 to 0.80 L/hr/kg) than in adults and the terminal elimination half-life (0.78 to 3.3 hours) is similar to or shorter than in adults. The pharmacokinetic properties in pediatric patients in the operating room as an adjunct to general anesthesia and in the intensive care environment are similar to those in adults.

In seriously ill neonates, however, the terminal elimination half-life of midazolam is substantially prolonged (6.5 to 12.0 hours) and the clearance reduced (0.07 to 0.12 L/hr/kg) compared to healthy adults or other groups of pediatric patients. It cannot be determined if these differences are due to age, immature organ function or metabolic pathways, underlying illness or debility.

Obese: In a study comparing normals (n=20) and obese patients (n=20) the mean half-life was greater in the obese group (5.8 vs 2.3 hrs.). This was due to an increase of approximately 50% in the Vd corrected for total body weight. The clearance was not significantly different between groups.

Geriatric: In three parallel group studies, the pharmacokinetics of midazolam administered IV or IM were compared in young (mean age 29, n=52) and healthy elderly subjects (mean age 73, n=53). Plasma half-life was approximately two-fold higher in the elderly. The mean Vd based on total body weight increased consistently between 15% to 100% in the elderly. The mean CI decreased approximately 25% in the elderly two studies and was similar to that of the younger patients in the other.

Congestive Heart Failure: In patients suffering from congestive heart failure, there appeared to be a two-fold increase in the elimination half-life, a 25% decrease in the plasma clearance and a 45% increase in the volume of distribution of midazolam.

Hepatic Insufficiency: Midazolam pharmacokinetics were studied after an IV single dose (0.075 mg/kg) was administered to 7 patients with biopsy proven alcoholic cirrhosis and 8 control patients. The mean half-life of midazolam increased 2.5-fold in the alcoholic patients. Clearance was reduced by 50% and the Vd increased by 25%. In another study in 21 male patients with cirrhosis, without ascites and with normal kidney function determined by creatinine clearance, no changes in the pharmacokinetics of midazolam or 1-hydroxy-midazolam were observed when compared to healthy individuals.

Renal Failure: Patients with renal impairment may have longer elimination half-lives for midazolam and its metabolites which may result in slower recovery.

Midazolam and 1-hydroxy-midazolam pharmacokinetics in 6 ICU patients who developed acute renal failure (ARF) were compared with a normal renal function control group. Midazolam was administered as an infusion (5 to 15 mg/hr). Midazolam clearance was reduced (1.9 vs 2.8 mL/min/kg) and the half-life was prolonged (7.6 vs 13 hr) in the ARF patients. The renal clearance of the 1-hydroxy-midazolam glucuronide was prolonged in the ARF group (4 vs 13 mL/min) and the half-life was prolonged (12 hr vs >25 hr). Plasma levels accumulated in all ARF patients to about ten times that of the parent drug. The relationship between accumulating metabolite levels and prolonged sedation is unclear.

In a study of chronic renal failure patients (n=15) receiving a single IV dose, there was a two-fold increase in the clearance and volume of distribution but the half-life remained unchanged. Metabolite levels were not studied.

Plasma Concentration-Effect Relationship: Concentration-effect relationships (after an IV dose) have been demonstrated for a variety of pharmacodynamic measures (e.g., reaction time, eye movement,
sedation) and are associated with extensive inter-subject variability. Logistic regression analysis of sedation scores and steady-state plasma concentration indicated that at plasma concentrations greater than 100 ng/mL, there was at least a 50% probability that patients would be sedated, but respond to verbal commands (sedation score = 3). At 200 ng/mL, there was at least a 50% probability that patients would be asleep, but respond to glabellar tap (sedation score = 4).

**Drug Interactions:** For information concerning pharmacokinetic drug interactions with midazolam, see PRECAUTIONS.

**INDICATIONS AND USAGE**

Midazolam hydrochloride injection, USP is indicated:

- intramuscularly or intravenously for preoperative sedation/amnesia/analgesia;
- intravenously as an agent for sedation/amnesia/amnesia prior to or during diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography, cardiac catheterization, oncology procedures, radiologic procedures, suare of lacerations and other procedures either alone or in conjunction with other CNS depressants;
- intravenously for induction of general anesthesia, before administration of other anesthetic agents.

With the use of narcotic premedication, induction of anesthesia can be attained within a relatively narrow dose range and in a short period of time. Intravenous midazolam can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia);
- continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.

Midazolam is associated with a high incidence of partial or complete impairment of recall for the next several hours (see CLINICAL PHARMACOLOGY).

**CONTRAINDICATIONS**

Injectable midazolam hydrochloride is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow-angle glaucoma. Benzodiazepines may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with midazolam hydrochloride; patients with glaucoma have not been studied.

**WARNINGS**

Midazolam hydrochloride must never be used without individualization of dosage particularly when used with other medications capable of producing central nervous system depression. Prior to the intravenous administration of midazolam hydrochloride in any dose, the immediate availability of oxygen, resuscitative drugs, age- and size-appropriate equipment for bag-valve-mask ventilation and intubation, and skilled personnel for the maintenance of a patent airway and support of ventilation should be ensured. Patients should be continuously monitored with some means of detection for early signs of hypoventilation, airway obstruction, or apnea, i.e., pulse oximetry. Hypoventilation, airway obstruction, and apnea can lead to hypoxia and/or cardiac arrest unless effective countermeasures are taken immediately. The immediate availability of specific reversal agents (flumazenil) is highly recommended. Vital signs should continue to be monitored during the recovery period. Because intravenous midazolam depresses respiration (see CLINICAL PHARMACOLOGY) 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/amnesia/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintaining a patent airway and supporting ventilation. When used for sedation/amnesia/amnesia, midazolam should always be titrated slowly in adult or pediatric patients. Adverse hemodynamic events have been reported in pediatric patients with cardiovascular instability; rapid intravenous administration should also be avoided in this population. See DOSAGE AND ADMINISTRATION for complete information.

Serious cardiorespiratory adverse events have occurred after administration of midazolam. These have included respiratory depression, airway obstruction, oxygen desaturation, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death or permanent neurologic injury. There have also been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations particularly in adult or pediatric patients with hemodynamic instability. Hypotension occurred more frequently in the sedation studies in patients premedicated with a narcotic.

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

Concomitant use of barbiturates, alcohol or other central nervous system depressants may increase the risk of hypoventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk adult and pediatric surgical patients, elderly patients and debilitated adult and pediatric patients require lower dosages, whether or not concomitant sedating medications have been administered. Adult or pediatric patients with COPD are unusually sensitive to the respiratory depressant effect of midazolam hydrochloride. Pediatric and adult patients undergoing procedures involving the upper airway such as upper endoscopy or dental care, are particularly vulnerable to episodes of desaturation and hypoventilation due to partial airway obstruction. Adult and pediatric patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly (see CLINICAL PHARMACOLOGY). Because elderly patients frequently have inefficient function of one or more organ systems and because dosage requirements have been shown to decrease with age, reduced initial dosage of midazolam hydrochloride is recommended, and the possibility of profound and/or prolonged effect should be considered.

Injectable midazolam should not be administered to adult or pediatric patients in shock or coma, or in acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of intravenous midazolam in adult or pediatric patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

There have been limited reports of intra-arterial injection of midazolam hydrochloride. Adverse events have included local reactions, as well as isolated reports of seizure activity in which no clear causal relationship was established. Precautions against unintended intra-arterial injection should be taken. Extravasation should also be avoided.

The safety and efficacy of midazolam following nonintravenous and nonintramuscular routes of administration have not been established. Midazolam hydrochloride should only be administered intramuscularly or intravenously.

The decision as to when patients who have received injectable midazolam, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized. Gross tests of recovery from the effects of midazolam (see CLINICAL PHARMACOLOGY) cannot be relied upon to predict reaction time under stress. It is recommended that no patient operate hazardous machinery or 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
Midazolam does not cause a clinically significant change in dosage, onset or duration of a single
against the increased intracranial pressure noted following administration of succinylcholine.

Although the possibility of minor interactive effects has not been fully studied, midazolam and
ethylene glycol. No interaction was observed in healthy subjects between midazolam and
pharmacodynamics of midazolam were investigated in a three-way crossover study (n=9). The half-life
the mean midazolam steady-state concentration from 57 to 71 ng/mL. Ranitidine increased the mean
decrease in plasma clearance of midazolam.

Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit
the P450-3A4 enzyme system such as cimetidine (not ranitidine), erythromycin, diltaizem, verapamil,
pronounced and/or prolonged respiratory effects of midazolam.

PRECAUTIONS

General: Intravenous doses of midazolam hydrochloride should be decreased for elderly and for
debilitated patients (see WARNINGS and DOSAGE AND ADMINISTRATION). These patients will
also probably take longer to recover completely after midazolam administration for the induction of
anesthesia.

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 anesthesia.

Use with Other CNS Depressants:
The efficacy and safety of midazolam in clinical use are functions of the dose administered, the clinical
status of the individual patient, and the use of concomitant medications capable of depressing the CNS.
Anticipated effects can range from mild sedation to deep levels of sedation virtually equivalent to a state of
general anesthesia where the patient may require external support of vital functions. Care must be taken
to individualize and carefully titrate the dose of midazolam hydrochloride to the patient’s underlying
medical/surgical condition, administer to the desired effect being certain to wait an adequate time for peak
CNS effects of both midazolam hydrochloride and concomitant medications, and have the
personnel and size-appropriate equipment and facilities available for monitoring and intervention (see
Based WARNING, WARNING/nos DOSAGE AND ADMINISTRATION). Practitioners administering midazolam hydrochloride must have the skills necessary to manage reasonably foreseeable adverse effects, particularly skills in airway management. For information regarding withdrawal (see DRUG ABUSE AND DEPENDENCE).

Information for Patients:
To assure safe and effective use of benzodiazepines, the following information and instructions should
be communicated to the patient when appropriate:
1. Inform your physician about any alcohol consumption and medicine you are now taking, especially
blood pressure medication and antibiotics, including drugs you buy without a prescription. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be
exercised regarding simultaneous ingestion of alcohol during benzodiazepine treatment
2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.
4. Patients should be informed of the pharmacological effects of midazolam, such as sedation and
amnesia, which in some patients may be profound. The decision as to when patients who have
received injectable midazolam hydrochloride, particularly on an outpatient basis, may again engage
in activities requiring complete mental alertness, operate hazardous machinery or drive a motor
vehicle must be individualized.
5. Patients receiving continuous infusion of midazolam in critical care settings over an extended period
of time, may experience symptoms of withdrawal following abrupt discontinuation.

Drug Interactions:
The sedative effect of intravenous midazolam is accentuated by any concomitantly administered
medication, which depresses the central nervous system, particularly narcotics (e.g., morphine,
meperidine and fentanyl) and also seconobarbital and droperidol. Consequently, the dosage of midazolam
should be adjusted according to the type and amount of concomitant medications administered and the
desired clinical response (see DOSAGE AND ADMINISTRATION).

Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit
the P450-3A4 enzyme system such as cimetidine (not ranitidine), erythromycin, diltaizem, verapamil,
ketonazole and itrazonazole. These drug interactions may result in prolonged sedation due to a
decrease in plasma clearance of midazolam.

The effect of single oral doses of 800 mg cimetidine and 300 mg ranitidine on steady-state
concentration of midazolam was examined in a randomized crossover study (n=8). Cimetidine increased
the mean midazolam steady-state concentration from 57 to 71 ng/mL. Ranitidine increased the mean
steady-state concentration to 82 ng/mL. No change in choice reaction time or sedation index was
detected after dosing with the H2 receptor antagonists.

In a placebo-controlled study, erythromycin administered as a 500 mg dose, tid, for 1 week (n=6),
reduced the clearance of midazolam following a single 0.5 mg/kg IV dose. The half-life was
approximately doubled.

Caution is advised when midazolam is administered to patients receiving erythromycin since this may
result in a decrease in the plasma clearance of midazolam.

The effects of diltaizem (60 mg tid) and verapamil (80 mg tid) on the pharmacokinetics and
pharmacodynamics of midazolam were investigated in a three-way crossover study (n=9). The half-life
of midazolam increased from 5 to 7 hours when midazolam was taken in conjunction with verapamil or
diltaizem. No interaction was observed in healthy subjects between midazolam and nifedipine.

In a placebo-controlled study, sapplainis administered as a 1200 mg dose, tid, for 5 days (n=12), a 56%
reduction in the clearance of midazolam following a single 8.05 mg/kg IV dose was observed. The
half-life was approximately doubled.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted
following use of intramuscular midazolam hydrochloride for premedication in adults.

The intravenous administration of midazolam hydrochloride decreases the minimum alveolar
concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the
dose of midazolam hydrochloride administered; no similar studies have been carried out in pediatric
patients but there is no scientific reason to expect that pediatric patients would respond differently than
adults.

Although the possibility of minor interactive effects has not been fully studied, midazolam and
pancuronium have been used together in patients without noting clinically significant changes in dosage,
one or duration in adults. Midazolam hydrochloride does not protect against the characteristic
circular changes noted after administration of succinylcholine or pancuronium and does not protect
against the increased intracranial pressure noted following administration of succinylcholine.
Midazolam does not cause a clinically significant change in dosage, one or duration of a single
Administration.
imitating dose of succinylcholine; no similar studies have been carried out in pediatric patients but there is no scientific reason to expect that pediatric patients would respond differently than adults.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, dexamethasone, d-tubocurarine, succinylcholine and other nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, prilocaine HCl and Cetaclain) have been observed in adults or pediatric patients. In neonates, however, severe hypotension has been reported with concomitant administration of fentanyl. This effect has been observed in neonates on an infusion of midazolam who received a rapid injection of fentanyl and in patients on an infusion of fentanyl who have received a rapid injection of midazolam.

Drug/Laboratory Test Interactions:
Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenesis: Midazolam maleate was administered with diet in mice and rats for 2 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 mammary tumors. In high-dose male rat there was a small but statistically significant increase in benign thyroid follicular cell tumors. Dosages of 9 mg/kg/day of midazolam maleate (25 times a human dose of 0.35 mg/kg) do not increase the incidence of tumors. The pathogenesis of induction of these tumors is not known. These tumors were found after chronic administration, whereas human use will ordinarily be of single or several doses.

Mutagenesis: Midazolam did not have mutagenic activity in Salmonella typhimurium (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes or in the micronucleus test in mice.

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

Pregnancy:
Teratogenic Effects: Pregnancy Category D (see WARNINGS).
Segment II teratology studies, performed with midazolam maleate injectable in rabbits and rats at 5 and 10 times the human dose of 0.35 mg/kg, did not show evidence of teratogenicity.
Nonteratogenic Effects: Studies in rats showed no adverse effects on reproductive parameters during gestation and lactation. Dosages tested were approximately 10 times the human dose of 0.35 mg/kg.

Labor and Delivery:
In human, measurable levels of midazolam were found in maternal venous serum, umbilical venous and arterial serum and amniotic fluid, indicating placental transfer of the drug. Following intramascular administration of 0.05 mg/kg of midazolam, both the venous and the umbilical arterial serum concentrations were lower than maternal concentrations.
The use of intravenous midazolam in obstetrics has not been evaluated in clinical studies. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, midazolam is not recommended for obstetric use.

Nursing Mothers:
Midazolam is excreted in human milk. Caution should be exercised when midazolam hydrochloride is administered to a nursing woman.

Pediatric Use:
The safety and efficacy of midazolam for sedation/anxiolysis/amnesia following single dose intramuscular administration, intravenously by intermittent injections and continuous infusion have been established in pediatric and neonatal patients. For specific safety monitoring and dosage guidelines see WARNINGS, CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, OVERDOSE, and DOSAGE AND ADMINISTRATION. UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE INCREMENTS OF MIDAZOLAM ON A MG/KG BASIS. As a group, pediatric patients generally require higher dosages of midazolam (mg/kg) than adults. Younger (less than six years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients, and may require closer monitoring. In obese PEDIATRIC PATIENTS, 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, or hypoventilation is increased. The health care practitioner who uses this medication in pediatric patients should be aware of and follow accepted professional guidelines for pediatric sedation appropriate to their situation.

Midazolam hydrochloride should not be administered by rapid injection to the neonatal population. Severe hypertension and seizures have been reported following rapid IV administration, particularly, with concomitant use of fentanyl.

Geriatric Use:
Because geriatric patients may have altered drug distribution and diminished hepatic and/or renal function, reduced doses of midazolam are recommended. Intravenous and intramuscular doses of midazolam should be decreased for elderly and for debilitated patients (see WARNINGS and DOSAGE AND ADMINISTRATION) and subjects over 70 years of age may be particularly sensitive. These patients will also probably take longer to recover completely after midazolam administration for the induction of anesthesia. Administration of IM and IV midazolam to elderly and high risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiopulmonary respiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiration, especially narcotics (see DOSAGE AND ADMINISTRATION).

Specific dosing and monitoring guidelines for geriatric patients are provided in the DOSAGE AND ADMINISTRATION section for premedicated patients for sedation/anxiolysis/amnesia following IV and IM administration, for induction of anesthesia following IV administration and for continuous infusion.

ADVERSE REACTIONS
See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs were the most frequently seen findings following parenteral administration of midazolam in adults and included decreased tidal volume and/or respiratory rate decrease (23.2% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. The majority of serious adverse effects, particularly those associated with oxygenation and ventilation, have been reported when midazolam hydrochloride is administered with other medications capable of depressing the central nervous system. The incidence of such events is higher in patients undergoing procedures involving the airway without the protective effect of an endotracheal tube, (e.g., upper endoscopy and dental procedures).

Adults:
The following additional adverse reactions were reported after intramuscular administration:

headache (1.3%)
Local effects at IM Injection site
The manifestations of midazolam overdosage reported are similar to those observed in other benzodiazepines, including sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma and untoward effects on vital signs. No evidence of specific organ toxicity from midazolam hydrochloride overdosage has been reported.

Treatment of Overdose: Treatment of injectable midazolam overdosage is the same as that followed for overdosage with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. Attention should be given to the maintenance of a patent airway and support of ventilation, including administration of oxygen. An intravenous infusion should be started. Should hypotension develop, treatment may include intravenous fluids or pressors. The following additional adverse reactions were reported subsequent to intravenous administration as a single sedative/anxiolytic/amnestic agent in adult patients:

<table>
<thead>
<tr>
<th>symptom</th>
<th>incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>headache</td>
<td>(3.8%)</td>
</tr>
<tr>
<td>dizziness</td>
<td>(2.5%)</td>
</tr>
<tr>
<td>numbness</td>
<td>(1.7%)</td>
</tr>
</tbody>
</table>

Pediatric Patients:
The following adverse events related to the use of IV midazolam hydrochloride in pediatric patients were reported in the medical literature: desaturation 4.6%, apnea 2.8%, hypotension 2.7%, paradoxical reactions 2.0%, hiccough 1.2 %, seizure-like activity 1.3% and nystagmus 1.3%. The majority of airway-related events occurred in patients receiving other CNS depressant medications and in patients where midazolam was not used as a single sedating agent.

Neonates: For information concerning hypotensive episodes and seizures following the administration of midazolam hydrochloride to neonates, see Boxed WARNING, CONTRAINDICATIONS.

WARNING/SANI PRECAUTIONS.
Other adverse experiences, observed mainly following IV injection as a single sedative/amnestic agent and occurring at an incidence of <1.0% in adult and pediatric patients, are as follows:

Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respiration, airway obstruction, tachypnea

Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm

Gastrointestinal: Acid taste, excessive salivation, retching

CNS/Neuromuscular: Retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, giddiness, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, ataxia, nystagmus, eyeshot, myoclonus, seizures, increased or decreased motor activity, hypertension, hypotension, tachycardia, tachypnea, bradycardia, bradypnea

Skin: Rash, pruritus, urticaria, erythema, urticarial, photosensitivity

Special Senses: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ear blocked, loss of balance, light-headedness

Respiratory: Prolonged expiration and relief of respiratory distress

Ingestion: Nausea, vomiting, abdominal distention, nausea, vomiting, diarrhea, constipation

Hypersensitivity: Allergic reactions including anaphylactoid reactions, hives, rash, pruritus

Miscellaneous: Yawning, lethargy, chill, weakness, tongue, faint feeling, hematoma

DRUG ABUSE AND DEPENDENCE
Midazolam is subject to Schedule IV control under the Controlled Substances Act of 1970. Midazolam was actively self-administered in primate models used to assess the positive reinforcing effects of psychoactive drugs. Midazolam produced physical dependence of a mild to moderate intensity in cynomolgus monkeys after 5 to 10 weeks of administration. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, hallucinations, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuation of benzodiazepines, including midazolam. Abdominal distention, nausea, vomiting, and tachycardia are prominent symptoms of withdrawal in infants. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. There is no consensus in the medical literature regarding tapering schedules; therefore, practitioners are advised to individualize therapy to meet patient's needs. In some case reports, patients who have had severe withdrawal reactions due to abrupt discontinuation of high-dose long-term midazolam, have been successfully weaned off of midazolam over a period of several days.

OVERDOSE
The manifestations of midazolam overdosage reported are similar to those observed with other benzodiazepines, including sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma and untoward effects on vital signs. No evidence of specific organ toxicity from midazolam hydrochloride overdosage has been reported.

Treatment of Overdose: Treatment of injectable midazolam overdosage is the same as that followed for overdosage with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. Attention should be given to the maintenance of a patent airway and support of ventilation, including administration of oxygen. An intravenous infusion should be started. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate countermeasures. There is no information as to whether peritoneal dialysis, forced diuresis or hemodialysis are of any value in the treatment of midazolam overdosage.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. There are anecdotal reports of reversal of adverse hemodynamic responses associated with midazolam hydrochloride following administration of flumazenil to pediatric patients. Prior to the administration of flumazenil, necessary measures should be instituted to secure the airway, assure adequate ventilation, and establish adequate intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for reedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. Flumazenil will only reverse benzodiazepine-induced effects but will not reverse the effects of other concomitant
DOSE AND ADMINISTRATION

Midazolam hydrochloride injection is a potent sedative agent that requires slow administration and individualization of dosage. Clinical experience has shown that midazolam hydrochloride at a concentration of 0.5 mg/mL, is compatible with 5% dextrose in water and 0.9% sodium chloride for up to 24 hours and with lactated Ringer's solution for up to 4 hours. Both the 1 mg/mL and 5 mg/mL formulations of midazolam may be diluted with 0.9% sodium chloride or 5% dextrose in water.

**Monitoring:** Patient response to sedative agents, and resultant respiratory status, is variable. Regardless of the intended level of sedation or route of administration, sedation is a continuum; a patient may move easily from light to deep sedation, with potential loss of protective reflexes. This is especially true in pediatric patients. Sedative doses should be individually titrated, taking into account patient age, clinical status and concomitant use of other CNS depressants. Continuous monitoring of respiratory and cardiac function is required (i.e., pulse oximetry).

**Adults and Pediatrics:** Sedation guidelines recommend a careful presedation history to determine how a patient's underlying medical conditions or concomitant medications might affect their response to sedation/analgnesia as well as a physical examination including a focused examination of the airway for abnormalities. Further recommendations include appropriate presedation fasting.

**Titration to effect with multiple small doses is essential for safe administration. It should be noted that adequate time to achieve peak central nervous system effect (3 to 5 minutes) for midazolam should be allowed between doses to minimize the potential for oversedation. Sufficient time must elapse between doses of concomitant sedative medications to allow the effect of each dose to be assessed before subsequent drug administration. This is an important consideration for all patients who receive intravenous midazolam.**

Immediate availability of resuscitative drugs and age- and size-appropriate equipment and personnel trained in their use and skilled in airway management should be assured (see WARNINGS).

**Pediatrics:** For deeply sedated pediatric patients a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

Intravenous access is not thought to be necessary for all pediatric patients sedated for a diagnostic or therapeutic procedure because in some cases the difficulty of gaining IV access would defeat the purpose of sedating the child; rather, emphasis should be placed upon having the intravenous equipment available and a practitioner skilled in establishing vascular access in pediatric patients immediately available.

### USUAL ADULT DOSE

**INTRAMUSCULARLY**

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

Midazolam hydrochloride should be injected deep in a large muscle mass. The recommended premedication dose of midazolam for good risk (ASA Physical Status I & II) adult patients below the age of 60 years is 0.07 to 0.08 mg/kg IM (approximately 5 mg IM) administered up to 1 hour before surgery.

**WARNINGs:** The dose must be individualized and reduced when IM midazolam is administered to patients with chronic obstructive pulmonary disease, other higher risk surgical patients, patients 60 or more years of age, and patients who have received concomitant narcotics or other CNS depressants (see ADVERSE REACTIONS).

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. The dose of 1 mg IM midazolam hydrochloride may suffice for some elderly patients if the anticipated intensity and duration of sedation is less critical. As with any potential respiratory depressant, these patients require observation for signs of cardiorespiratory depression after receiving IM midazolam.

**INTRAVENOUSLY**

Sedation/amnesia/amnesia for procedures (See INDICATIONS AND USAGE): Narcotic premedication results in less variability in patient response and a reduction in dosage of midazolam. For general anesthesia for induction and maintenance with potent inhalation anesthetics, midazolam should be titrated to effect (e.g., the initiation of slurred speech). Some patients may respond to as little as 1 mg. No more than 2.5 mg should be given over a period of at least 2 minutes. Wait an additional 2 or more minutes after each increment to fully evaluate the sedative effect. A total dose greater than 5 mg is not usually necessary to reach the desired endpoint.

If norectic premedication or other CNS depressants are used, patients will require approximately 30% less midazolam than unpremedicated patients.

1. Healthy Adults Below the Age of 60: Titrate slowly to the desired effect, (e.g., the initiation of slurred speech). Some patients may respond to as little as 1 mg. No more than 1.5 mg should be given over a period of no less than 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If further titration is necessary, continue to titrate, using smaller increments, to the desired level of sedation. Wait an additional 2 or more minutes after each increment to fully evaluate the sedative effect. A total dose greater than 5 mg is not usually necessary to reach the desired endpoint.

2. Patients Age 60 or Older, and Debilitated or Chronically Ill Patients: Because the danger of hypoventilation, airway obstruction, or apnea is greater in elderly patients and those with chronic disease states or decreased pulmonary reserve, and because the peak effect may take longer in these patients, increments should be smaller and the rate of injection slower. Titrate slowly to the desired effect, (e.g., the initiation of slurred speech). Some patients may respond to as little as 1 mg. No more than 1.5 mg should be given over a period of no less than 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If additional titration is necessary, it should be given at a rate of no more than 1 mg over a period of 2 minutes, waiting an additional 2 or more minutes each time to fully evaluate the sedative effect. Total doses greater than 3.5 mg are not usually necessary.

If concomitant CNS depressant medications are used in these patients, they will require at least 50% less midazolam than healthy young unpremedicated patients.
Individual response to the drug is variable, particularly when a narcotic premedication is not used. The dosage should be titrated to the desired effect according to the patient's age and clinical status.

When midazolam is used before other intravenous agents for induction of anesthesia, the initial dose of each agent may be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents.

Unpremedicated Patients: In the absence of premedication, an average adult under the age of 55 years will usually require an initial dose of 0.3 to 0.35 mg/kg for induction, administered over 20 to 30 seconds and allowing 2 minutes for effect. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used, induction may take up to 1 minute to complete with inhalational anesthetics. In resistant cases, up to 0.6 mg/kg total dose may be used for induction, but such larger doses may prolong recovery.

Unpremedicated patients over the age of 55 years usually require less midazolam for induction; an initial dose of 0.3 mg/kg is recommended.

Unpremedicated patients with severe systemic disease or other dehiscence usually require less midazolam for induction. An initial dose of 0.2 to 0.25 mg/kg will usually suffice, in some cases, as little as 0.15 mg/kg may suffice.

Premedicated Patients: When the patient has received sedative or narcotic premedication, particularly narcotic premedication, the range of recommended doses is 0.15 to 0.35 mg/kg. In average adults below the age of 55 years, a dose of 0.25 mg/kg, administered over 20 to 30 seconds and allowing 2 minutes for effect, will usually suffice. The initial dose of 0.2 mg/kg is recommended for good risk (ASA I & II) surgical patients over the age of 55 years. In some patients with severe systemic disease or dehiscence, as little as 0.15 mg/kg may suffice.

Narcotic premedication frequently used during clinical trials included fentanyl (1.5 to 2 mcg/kg IV, administered 5 minutes before induction), morphine (dosage individualized, up to 0.15 mg/kg IM), and meperidine (dosage individualized, up to 1 mg/kg IM). Sedative premedications were hydroxyzine pamoate (100 mg orally) and sodium secobarbital (200 mg orally). Except for intravenous fentanyl, administered 5 minutes before induction, all other premedications should be administered approximately 1 hour prior to the time anticipated for midazolam induction.

Midazolam can be used to sedate pediatric patients to facilitate less traumatic insertion of an intravenous catheter for titration of additional medication.

**Induction of Anesthesia:**

For induction of general anesthesia, before administration of other anesthetic agents.

**Usual Adult Dose:** If a loading dose is necessary to rapidly initiate sedation, 0.01 to 0.05 mg/kg (approximately 0.2 to 4 mg for a typical adult) may be given slowly or infused over several minutes. This dose may be repeated at 10 to 15 minute intervals until adequate sedation is achieved. For maintenance of sedation, the usual initial infusion rate is 0.02 to 0.1 mg/kg/hr (1 to 7 mg/hr). Higher loading or maintenance infusion rates may occasionally be required in some patients. The lowest recommended doses should be used in patients with residual effects from anesthetic drugs, or in those concurrently receiving other sedatives or opioids.

**CONTINUOUS INFUSION**

Midazolam hydrochloride 5 mg/mL formulation is recommended diluted to a concentration of 0.5 mg/mL with 0.9% sodium chloride or 5% dextrose in water.

Injectable midazolam hydrochloride can also be used during maintenance of anesthesia, for surgical procedures, as a component of balanced anesthesia. Effective narcotic premedication is especially recommended in such cases.

**OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (BAA/S)**

<table>
<thead>
<tr>
<th>Responsiveness</th>
<th>Speech</th>
<th>Facial Expression</th>
<th>Eyes</th>
<th>Composite Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>clears name spoken in normal tone</td>
<td>normal</td>
<td>normal</td>
<td>clear, no ptosis</td>
<td>5 (alert)</td>
</tr>
<tr>
<td>Lethargic response to name spoken in normal tone</td>
<td>mild slowing or thickening</td>
<td>mild relaxation</td>
<td>glazed or mild ptosis (less than half the eye)</td>
<td>3</td>
</tr>
<tr>
<td>Responds only after name is called loudly or repeatedly, slurring or prominent slowing of normal speech (clack jaw), slurred and marked words</td>
<td>-</td>
<td>3 (glazed) or more</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Does not respond to mild prodding or shaking</td>
<td>-</td>
<td>-</td>
<td>1 (deep sleep)</td>
<td></td>
</tr>
</tbody>
</table>

**FREQUENCY OF OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION COMPOSITE SCORES IN ONE STUDY OF PEDIATRIC PATIENTS UNDERGOING PROCEDURES WITH INTRAVENOUS MIDAZOLAM FOR SEDATION**

<table>
<thead>
<tr>
<th>Age Range (years)</th>
<th>n</th>
<th>OAA/S Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (deep sleep)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3-2</td>
<td>16</td>
<td>6 (36%)</td>
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<tr>
<td>&gt;2-5</td>
<td>22</td>
<td>9 (41%)</td>
</tr>
<tr>
<td>&gt;5-12</td>
<td>34</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>&gt;12-17</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Total (1-17)</td>
<td>90</td>
<td>16 (18%)</td>
</tr>
</tbody>
</table>

**INTRAMUSCULARLY**

For sedation/anesthesia prior to anesthesia or for procedures, intramuscular midazolam can be used to sedate pediatric patients to facilitate less traumatic insertion of an intravenous catheter for titration of additional medication.

**USUAL PEDIATRIC DOSE (NON-NEONATAL)**

Sedation after intramuscular midazolam is age and dose dependent: higher doses may result in deeper and more prolonged sedation. Doses of 0.1 to 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 have been used. Although not systematically studied, the total dose usually does not exceed 10 mg. If midazolam is given with an opioid, the initial dose of each must be reduced.
INTRAVENOUSLY BY 
INTERMITTENT INJECTION
For sedation/anxiolysis/amnesia prior to and during procedures or prior to anesthesia.

CONTINUOUS INTRAVENOUS INFUSION
For sedation/anxiolysis/amnesia in critical care settings.

HOW SUPPLIED
Package configuration containing preservative-free midazolam hydrochloride equivalent to 1 mg midazolam USP/mL.
MIDAZOLAM HYDROCHLORIDE
midazolam hydrochloride injection

**Product Information**
- **Product Type**: HUMAN PRESCRIPTION DRUG
- **Item Code (Source)**: NDC: 55648-
- **Route of Administration**: INTRAMUSCULAR, INTRAVENOUS
- **DEA Schedule**: CII

**Active Ingredient/Active Moiety**
- **Ingredient Name**: MIDAZOLAM HYDROCHLORIDE (UNII: W7TTW573JJ) (MIDAZOLAM - UNII: R60L0SM5BC)
- **Basis of Strength**: MIDAZOLAM
- **Strength**: 1 mg in 1 mL

**Inactive Ingredients**
- **Ingredient Name**: HYDROCHLORIC ACID (UNII: QTT17582CB)
- **Strength**: 1 mg in 1 mL
- **Ingredient Name**: SODIUM CHLORIDE (UNII: 451W47IQ8X)
- **Strength**: 1 mg in 1 mL
- **Ingredient Name**: SODIUM HYDROXIDE (UNII: 55X04QC32I)

**Packaging**

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<td>9/9/2012</td>
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</tr>
<tr>
<td>25</td>
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**Marketing Information**

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# MIDAZOLAM HYDROCHLORIDE

**midazolam hydrochloride injection**

## Product Information

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## Active Ingredient/Active Mixture

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<th>Ingredient Name</th>
<th>Basis of Strength</th>
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<tr>
<td>MIDAZOLAM HYDROCHLORIDE (UNII: W7TTW573JJ)</td>
<td>MIDAZOLAM - UNII:R60L0SM5BC</td>
<td>5 mg in 1 mL</td>
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## Inactive Ingredients

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<tr>
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<tr>
<td>HYDROCHLORIC ACID (UNII: QTT17582CB)</td>
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<td>2</td>
<td>NDC:55648-765-85</td>
<td>1 mL in 1 VIAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NDC:55648-765-86</td>
<td>2 mL in 1 VIAL</td>
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<td></td>
</tr>
<tr>
<td>4</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
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<td>10 in 1 CARTON</td>
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## Marketing Information

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## Labeler

- Wockhardt Limited (650693153)

## Registrant

- Wockhardt Limited (650693153)

## Establishment

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<th>Address</th>
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<th>Business Operations</th>
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<td>676257570</td>
<td>476237578</td>
<td>ANALYSIS(55648-764, 55648-765), MANUFACTURE(55648-764, 55648-765), PACK(55648-764, 55648-765), LABEL(55648-764, 55648-765)</td>
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