

45836K /Revised: April 2024

Midazolam Injection, USP

For intramuscular or intravenous use only NOT FOR USE IN NEONATES

Personnel and Equipment for Monitoring and Resuscitation
Adults and Pediatrics: Intravenous midazolam has been associated with resniratory denression and resniratory arrest lesnecially when used for sedation in noncritical care settings. In some cases, where this was not recognized promotly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous midazolam should be used only in hospital or ambulatory care settings, including physicians' and dental offices, that provide for continuous

settings, including physicians and dental ortices, that provide for continuous monitoring of respiratory and cardiac function, e.g., 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 r performing the procedure, should monitor the patient throughou

Risks from Concomitant Use with Opioids Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Monitor patients for respiratory ssion and sedation (see WARNINGS, PRECAUTIONS, Drug Interactions

<u>Individualization of Dosage</u> Midazolam must never be used without individualization of dosage. 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, sand 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

Neonates: Midazolam 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:

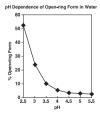
Midazolam Injection, USP is a water-soluble benzodiazenine available as a sterile, non pyrogenic parenteral dosage form for intravenous or intramuscular injection. Each mL contains midazolam hydrochloride equivalent to 1 mg or 5 mg midazolam compounded with 0.8% sodium chloride and 0.01% edetate disodium, with 1% benzyl alcohol as preservative; the pH is adjusted to 3 to 3.6 with hydrochloric acid and, if necessary,

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 following structural

C10H10CIFN0 • HCI

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

The following chart plots the percentage of midazolam present as the open-ring form as a function of pH in aqueous solutions. 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:

zolam is a short-acting benzodiazepine central nervous system (CNS) depressant

The effects of midazolam 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 tested the following day, 73% of the patients who received midazolam 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

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 umbar nuncture or hone marrow aspiration, 88% of natients had impaired recall vs 9% 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 is given IV as an anesthetic induction agent, induction of anesthesia occurs in approximately 1.5 minutes when parcotic premedication has been administered and in 2 to 2.5 minutes without narcotic premedication or other sedative premedication. Some impairment in a test of memory was noted in 90% of the patients studied. A dose response study of pediatric patients premedicated with 1 mg/kg intranuscular (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 to 140 seconds. This group was ompared with pediatric patients who were given thiopental 5 mg/kg IV; 6 out of 6 closed their eyes at  $20 \pm 3.2$  seconds. Midazolam did not dependably induce anesthesia at this ose 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 competency) 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 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 intracranial pressure with midazolam and with thiopental during intuation. No similar studies have been reported in pediatric patients.

The usual recommended intramuscular premedicating doses of midazolam do not

depress the ventilatory response to carbon dioxide stimulation to a clinically significant extent in adults. Intravenous induction doses of midazolam 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 natients with chronic ructive pulmonary disease (COPD). Sedation with IV midazolam does not adversely affect the mechanics of respiration (resistance, static recoil, most lung volume measure ments); total lung capacity and peak expiratory flow decrease significantly but static compliance and maximum expiratory flow at 50% of awake total lung capacity (V<sub>max</sub>) increase. In one study of pediatric patients under general anesthesia, intramuscular midazolam (100 mcg/kg 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 was associated with a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume and systemic vascular resistance. Slow heart rates (learn a fish 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 (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 0.30 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) ndicating non-linear kinetics in this dose range.

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The absolute bioavailability of the intramuscular route was greater than 90% in a crossove The absolute bloavailability of the inframuscular route was greater than 90% in a crossover study in which healthy subjects (n=17) were administered a 7.5 mg IV or IM dose. The mean peak concentration ( $C_{max}$ ) and time to peak ( $T_{max}$ ) following the IM dose was 90 ng/mL (20% CV) and 0.5 hour (50% CV).  $C_{max}$  for the 1-hydroxy metabolite following the IM dose was 8 ng/mL ( $T_{max}$ =1.0 hour). Following IM administration,  $C_{max}$  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 to 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 pediatric patients older than 1 year, midazolam is approximately 97% bound to plasma protein, principally albumin and that for 1-hydroxy metabolite

In vitro studies with human liver microsomes indicate that the hiotransformation 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 5% or less. Small amounts of a dihydroxy derivative 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-hvdroxv-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-hydroxy-midazolam 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, iver disease (cirrhosis) or conditions which diminish cardiac output and hepatic blood

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=5). Following a single IV infusion in 5 healthy volunteers, 45% to 57% of the dose was excreted in the urine as -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 pharmaco-

kinetic 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 during and following continuous intravenous infusion in pediatric natients 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.

pathways, underlying illness or debility.

normals (n=20) and obese patients (n=20) the mean half-life was greater in the obese group (5.9 vs 2.3 hours). 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.

Geridatric: In three parallel groups.

Geridatric: 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 in two studies and was similar to that of the younger patients in the other.

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 40% increase in the volume of distribution of midazolam.

Hepatic Impairment: 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 20%. In another study in 21 male natients with cirrhosis, without ascites and with normal kidney function as mined by creatinine clearance, no changes in the pharmacokinetics of midazolam -hydroxy-midazolam were observed when compared to healthy individuals.

Renal Impairment: 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 hours) in the ARF patients. The renal clearance of the 1-hydroxy-midazolam glucuronide was prolonged in the ARF group (4 vs 136 mL/min) and the half-life was prolonged (12 vs > 25 hours). 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 inchanged. 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 intersubject variability. Logistic regression analysis of sedation scores and steady-state plasma n 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)

# nformation concerning pharmacokinetic drug interactions with midazolam (see

# PRECAUTIONS)

### INDICATIONS AND USAGE: Midazolam injection is indicated:

Drug Interactions

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

# CONTRAINDICATIONS:

niectable midazolam is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with a known hyperschall by the drug. Benzodiazepines may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. Measurements of intraocular pressure in patients without eve disease show a moderate lowering following induction with midazolam; patients with oma have not been studied. Midazolam is not intended for intrathecal or epidural administration due to the presence

of the preservative benzyl alcohol in the dosage form. Midazolam is contraindicated for use in premature infants because the formulation contains benzyl alcohol (see **WARNINGS** and PRECAUTIONS. Pediatric Use).

### Personnel and Equipment for Monitoring and Resuscitation Prior to the intravenous administration of midazolam 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 for early signs of hypoventilation, airway obstruction, or apnea with means readily available (e.g., 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 (flurnazenii) is highly recommended. Vital signs should continue to be monitored during the recovery period. Because intravenous midazolam can depress respiration (see CLINICAL PHARMACOLOGY), especially when used concomitantly with opioid agonists and other sedatives (see **DOSAGE AND ADMINISTRATION**), it should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintaining a patent airway and supporting ventilation. When used for sedation/anxiolysis/amnesia, midazolan 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)

### Risks from Concomitant Use with Onioids

Concomitant use of benzodiazepines, including midazolam, and opioids may result in profound sedation, respiratory depression, coma, and death. If a decision is made to use pioids, monitor patients closely for respiratory depression and sedation (see PRECAUTIONS, Drug Interactions).

### Risk of Respiratory Adverse Events

Serious cardiorespiratory adverse events have occurred after administration of midazolam These have included respiratory depression, airway obstruction, oxygen desaturation, annea, 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 nediatric natients with hemodynamic instability. Hypotension occurred more frequently in the sedation studies in patients premedicated with a narcotic.

# Individualization of Dosane

Midazolam must never be used without individualization of dosage particularly when used with other medications capable of producing central nervous system depression. iee DOSAGE AND ADMINISTRATION for complete information

### Other Adverse Events

eactions such as agitation, involuntary movements (including tonic/clonic movement and muscle tremor), 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; however consideration should be given to the ibility 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. Reversal of such responses with flumazenil has been reported in pediatric patients.

### Concomitant Use of Central Nervous System Depressants Concomitant use of barbiturates, alcohol or other central nervous system depressant

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.

# **Debilitation and Comorbid Considerations**

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 unusuall sensitive to the respiratory depressant effect of midazolam. Pediatric and adult patient undergoing procedures involving the upper airway such as upper endoscopy or dental care, are particularly uninerable 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 is recommended, and the possibility of

will age, reduced initial observed in induction in Seconiminators, 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

### Risk of Intra-arterial Injection

There have been limited reports of intra-arterial injection of midazolam. 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 action 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 should only be administered intramuscularly or intravenously.

### Return to Full Cognitive Function

Midazolam is associated with a high incidence of partial or complete impairment of recall for the next several hours. 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 mi idualized. 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 longer. For pediatric patients, particular care should be taken to assure safe ambulation.

# Neonatal Sedation and Withdrawal Syndrome Use of midazolam late in pregnancy can result in sedation (respiratory depression,

lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness tremors, inconsolable crying, and feeding difficulties) in the neonate (see PRECAUTIONS Pregnancy). Monitor neonates exposed to midazolam during pregnancy or labor for signs sedation and monitor neonates exposed to midazolam during pregnancy for signs of withdrawal: manage these negnates accordingly

### Usage in Preterm Infants and Neonates

bage in Freein infants and neonates Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications (including midazolam) containing this preservative must take into account the total amount of benzyl alcohol administered. The recommended dosage range of midazolam for preterm and term infants includes amounts of benzy alcohol well below that associated with toxicity; however the amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommende dosages or other medications containing this preservative, the practitioner must conside the daily metabolic load of benzyl alcohol from these combined sources (see WARNINGS and PRECAUTIONS, Pediatric Use).

# Pediatric Neurotoxicity

Published animal studies demonstrate that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive deficits when used for onger than 3 hours. The clinical significance of these findings is not clear. However, base on the available data, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life but may extend out to approximately three years of age in humans (see PRECAUTIONS, Pregnancy and Pediatric Use and Animal Toxicology and/or Pharmacology).

Some published studies in children suggest that similar deficits may occur after repeated or prolonged exposures to anesthetic agents early in life and may result in adverse cognitive or behavioral effects. These studies have substantial limitations, and it is not clear if the observed effects are due to the anesthetic/sedation drug administration or other factors such as the surgery or underlying illness.

Anesthetic and sedation drugs are a necessary part of the care of children needing

surgery, other procedures, or tests that cannot be delayed, and no specific medications have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anesthesia should take into consideration the benefits of the procedure weighed against the potential risks. PRECAUTIONS:

# General

Intravenous doses of midazolam 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

### the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia. The efficacy and safety of midazolam in clinical use are functions of the dose adminis-

tered, the clinical status of the individual patient, and the use of concomitant medications capable of depressing the CNS. Anticipated effects range from mild sedation to deer 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 to the patient's underlying medical/surgical conditions, administer to the desired effect being certain to wait an adequate time for peak CNS effects of both midazolam and concomitant medications, and have the personne and size-appropriate equipment and facilities available for monitoring and intervention (see BOXED WARNING, WARNINGS and DOSAGE AND ADMINISTRATION). Practitioners administering midazolam must have the skills necessary to manage reasonably foresee able adverse effects, particularly skills in airway management. For information regarding withdrawal (see **DRUG ABUSE AND DEPENDENCE**).

Midazolam does not protect against the increase in intracranial pressure or against

# 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 The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect. loss, or other adverse ingestion of alcohol during benzodiazepine treatment.

  Inform your physician if you are pregnant or are planning to become pregnant.
- Inform your physician if you are nursing.Patients should be informed of the pharmacological effects of midazolam, such as
- sedation and amnesia, which in some natients may be profound. 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.

  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. 6. Effect of anesthetic and sedation drugs on early brain development Studies
- conducted in young animals and children suggest repeated or prolonged use of general anesthetic or sedation drugs in children younger than 3 years may have negative effects on their developing brains. Discuss with parents and caregivers the benefits, risks, and timing and duration of surgery or procedures requiring anesthetic and sedation drugs

### Advise pregnant females that use of midazolam late in pregnancy can result in sedation

(respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia rritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in newborns (see WARNINGS: Neonatal Sedation and Withdrawal Syndrome and PRECAUTIONS regnancy) Instruct nationts to inform their healthcare provider if they are pregnant

Instruct patients to notify their healthcare provider if they are breastfeeding or intend to breastfeed. Instruct breastfeeding patients receiving midazolam to monitor infants for excessive sedation, poor feeding, and poor weight gain, and to seek medical attention if they notice these signs. A lactating woman may consider pumping and discarding breastmilk for at least 4 to 8 hours after receiving midazolam for sedation or anesthesia to minimize drug exposure to a breastfed infant (see **Precautions**, **Nursing Mothers**).

## Drug Interactions

Effect of Concomitant Use of Benzodiazepines and Opioids
The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABA<sub>A</sub> sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential fo odiazepines to significantly worsen opioid-related respiratory depression exists. Monitor natients closely for respiratory depression and sedation

## Other CNS Depressants

The sedative effect of intravenous midazolam is accentuated by any concomitant dministered medication, which depresses the central nervous system, particularly onioids (e.g., morphine, meneridine and fentanyl) and also secobarbital and droperido 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)

### Other Drug Interactions

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 diltiazem veranamil ketoconazole and itraconazole. Thèse drug interactions sult 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 concentrations of oral midazolam was examined in a randomized crossover stud

n=8). Cimetidine increased the mean midazolam steady-state concentration from

57 to 71 ng/mL. Ranitidine increased the mean steady-state concentration to 62 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, three

times a day, for 1 week (n=6), reduced the clearance of midazolam following a single 0.5 mg/kg IV doss. The half-life was approximately doubler 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 diltiazem (60 mg three times a day) and verapamil (80 mg three times a day) on the pharmacokinetics and pharmacodynamics of oral 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 diltiazem. No interaction was observed in healthy subjects between midazolam and nifedipine.

In a placebo-controlled study where saguinavir or placebo was administered orally as a 1,200 mg dose, three times a day, for 5 days (n=12), a 56% reduction in the clearance of midazolam following a single 0.05 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 for premedication in adults. The intravenous administration of midazolam decreases the minimum alveolar concen

tration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of midazolam administered; no similar studies have been carried out i pediatric patients but there is no scientific reason to expect that pediatric patients would spond 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, onset or duration in adults. Midazolam does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium and does not protect against the increased intracrania pressure noted following administration of succinvlcholine. Midazolam does not cause a clinically significant change in dosage, onset or duration of a single intubating dose o succinvlcholine; 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

# 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 hepatic tumors. In high-dose male rats there was a small but statistically significant increase in benign thyroid follicular cell

tumors. Dosages of 9 mg/kg/day of midazolam maleate (4 times a human induction dose of 0.35 mg/kg based on body surface area comparison) 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 typhimuriun (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes or in the

Impairment of Fertility: Male rats were treated orally with 1, 4, or 16 mg/kg midazolam beginning 62 days prior to mating with female rats treated with the same doses for 14 days prior to mating to Gestation Day 13 or Lactation Day 21. The high dose produced an equivalent exposure (AUC) as 4 mg/kg intravenous midazolam (1.85 times the human induction dose of 0.35 mg/kg based on body surface area comparison). There were no adverse effects on either male or female fertility noted.

# Risk Summary

micronucleus test in mice

Neonates born to mothers using benzodiazepines late in pregnancy have been reported to experience symptoms of sedation and/or neonatal withdrawal (see WARNINGS: Neonatal Sedation and Withdrawal Syndrome, and Clinical Considerations). Available data from ublished observational studies of pregnant women exposed to benzodiazepines do not port a clear association with benzodiazepines and major birth defects (see **Data**).

outcomes. In the U.S. general population, the estimated risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. Clinical Considerations

# Fetal/Neonatal Adverse Reactions

Benzodiazepines cross the placenta and may produce respiratory depression, hypotonia, and sedation in neonates. Monitor neonates exposed to Midazolam injection during regnancy or labor for signs of sedation, respiratory depression, hypotonia, and feeding roblems Monitor neonates exposed to Midazolam injection during pregnancy for signs f withdrawal. Manage these neonates accordingly (see WARNINGS: Neonatal Sedation and Withdrawal Syndrome).

Published data from observational studies on the use of benzodiazepines during preg-nancy do not report a clear association with benzodiazepines and major birth defects.

Although early studies reported an increased risk of congenital malformations with diazepam and chlordiazepoxide, there was no consistent pattern noted. In addition, the majority of more recent case-control and cohort studies of benzodiazepine use during regnancy, which were adjusted for confounding exposures to alcohol, tobacco and other nedications, have not confirmed these findings.

# nimal Nata

Pregnant rats were treated with midazolam using intravenous doses of 0.2, 1, and mg/kg/day (0.09, 0.46, and 1.85 times the human induction dose of 0.35 mg/kg ased on body surface area comparisons) during the period of organogenesis (Gestation lay 7 through 15). Midazolam did not cause adverse effects to the fetus at doses of up to .85 times the human induction dose. All doses produced slight to moderate ataxia. The

high dose produced a 5% decrease in maternal body weight gain compared to control. Preparant rabbits were treated with midazolam using intravenous doses of 0.2, 0.6, and 2 mg/kg/day (0.09, 0.46, and 1.85 times the human induction dose of 0.35 mg/kg ased on body surface area comparisons) during the period of organogenesis (Gestation bay 7 to 18). Midazolam did not cause adverse effects to the fetus at doses of up to 1.85 times the human induction dose. The high dose was associated with findings of

taxia and sedation but no evidence of maternal toxicity. Pregnant rats were administered midazolam using intravenous doses of 0.2, 1, and mg/kg/day (0.09, 0.46, and 1.85 times the human induction dose of 0.35 mg/kg based A myndudy (U.S.) 1947, alar 1955 miles are infinited induction dose or 35 mg/ng days on body surface area comparisons) during late gestation and through lactation (Gestation Day 15 through Lactation Day 21). All doses produced ataxia. The high dose produced a slight decrease in maternal body weight gain compared to control. There were no clear adverse effects noted in the offspring. The study included no functional assessments of the pups, such as learning and memory testing or reproductive capacity.

In a published study in primates, administration of an anesthetic dose of ketamine to hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the etus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis

# correlates with long-term cognitive deficits (see WARNINGS, Pediatric Neurotoxicity, PRECAUTIONS, Pediatric Use, and Animal Toxicology and/or Pharmacology). Nursing Mothers

he effects of midazolam on lactation are unknown. Because of the potential for serious dverse reactions, including sedation and withdrawal symptoms in breastfed infants, dvise patients that breastfeeding is not recommended during treatment with midazolam.

There are reports of sedation, poor feeding and poor weight gain in infants exposed to enzodiazepines through breast milk. Based on data from published studies, midazolam

present in human milk in low levels (see Data). There are no data on the effects of midazolam on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Midazolam injection and any potential adverse effects on

infants exposed to Midazolam injection through breast milk should be monitored for sedation, poor feeding and poor weight gain. A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk during treatment for a range of t least 4 to 8 hours after midazolam administration in order to minimize drug exposure o a breastfed infant.

the breastfed infant from Midazolam injection or from the underlying maternal condition

### Pediatric Use he 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 nonitoring and dosage quidelines see BOXED WARNING, CLINICAL PHARMACOLOGY VDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, OVERDOSAGE and DOSAGE AND ADMINISTRATION LINITIES ADJULT 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 do 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 healthcare 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 should not be administered by rapid injection in the neonatal population evere hypotension and seizures have been reported following rapid IV administration, particularly with concomitant use of fentanyl.

Midazolam contain benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome", (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages greater than 99 mg/kg/day in neonates and low-birth-weight neonates. Additional

symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-hirth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

<u>Animal Data</u>
Published juvenile animal studies demonstrate that the administration of anesthetic and sedation drugs, such as Midazolam Injection USP, that either block NMDA receptors or potentiate the activity of GABA during the period of rapid brain growth or synaptogenesis, results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of destation through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of ketamine that produced a light surgical plane of anesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer of isoflurane increased neuronal cell loss. Data from isoflurane-treated rodents and ketamine-treated primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory. The clinical significance of these nonclinical findings is not known, and healthcare providers should balance the benefits of appropriate anesthesia in pregnant women, neonates, and young children who require procedures with the notential risks suggested by the nonclinica data (see WARNINGS, Pediatric Neurotoxicity, PRECAUTIONS, Pregnancy, and Anima Inxicology and/or Pharmacology)

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate diazepam, hydroxyzine, d-tubocurarine, succinylcholine and other nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed in adults or pediatric natients. In peopates, however evere 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

### 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 longe to recover completely after midazolam administration for the induction of anesthesia Administration of IM and IV midazolam to elderly and/or high-risk surgical patier has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received othe central nervous system depressants capable of depressing respiration, especially narcotics (see DOSAGE AND ADMINISTRATION).

Specific dosing and monitoring guidelines for genatric 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 (23.3% 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 is administered with other medications canable 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

The following additional adverse reactions were reported after intramuscular

headache (1.3%)	Local effects at IM Injection site
	pain (3.7%)
	induration (0.5%)
	redness (0.5%)
	muscle stiffness (0.3%)

Administration of IM midazolam to elderly and/or higher risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespira tory depression. In most of these cases, the patients also received other central ner system depressants capable of depressing respiration, especially narcotics (see DOSAGI AND ADMINISTRATION)

The following additional adverse reactions were reported subsequent to intravenous administration as a single sedative/anxiolytic/amnestic agent in adult patients:

_		
hiccoughs (3.9%)	Local effects at the IV site	
nausea (2.8%)	tenderness (5.6%)	
vomiting (2.6%)	pain during injection (5.0%)	
coughing (1.3%)	redness (2.6%)	
"oversedation" (1.6%)	induration (1.7%)	
headache (1.5%)	phlebitis (0.4%)	
drowsiness (1.2%)		

### Pediatric Patients

The following adverse events related to the use of IV midazolam in pediatric patients wer reported in the medical literature: desaturation 4.6%, apnea 2.8%, hypotension 2.7% paradoxical reactions 2.0%, hiccough 1.2%, seizure-like activity 1.1% and nystagmus 1.1% The majority of airway-related events occurred in patients receiving other CNS depressing medications and in patients where midazolam was not used as a single sedating agen

For information concerning hypotensive episodes and seizures following the admir neonates (see BOXED WARNING, CONTRAINDICATIONS WARNINGS and PRECAUTIONS).

- Other adverse experiences, observed mainly following IV injection as a single sedative/ anxiolytic/amnesia agent and occurring at an incidence of <1.0% in adult and pediatric patients, are as follows Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing,
- shallow respirations, airway obstruction, tachypnea Cardiovascular Bigenniny, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm
- Gastrointestinal: Acid taste, excessive salivation, retching CNS/Neuromuscular: Retrograde amnesia, euphoria, hallucination, confusion, arqui mentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia dizziness, dysphoria, slurred speech, dysphonia, paresthesia

Special Senses: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements USUAL ADULT DOSE of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance,

light-headedness Integumentary: Hive-like elevation at injection site, swelling or feeling of burning,

Hypersensitivity: Allergic reactions including anaphylactoid reactions, hives, rash, Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma

### DRUG ABUSE AND DEPENDENCE:

warmth or coldness at injection site

Midazolam is a Schedule IV control substance.

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 cyno-

molgus 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 diazenam

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 discontinuance 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.

# OVERDOSAGE

Unical Presentation rerdosage of benzodiazepines is characterized by central nervous system depression ranging from drowsiness to coma. In mild to moderate cases, symptoms can include drowsiness, confusion, dysarthria, lethargy, hypnotic state, diminished reflexes, ataxia, and hypotonia. Rarely, paradoxical or disinhibitory reactions (including agitation, irritability, sivity, violent behavior, confusion, restlessness, excitement, and talkativeness may occur. In severe overdosage cases, patients may develop respiratory depression and coma. Overdosage of benzodiazepines in combination with other CNS depressants (including alcohol and opioids) may be fatal (see WARNINGS: Abuse, Misuse, and Addiction). Markedly abnormal (lowered or elevated) blood pressure, heart rate, or respiratory rate raise the concern that additional drugs and/or alcohol are involved in the overdosage

### Management of Overdose

Management of verticose n managing benzodiazepine overdosage, employ general supportive measures, including ntravenous fluids and airway maintenance. Flumazenil, a specific benzodiazepine eceptor antagonist indicated for the complete or partial reversal of the sedative effects of benzodiazepines in the management of benzodiazepine overdosage, can lead to withdrawal and adverse reactions, including seizures, particularly in the context of mixed overdosage with drugs that increase seizure risk (e.g., tricyclic and tetracyclic antidepressants) and in patients with long-term benzodiazepine use and physical dependency. The risk of withdrawal seizures with flumazenil use may be increased in patients with epilepsy. Flumazenil is contraindicated in patients who have received a benzodiazenine for control of a potentially life-threatening condition (e.g., status epilepticus). If the decision is made to use flumazenil, it should be used as an adjunct to, not as a substitute for, upportive management of benzodiazepine overdosage. See the flumazenil injection rescribing Information

Consider contacting a poison center (1-800-222-1222), poisoncontrol.org, or a medical toxicologist for additional overdosage management recommendations.

### DOSAGE AND ADMINISTRATION:

NOTE: CONTAINS BENZYL ALCOHOL (see WARNINGS and PRECAUTIONS, Pediatric Use) Midazolam injection is a potent sedative agent that requires slow administration and ndividualization of dosage. Clinical experience has shown midazolam to be 3 to 4 times

as potent per mg as diazepam.

BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE

BETT STORY ADVENTION AND LIFE-THREATENING CARDIORESPIRATORY ADVENTION AND L EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM MIDAZOLAM INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS Excessive single doses or rapid intravenous administration may result in respiratory depression, airway obstruction and/or arrest. The potential for these latter effects is increased in debilitated patients, those receiving concomitant medications capable of depressing the CNS, and patients without an endotracheal tube but undergo procedure involving the upper airway such as endoscopy or dental (see **BOXED WARNING** and WARNINGS

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported in adult and pediatric patients. Should such reactions occur, caution should be exercised before continuing administration of midazolam (see WARNINGS). Midazolam injection should only be administered IM or IV (see WARNINGS)

Care should be taken to avoid intra-arterial injection or extravasation (see WARNINGS).

Midazolam injection may be mixed in the same syringe with the following frequently

used premedications: morphine sulfate, meperidine, atropine sulfate or scopolamine. Midazolam, 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

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).

(i.e., pulse oxiniterly).

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/analgesia 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) nidazolam should be allowed between doses to minimize the potential for oversed tion. 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 Pediatrics: For deeply sedated pediatric patients a dedicated individual, other than

the practitioner performing the procedure, should monitor the patient throughout the 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.

INTRAMUSCUL ARIV For preoperative sedation anxiolysis/amnesia nduction of sleepiness or drowsiness and relief to impair memory o

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

For intramuscular use, The dose must be individualized and reduced when midazolam should be injected deep in a large obstructive pulmonary disease, other higher risk surgical patients, patients 60 or more years of age, and patients 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 preopera-tive period. The dose of 1 mg IM midazolam may suffice for some older patients if the anticipated intensity and duration of sedation is less critical. As with any potential respiratory depressant these nations require observation for signs of cardiorespiratory depression after receiving IM midazolam.

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

When used for sedation/anxiolysis/amnesia for a procedure,

dosage must be individualized and titrated. Midazolan

should always be titrated slowly; administer over at least

fully evaluate the sedative effect. Individual response will vary with age, physical status and concomitant medica-

tions, but may also vary independent of these factors (see WARNINGS concerning cardiac/respiratory arrest/airway

obstruction/hypoventilation)

minutes and allow an additional 2 or more minutes to

### INTRAVENOUSLY Sedation/anxiolysis/

(See INDICATIONS AND USAGE): Narcotic n less variability in patient response and a reduction in dosage of midazolam For peroral procedures, the use of ar innropriate topical anes For bronchoscopic procedures, the use o narcotic premedication is

recommended for seda ion/anxiolysis/amnesia for procedures to facilitate the 1 mg/mL and the may be diluted with 5% dextrose in water

Midazolam injection 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 2.5 mg should be given over a period of at least 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If further titration is necessary continue to titrate using small increments to the appropriate 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. If narcotic premedication or other CNS depressant

are used, patients will require approximately 30% less nidazolam than unpremedicated patients 2. Patients Age 60 or Older, and Debilitated or Chronically

III 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 premedications are

used in these patients, they will require at least 50% less midazolam than healthy young unpremedicated patients.

3. Maintenance Dose: Additional doses to maintain the desired level of sedation may be given in increments of 25% of the dose used to first reach the sedative endpoint, but again only by slow titration, especially in the elderly and chronically ill or debilitated nation hese additional doses should be given only after a thorough clinical evaluation clearly indicates the need

administration of other anesthetic agents.

Induction of Anesthesia: Individual response to the drug is variable, particularly when For induction of general a narcotic premedication is not used. The dosage should anesthesia, before 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 instead be completed 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 quire less midazolam for induction; an initial dose of 0.3 mg/kg is recommended. Unpremedicated patients with severe systemic disease or other debilitation 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 natient has received

sedative or narcotic premedication, particularly narcotic emedication, the range of recommended doses is 0.15 to

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 debilitation, 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, adminis 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 namoate (100 mg orally) and sodium secobarbital (200 mg orally). Except for intravenous fentanyl, administered 5 minutés before induction, all other pre-medications should be administered approximately 1 hour prior to the time anticipated for midazolam induction.

surgical procedures, as a anesthesia Effective especially recommended

Injectable midazolam can Incremental injections of approximately 25% of the induction also be used during maintenance of anesthesia, for dose should be given in response to signs of lightening of anesthesia and repeated as necessary.

CONTINUOUS INFUSION or continuous infusion midazolam 5 mg/mL for-mulation is recommended diluted to a concentration of 0.5 mg/mL with 0.9% sodium chloride or 5% dextrose in water.

Usual Adult Dose: If a loading dose is necessary to rapidly initiate sedation. 0.01 to 0.05 mg/kg (approximately 0.5 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 0.10 mg/kg/hr (1 to 7 mg/hr). Higher loading or maintenance infusion rates may occasionally be required in some natients. The lowest recommended doses should be used in patients with residual effects from anesthetic drugs, or in those concurrently receiving other sedatives or opioids

Individual response to midazolam is variable. The influsion rate should be titrated to the desired level of sedation, taking into account the patient's age, clinical status and current medications. In general, midazolam should be infused at the lowest rate that produces the desired level of sedation Assessment of sedation should be performed at regular intervals and the midazolam infusion rate adjusted up or down by 25% to 50% of the initial infusion rate so as to assure adequate titration of sedation level. Larger adjust-

ments or even a small incremental dose may be necessary if rapid changes in the level of sedation are indicated. In addition the infusion rate should be decreased by 10% to 25% every few hours to find the minimum effective infusion rate. Finding the minimum effective infusion rate decreases the potential accumulation of midazolam and provides for the most rapid recovery once the infusion is minated. Patients who exhibit agitation, hypertension, o tachycardia in response to noxious stimulation, but who are otherwise adequately sedated, may benefit from concurrent administration of an opioid analgesic. Addition of an opioid will generally reduce the minimum effective midazolam

# PEDIATRIC PATIENTS

Responds readily

to name spoken in

Letharnic response

to name spoken in

Responds only after name is called loudly

Responds only after

mild prodding or

Does not respond

shaking

to mild prodding or

and/or repeatedly

normal tone

normal tone

UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GEN-FRALLY RECEIVE INCREMENTS OF MIDAZOLAM ON A MG/KG BASIS. As a group, pediatric patients generally require higher dosages of midazolam (mg/kg) than do adults. Younger (less than six years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients, and may require close monitoring (see tables below). 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. For appropriate patient monitoring, see BOXED WARNING, WARNINGS, DOSAGE AND ADMINISTRATION, Monitoring. The healthcare practi-tioner who uses this medication in pediatric patients should be aware of and follow accepted professional guidelines for pediatric sedation appropriate to their situation.

Eves

clear, no ptosis

ptosis (less than

half the eye)

glazed and

(half the eve or

OBSERVER'S ASSESSMENT OF

ALERTNESS/SEDATION (OAA/S)

Assessment Categories

Sneech

normal

mild slowing or

thickening

slurring or

prominent

slowing

recognizable

Facial

normal

marked

relaxation

(slack iaw)

# CONTINUOUS INTRAVENOUS

Composite

Score

5 (alert)

1 (deep sleep)

For sedation/anxiolysis

# amnesia in critical care settings. 0.2 mg/kg administered over at least 2 to 3 minutes can be used to establish the desired clinical effect IN PATIENTS WHOSE TRACHEA IS INTUBATED. (Midazolam should loading dose may be followed by a continuous intravenous

not be administered as a rapid intravenous dose.) This infusion to maintain the effect. An infusion of midazolam has been used in patients whose trachea was intubated but who were allowed to breathe spontaneously. Assisted ventilation is recommended for pediatric patients who are receiving other central nervous system depressan medications such as opioids. Based on pharmacokinetic parameters and reported clinical experience, continuous a rate of 0.06 to 0.12 mg/kg/hr (1 to 2 mcg/kg/min). The 25% of the initial or sub sequent infusion rate) as required or supplemental intravenous doses of midazolam can be administered to increase or maintain the desired effect Frequent assessment at regular intervals using standard pain/sedation scales is recommended. Drug elimination may be delayed in patients receiving erythro other P450-3A4 enzyme inhibitors (see PRECAUTIONS, **Drug Interactions**) and in patients with liver dysfunction, low cardiac output (especially those requiring inotropic support), and in neonates.

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

(years)	n	UAA/S Score				
		1 (deep sleep)	2	3	4	5 (alert)
1 to 2	16	6 (38%)	4 (25%)	3 (19%)	3 (19%)	0
>2 to 5	22	9 (41%)	5 (23%)	8 (36%)	0	0
>5 to 12	34	1 (3%)	6 (18%)	22 (65%)	5 (15%)	0
>12 to 17	18	0	4 (22%)	14 (78%)	0	0
Total (1 to 17)	90	16 (18%)	19 (21%)	47 (52%)	8 (9%)	0

INTRAVENOUSLY

INJECTION

BY INTERMITTENT

## INTRAMUSCULARLY USUAL PEDIATRIC DOSE (NON-NEONATAL)

For sedation/anxiolysis/ Sedation after intramuscular midazolam is age and dose dependent: higher doses may result in deeper and amnesia prior to anesmore prolonged sedation. Doses of 0.1 to 0.15 mg/kg are usually effective and do not prolong emergence from thesia or for procedures can be used to sedate general anesthesia. For more anxious patients, doses up to 0.5 mg/kg have been used. Although not systematically facilitate less traumatic studied the total dose usually does not exceed 10 mg midazolam is given with an opioid, the initial dose of each insertion of an intravenous catheter for titration of must be reduced. additional medication.

# LISUAL PEDIATRIC DOSE (NON-NEONATAL)

For sedation/anxiolysis/ It should be recognized that the depth of sedation/anxiolysis amnesia prior to and during procedures or prior during procedures or prior during by the security of procedures or prior during procedures or prior during the security of prior during the securi anxiolysis in the preoperative period is quite different from the deep sedation and analgesia required for an endoscopic procedure in a child. For this reason, there is a broad range of dosage. For all pediatric patients, regardless of the indications for sedation/anxiolysis, it is vital to titrate midazolam and other concomitant medications slowly to the desired clinical effect. The initial dose of midazolam should be administered over 2 to 3 minutes. Since midazolam is water soluble, it takes approximately three times longe than diazepam to achieve peak EEG effects, therefore one must wait an additional 2 to 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. If other medications capable of depressing the CNS are coadministered, the neak effect of those concomitant medications must be considered and the dose of midazolam adjusted. The importance of drug titration to effect is vital to the safe sedation/anxiolysis of the pediatric natient. The total dose of midazolam will depend on nation esponse, the type and duration of the procedure, as well as the type and dose of concomitant medications.

- Pediatric patients less than 6 months of age: Limited information is available in non-intubated pediatric patients less than 6 months of age. It is uncertain when the patient transfers from neonatal physiology to pediatric physiology, therefore the dosing recommendations are unclear. Pediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful monitoring are essential.
- 2. Pediatric patients 6 months to 5 years of age: Initial dose 0.05 to 0.1 mg/kg; total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint but usuall does not exceed 6 mg. Prolonged sedation and risk of proventilation may be associated with the higher doses
- 3. Pediatric patients 6 to 12 years of age: Initial dose 0.025 to 0.05 mg/kg; total dose up to 0.4 mg/kg may be needed to reach the desired end-point but usually does not exceed 10 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses. 4. Pediatric patients 12 to 16 years of age: Should be dosed
- as adults. Prolonged sedation may be associated with higher doses; some patients in this age range will require higher than recommended adult doses but the total dose usually does not exceed 10 mg.

  The dose of midazolam must be reduced in patients
- premedicated with opioid or other sedative agents including midazolam. Higher risk or debilitated patients may require lower dosages whether or not concomitant sedating medications have been administered (see WARNINGS).

# USUAL PEDIATRIC DOSE (NON-NEONATAL)

To initiate sedation, an intravenous loading dose of 0.05 to

### Hypotension may be observed in patients who are critically ill, particularly those receiving opioids and/or when midazolam is rapidly administered. When initiating an infusion with midazolam in hemody-

namically compromised patients, the usual loading dose of midazolam should be titrated in small increments and the patient monitored for hemodynamic instability (e.g hypotension). These patients are also vulnerable to the respiratory depressant effects of midazolam and require careful monitoring of respiratory rate and oxygen saturation.

# CONTINUOUS

LISUAL NEONATAL DOSE

For sedation in critical Based on pharmacokinetic parameters and reported clinical experience in preterm and term neonates WHOSE TRACHEA WAS INTUBATED, continuous intravenous infusions of midazolam should be initiated at a rate of 0.03 mg/kg/h 0.5 mcg/kg/min) in neonates <32 weeks and 0.06 mg/kg/hr (1 mcg/kg/min) in neonates >32 weeks. 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. The rate of infusion should be carefully and frequently reassessed, particuarly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug ccumulation. This is particularly important because of the potential for adverse effects related to metabolism of the benzyl alcohol (see WARNINGS, Usage in Preterm Infants and Neonates).

Hypotension may be observed in patients who are criti-

cally ill and in preterm and term infants, particularly those receiving fentanyl and/or when midazolam is administered rapidly. Due to an increased risk of annea extreme caution is advised when sedating preterm and former preterm patients whose trachea is not intubated

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit

Midazolam Injection, USP, package configurations containing midazolam hydrochloride equivalent to 1 mg midazolam/mL

Product Code	Unit of Sale	Strength	Each
RF410102	NDC 63323-411-27 Unit of 25	2 mg per 2 mL (1 mg per mL), 2 mL fill, in a 2 mL vial.	NDC 63323-411-22 2 mL Vial This product contains an RFID.
410102	NDC 63323-411-12	2 mg per 2 mL (1 mg per mL),	NDC 63323-411-15
	Unit of 25	2 mL fill, in a 2 mL vial.	2 mL Vial
411105	NDC 63323-411-25	5 mg per 5 mL (1 mg per mL),	NDC 63323-411-18
	Unit of 25	5 mL fill, in a 5 mL vial.	5 mL Vial
410110	NDC 63323-411-10	10 mg per 10 mL (1 mg per mL),	NDC 63323-411-13
	Unit of 10	10 mL fill, in a 10 mL vial.	10 mL Vial

Midazolam Injection, USP package configurations containing midazolam hydrochloride equivalent to 5 mg midazolam/mL

Product Code	Unit of Sale	Strength	Each
411201	NDC 63323-412-25	5 mg per 1 mL (5 mg per mL),	NDC 63323-412-18
	Unit of 25	1 mL fill, in a 2 mL vial.	2 mL Vial
410202	NDC 63323-412-02	10 mg per 2 mL (5 mg per mL),	NDC 63323-412-03
	Unit of 10	2 mL fill, in a 2 mL vial.	2 mL Vial
410210	NDC 63323-412-10	50 mg per 10 mL (5 mg per mL),	NDC 63323-412-13
	Unit of 10	10 mL fill, in a 10 mL vial.	10 mL Vial

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]

The container closure is not made with natural rubber latex.

Animal Toxicology and/or Pharmacology
Published studies in animals demonstrate that the use of anesthetic agents during the
period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morpholog and neurogenesis. Based on comparisons across species, the window of vulnerabilit to these changes is believed to correlate with exposures in the third trimester through the st several months of life, but may extend out to approximately 3 years of age in humans

In primates, exposure to 3 hours of an anesthetic regimen that produced a light surgical plane of anesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with subtle but prolonged cognitive deficits in learning and memory. The clinical significance of these nonclinical findings is not known, and healthcare providers should balance the benefits of appropriate anesthesia in neonates and young children who require procedures against the potential risks suggested by the nonclinical data (see WARNINGS, *Pediatric Neurotoxicity* and PRECAUTIONS, Pregnancy and Pediatric Use

For more information concerning this drug, please call Fresenius Kabi USA, LLC at

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.



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