

IN THE ARKANSAS SUPREME COURT

State of Arkansas *et al.*

Appellants

v. Case No. CV-17-317

McKesson Medical-Surgical, Inc.

Appellee

Motion for Leave to File *Amicus* Brief

Fresenius Kabi USA, LLC, and West-Ward Pharmaceuticals Corp. (the Manufacturers), for their motion for leave to file *amicus* brief under Arkansas Supreme Court Rule 4-6, state:

- 1. The Manufacturers have unique insight into McKesson's arguments and the public-health risks of using the medicines here for capital punishment.**

McKesson has raised issues that include the troubling circumstances under which the State of Arkansas obtained McKesson's vecuronium bromide. As the apparent manufacturers of the other two drugs that Arkansas plans to use in the executions, the Manufacturers provide unique insight into

McKesson's arguments and the public-health risks of using these drugs for capital-punishment purposes.

1.1. Fresenius Kabi USA, LLC (Fresenius Kabi)

Fresenius Kabi is focused on the care of critically and chronically ill patients. One drug in its portfolio is potassium chloride, which is marketed globally, including in the United States through Fresenius Kabi USA, LLC.¹ Fresenius Kabi supplies a significant portion of the potassium chloride in the United States. Over the past several years, the United States has faced shortages of potassium chloride – most recently listed on

¹ Fresenius Kabi USA, LLC was known until August 2012 as APP Pharmaceuticals, LLC, when its name was changed. Certain of its drugs still carry labeling and packaging referring to APP Pharmaceuticals. For simplicity, we refer to Fresenius Kabi throughout this motion even where labeling reflects the name APP.

April 4, 2017² – and Fresenius Kabi has worked closely with the U.S. Food and Drug Administration during these times to ensure supply of this drug.

Fresenius Kabi has sought to ensure that its medicines will not be used for capital punishment. It has made its position clear in public, has notified state authorities and departments of correction, and has instituted distribution controls to ensure that the drugs are only used to save and sustain lives of patients. As more fully explained in the *amicus* brief, Fresenius Kabi has instituted measures to safeguard supply of lifesaving medicines for patient care by prohibiting the use of certain of its products for lethal injection.

If the State of Arkansas has obtained Fresenius Kabi-manufactured potassium chloride to use in capital punishment—as appears to be the case—it would have been contrary to and in

² See <https://www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortage-Detail.aspx?id=696> (last visited on April 20, 2017).

violation of the company's contractual supply-chain controls. *See* Exhibit A (redacted label and package insert showing that the potassium chloride originated from Fresenius Kabi, which has been represented to be the potassium chloride that may be used in the impending lethal injections in Arkansas). Fresenius Kabi seeks to appear in this matter as *amicus curiae* to share with the Court the supply-chain controls that it and other pharmaceutical companies have implemented and the public-health risks of diverting lifesaving medicines from the healthcare industry to the Department of Correction for capital-punishment purposes.

2.2. West-Ward Pharmaceuticals Corp. (West-Ward)

West-Ward, a wholly-owned subsidiary of Hikma PLC, manufactures and supplies high-quality, generic medicines across the United States, including midazolam. The World Health Organization has included midazolam on its “List of Essential Medicines” as a sedative.

http://www.who.int/medicines/publications/essentialmedicines/EML_2015_FINAL_amended_NOV2015.pdf?ua=1 (last visited April 20, 2017). West-Ward is an important supplier of

midazolam for not only Arkansas but also the entire United States, supplying approximately one-third of the United States market demand by volume for this critical medicine.

West-Ward has also sought to ensure that its medicines will not be used for capital punishment since, being committed to improving and saving lives, it is inconsistent with West-Ward's mission and core values. West-Ward has publicly made its position clear through the posting of its position on its and its corporate parent's websites and through direct correspondence with attorneys general, governors, and departments of correction in various states. Further, West-Ward instituted distribution controls to ensure that the drugs are not used in connection with lethal-injection protocols, including instructing that such medicines be sold only to pre-authorized customers who agree not to sell them to departments of correction, other entities that intend to use them for lethal injection, secondary distributors, or retail pharmacies.

Despite these controls, it appears as if West-Ward's midazolam may have been obtained and is intended to be used in

connection with capital punishment in Arkansas. *See* Exhibit B (redacted label and package insert of midazolam product alleged to be used in the executions). This suggests a violation of the above-described contractual controls. West-Ward seeks to appear in this matter as *amicus curiae* to share with the Court the public-health risks of diverting this critical medicine from advancing human health and quality of life to ending human life.

2. Because the proposed *amicus* brief here involves an issue of public importance and the Manufacturers have unique insight into the arguments raised, the Court should allow the brief.

The Court has “traditionally welcomed” *amicus* briefs where there is a “possibility that an *amicus* brief will have legal significance.” *Ferguson v. Brick*, 279 Ark. 168, 173, 649 S.W.2d 397, 399 (1983). If a nonparty raises issues that might be of legal significance or if the nonparty has unique information or perspectives, then this Court allows the nonparty to file an *amicus* brief. *See Holiday Inn v. Coleman*, 29 Ark. App. 157, 157, 778 S.W.2d 649, 649 (1989).

As shown above, the Manufacturers bring unique knowledge, experience, and perspective to this case. They manufacture lifesaving medicines. But the State of Arkansas appears to be about to use some of those medicines to end life rather than save it. This is so despite the Manufacturers' implementation of distribution protocols to prevent this and the public-health risk that could result from use of these medicines for capital punishment.

As manufacturers of the drugs at issue, the Manufacturers are in a position to highlight the public-health risk of using the drugs as part of Arkansas's lethal-injection program. They respectfully ask the Court to grant their motion for leave to file the *amicus* brief attached as Exhibit C to this motion.

Respectfully submitted,

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By: /s/ Brett D. Watson
Brett D. Watson
Ark. Bar No. 2002182

Certificate of Service

A copy of the foregoing has been conventionally filed and notice of filing has been sent to all counsel of record on April 20, 2017, via the CM/ECF system.

/s/ Brett D. Watson
Brett D. Watson

**CERTIFICATE OF COMPLIANCE AND IDENTIFICATION
OF PAPER DOCUMENTS NOT IN PDF FORMAT**

Certification:

I hereby certify that I have submitted and served on opposing counsel an unredacted document and, if required, a redacted PDF document that comply with the Rules of the Supreme and the Court of Appeals. The PDF documents are identical to the corresponding parts of the paper documents from which they were created as filed with the Court. To the best of my knowledge, information, and belief formed after scanning the PDF documents for viruses with an antivirus program, the PDF documents are free of computer viruses. A copy of this certificate has been submitted with the paper copies filed with the Court and has been served on all opposing parties.

Identification of paper documents not in PDF format:

The following original paper documents are not in PDF format and are not included in the PDF document(s): None.

/s/ Brett D. Watson
Brett D. Watson

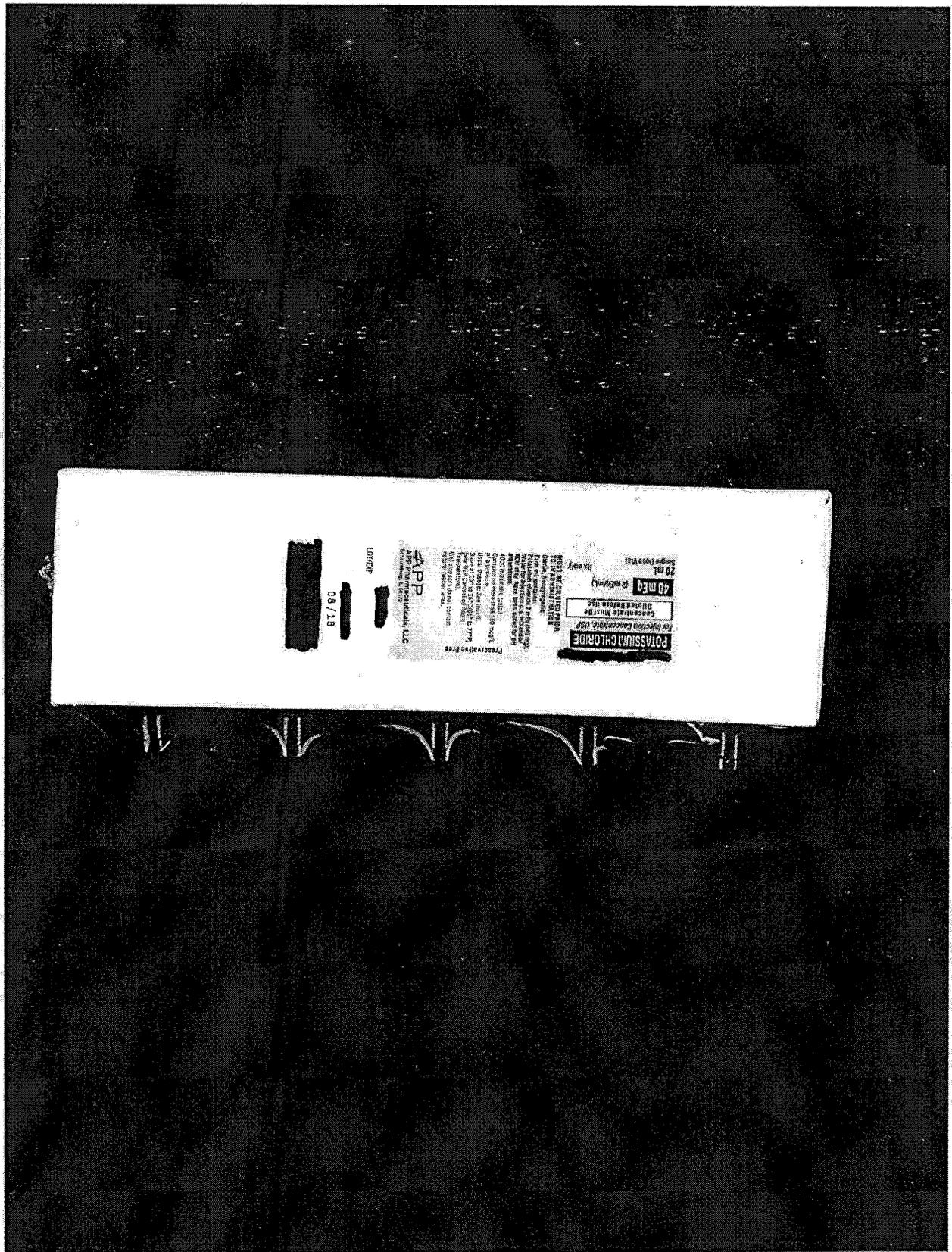


Exhibit A

APP



45767F/Revised: April 2008

POTASSIUM CHLORIDE
FOR INJECTION CONCENTRATE, USP

Concentrate Must Be Diluted Before Use

FOR INTRAVENOUS INFUSION ONLY

MUST BE DILUTED PRIOR TO INJECTION

DESCRIPTION:
Potassium Chloride for Injection Concentrate, USP is a sterile, nonpyrogenic concentrated solution of Potassium Chloride, USP in Water for Injection to be administered by intravenous infusion only after dilution in a larger volume of fluid.

Each mL of Potassium Chloride for Injection Concentrate contains 2 mEq of K⁺ and Cl⁻ equivalent to 149 mg of potassium chloride and has an osmolality of 4000 mOsmol/L (calc). A more concentrated Potassium Chloride for Injection Concentrate is also available. Each mL of this injection contains 3 mEq of K⁺ and Cl⁻ equivalent to 224 mg of potassium chloride and has an osmolality of 6000 mOsmol/L (calc). pH (4.0-8.0) may have been adjusted with hydrochloric acid and if necessary, potassium hydroxide.

Some packages are intended for multiple dose use and contain preservatives (0.05% methylparaben and 0.005% propylparaben). A summary of the available products is presented in the HOW SUPPLIED section.

Potassium Chloride for Injection Concentrate (appropriately diluted) is a parenteral fluid and electrolyte replenisher.

CLINICAL PHARMACOLOGY:
Potassium is the chief cation of body cells (160 mEq/L of intracellular water) and is concerned with the maintenance of body fluid composition and electrolyte balance. Potassium participates in carbohydrate utilization and protein synthesis, and is critical in the regulation of nerve conduction and muscle contraction, particularly in the heart. Chloride, the major extracellular anion, closely follows the metabolism of sodium, and changes in the acid-base balance of the body are reflected by changes in the chloride concentration.

Normally about 80 to 90% of the potassium intake is excreted in the urine, the remainder in the stools and to a small extent, in the perspiration. The kidney does not conserve potassium well, so that during fasting, or in patients on a potassium-free diet, potassium loss from the body continues resulting in potassium depletion. A deficiency of either potassium or chloride will lead to a deficit of the other.

INDICATIONS AND USAGE:
Potassium Chloride for Injection Concentrate, USP is indicated in the treatment of potassium deficiency states when oral replacement is not feasible.

CONTRAINDICATIONS:
Potassium Chloride for Injection Concentrate is contraindicated in diseases where high potassium levels may be encountered, and in patients with hyperkalemia, renal failure and in conditions in which potassium retention is present.

WARNINGS:
WARNING: This product contains aluminum. Aluminum may reach toxic

Injection Concentrate is also available. Each ml. of this injection contains 3 mEq of K⁺ and Cl⁻ equivalent to 224 mg of potassium chloride and has an osmolarity of 6000 mOsm/L (calc). pH (4.0-8.0) may have been adjusted with hydrochloric acid and if necessary, potassium hydroxide.

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WARNINGS:

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged paravenous administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive paravenous levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

To avoid potassium intoxication, do not infuse these solutions rapidly. In patients with renal insufficiency, administration of potassium chloride may cause potassium intoxication and life-threatening hyperkalemia.

The administration of intravenous solutions can cause fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema. The risk of dilutional states is inversely proportional to the electrolyte concentration. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentration.

PRECAUTIONS:

General

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged paravenous therapy or whenever the condition of the patient warrants such evaluation. Significant deviations from normal concentrations may require the use of additional electrolyte supplements, or the use of electrolyte-free dextrose solutions to which individualized electrolyte supplements may be added.

Potassium therapy should be guided primarily by serial electrocardiograms, especially in patients receiving digitalis. Serum potassium levels are not necessarily indicative of tissue potassium levels. Solutions containing potassium should be used with caution in the presence of cardiac disease, particularly in

the presence of renal disease, and in such instances, cardiac monitoring is recommended.

Solutions containing dextrose should be used with caution in patients with overt or known subclinical diabetes mellitus, or carbohydrate intolerance for any reason.

If the administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

Pregnancy

Teratogenic Effects: Pregnancy Category C—Animal reproduction studies have not been conducted with potassium chloride. It is also not known whether potassium chloride can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Potassium chloride should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS:

Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation, hypervolemia, and hyperkalemia.

Too rapid infusion of hypertonic solutions may cause local pain and, rarely, vein irritation. Rate of administration should be adjusted according to tolerance.

Reactions reported with the use of potassium-containing solutions include nausea, vomiting, abdominal pain and diarrhea. The signs and symptoms of potassium intoxication include paresthesias of the extremities, areflexia, muscular or respiratory paralysis, mental confusion, weakness, hypotension, cardiac arrhythmias, heart block, electrocardiographic abnormalities and cardiac arrest. Potassium deficits result in disruption of neuromuscular function, and intestinal ileus and dilatation.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

OVERDOSAGE:

In the event of fluid overload during parenteral therapy, reevaluate the patient's condition, and institute appropriate corrective treatment.

In the event of overdosage with potassium-containing solutions, discontinue the infusion immediately and institute corrective therapy to reduce serum potassium levels.

Treatment of hyperkalemia includes the following:

1. Dextrose Injection, USP, 10% or 25%, containing 10 units of crystalline insulin per 20 grams of dextrose administered intravenously, 300 to 500 mL/hour.
2. Absorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally and as retention enema.
3. Hemodialysis and peritoneal dialysis. The use of potassium-containing foods or medications must be eliminated. However, in cases of digitalization, too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

DOSAGE AND ADMINISTRATION:

Potassium Chloride for Injection Concentrate must be diluted before administration. Care must be taken to ensure there is complete mixing of the potassium chloride with the large volume fluid, particularly if soft or bag type containers are used.

The dose and rate of administration are dependent upon the specific condition of each patient.

If the serum potassium level is greater than 2.5 mEq/L, potassium can be given at a rate not to exceed 10 mEq/hour and in a concentration of up to 40 mEq/L. The 24 hour total dose should not exceed 200 mEq.

If urgent treatment is indicated (serum potassium level less than 2 mEq/L and electrocardiographic changes and/or muscle paralysis), potassium chloride may be infused very cautiously at a rate of up to 40 mEq/hour. In such cases, continuous cardiac monitoring is essential. As much as 400 mEq may be administered in a 24 hour period. In critical conditions, potassium chloride may be administered in saline (unless contraindicated) rather than in dextrose containing fluids, as dextrose may lower serum potassium levels.

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Prior to entering a vial, cleanse the rubber closure with a suitable antiseptic agent.

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

HOW SUPPLIED:

The following are packaged in plastic vials.

Product No.	NDC No.	Total Potassium Ion	Potassium Chloride per mL	Volume
96505	63323-965-05	10 mEq (0.29 g)	149 mg	5 mL in a 10 mL vial
96510	63323-965-10	20 mEq (0.78 g)	149 mg	10 mL in a 10 mL vial
96515	63323-965-15	30 mEq (1.17 g)	149 mg	15 mL in a 20 mL vial
96520	63323-965-20	40 mEq (1.56 g)	149 mg	20 mL in a 20 mL vial

These are Single Dose Vials, no preservative added, packaged 25 vials per tray. Unused portion of vial should be discarded.

Product No.	NDC No.	Total Potassium Ion	Potassium Chloride per mL	Volume
96730	63323-967-30	80 mEq (2.35 g)	149 mg	30 mL in a 30 mL vial

This is a Multiple Dose Vial, preserved with 0.05% methylparaben and 0.005% propylparaben, packaged 25 vials per tray.

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

Use only if solution is clear, seal intact and undamaged.

Vial stoppers do not contain natural rubber latex.

APP
APP Pharmaceuticals, LLC
 Schaumburg, IL 60173

45767F
 Revised: April 2008





Midazolam Injection, USP



Adult and Pediatric: Intravenous midazolam 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 or 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 monitoring of respiratory and cardiac function, i.e., pulse oximetry. Immediate availability of resuscitative drugs and age- and size-appropriate equipment for bag-valve-mask ventilation and intubation, and personnel trained in their use and skilled in airway management should be available. (See WARNINGS.) For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

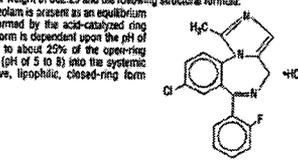
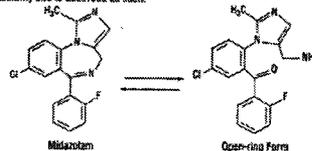
The initial intravenous dose for sedation in adult patients may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other central nervous system (CNS) 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/analgesia is age, procedure and route dependent (see DOSAGE AND ADMINISTRATION for complete information).

Warnings: 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).

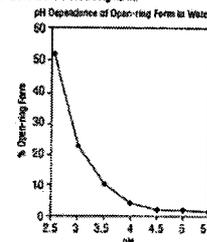
DESCRIPTION

Midazolam 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 in sterile water for injection. In addition, each mL contains the following inactive ingredients: 0.8% sodium chloride and 0.01% edetate disodium, with 1% benzyl alcohol as preservative; the pH is adjusted to 2.5-5.7 with sodium hydroxide and, if necessary, hydrochloric acid.

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-4-(2-fluorophenyl)-1-methyl-4H-imidazo[5,1-b] [1,4] benzodiazepine hydrochloride. Midazolam hydrochloride has the molecular formula $C_{17}H_{14}ClFN_3$ • HCl, a calculated molecular weight of 362.25 and the following structural formula:



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: 2.5 to 5.7. 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 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 after IM administration in adults. 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 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 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, 85% of patients had impaired recall vs 9% of the placebo controls. In another pediatric endoscopy study, 91% of midazolam treated patients were amnesic compared with 35% of patients who had received tertiary alone.

When midazolam is given IV as an anesthetic induction agent, induction of anesthesia occurs in approximately 1.5 minutes when nitrous preoxygenation has been administered and in 2 to 2.5 minutes without narcotic premedication or other sedative premedication. Some impairment in least of memory was noted in 30% of the patients studied. A dose response study of pediatric patients premedicated with 1.0 mg/kg intramuscular (IM) atropine found that only 4 out of 8 pediatric patients who received 500 mcg/kg IV midazolam lost consciousness, with eye closing at 1:00 ± 1:40 seconds. This group was compared with pediatric patients who were given thiopental 5 mg/kg IV; 8 out of 6 closed their eyes at 0:30 ± 3:3 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, inability to discharge from the recovery room, return to baseline finger dexterity) 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 compliance (subarachnoid screw measurements) show comparable elevations of intracranial pressure with midazolam and with thiopental during intubation. No similar studies have been reported in pediatric patients.

The usual recommended intramuscular premedication 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 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 tidal volume and maximum expiratory flow at 50% of awake total lung capacity (V_{50}) 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 canine 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 (less than 60/minute), particularly in patients taking propranolol for angina, tended to rise slightly; faster heart rates (e.g., 60/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 pharmacologically inactive 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 (V_d), 1.0 to 3.1 L/kg; elimination half-life, 1.8 to 8.4 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 ($n=5$) indicating non-linear kinetics in this dose range.

Absorption: The absolute bioavailability of the intramuscular 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 hr (50% CV). C_{max} for the 1-hydroxy metabolite following the IM dose was 8 ng/mL ($T_{max}=1.0$ hr).

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 (V_d) 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 V_d . 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 **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. Study to seventy percent of the biotransformation products is 1-hydroxy-midazolam (also termed alpha-hydroxymidazolam) while 4-hydroxy-midazolam is formed in smaller amounts. A dihydroxy derivative have also been detected but not quantitated. The principal urinary excretion products are glucuronide conjugates of the hydroxyated 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-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, 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 0.3% ($n=5$). 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.

Pharmacokinetic-Clinical Correlation: The pharmacokinetic profile of midazolam following continuous infusion, based on 262 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. Intermittent 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 **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 *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 (0.18 to 0.80 L/min/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 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 (0.5 to 12.0 hours) and the clearance reduced (0.07 to 0.12 L/min/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 normal (n=20) and obese patients (n=20) the mean half-life was greater in the obese group (5.0 vs 2.3 hrs). This was due to an increase of approximately 50% in the V_d 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 V_d based on total body weight increased consistently between 15% to 100% in the elderly. The mean Cl decreased approximately 25% in the elderly in 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 40% 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 V_d increased by 20%. In another study in 21 male patients with cirrhosis, without ascites and with normal kidney function as 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 8 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 (7.5 vs 13 hr) in the ARF patients. The renal clearance of the 1-hydroxy-midazolam glucuronide was prolonged in the ARF group (4 vs 135 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 2-fold increase in the clearance and volume of distribution but the half-life remained unchanged. Metabolite levels were not studied.

Plasma Concentration-Effect Relationships: 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 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 injection is indicated:

- intramuscularly or intravenously for preoperative sedation/amnesia/analgesia;
- intravenously as an agent for sedation/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 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 sedation/analgesia with 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 is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow-angle glaucoma who may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with midazolam; patients with glaucoma have not been studied.

Midazolam injection is not intended for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol in the dosage form.

WARNINGS

Midazolam 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 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 assured. Patients should be continuously monitored with some means of detection for early signs of hypoventilation, airway obstruction, apnea, laryngospasm, hyperventilation, airway obstruction and apnea can lead to hypoxia and/or cardiac arrest without intensive cardiovascular monitoring. 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 respiratory rate, rapid intravenous administration should also be avoided in this population. See **DOSSAGE AND ADMINISTRATION** for complete information.

Serious cardiovascular 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 apnea and hypotension due to partial airway obstruction. Adult and pediatric patients with obstructive pulmonary disease and 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 tremor), hyperactivity and combatsiveness have been reported in both adult and pediatric patients. These reactions may be due to inadequate or excessive dosing or abrupt administration of midazolam; however, consideration should be given to the possibility of central hypoxia or true neuroleptic 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 barbiturates, alcohol or other central nervous system depressants may increase the risk of hypoventilation, airway obstruction, desaturation of oxygen 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. 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 partial respiratory 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 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. 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 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 loss 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.

Use in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chloridazepoxide) has been suggested in several studies. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus. Withdrawal symptoms of the barbiturate type have occurred after the cessation of benzodiazepines (see **DRUG ABUSE AND DEPENDENCE** section).

Use in Preterm Infants and Neonates: Rapid injection should be avoided in the neonatal population. Midazolam administered rapidly as an intravenous injection (less than 2 minutes) has been associated with severe hypotension in neonates, particularly when the patient has also received fentanyl. Likewise, severe hypotension has been observed in neonates receiving a continuous infusion of midazolam who then receive a rapid intravenous injection of fentanyl. Children have been reported to have had respiratory depression following intravenous administration.

The neonate also has reduced cardiac immature organ function and is also vulnerable to profound and/or prolonged respiratory effects of midazolam. 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 death, 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 their sedation 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 benzyl 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 recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources.

PRECAUTIONS

General: Intravenous doses of midazolam should be decreased for elderly and for debilitated patients (see **WARNINGS** and **DOSSAGE 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 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 to the patient's underlying medical/surgical conditions, administer to the desired effect being certain to wait an adequate time for the CNS effect to be established and to avoid concomitant medications, and have the means of size-appropriate equipment and facilities available for monitoring and intervention (see **BOX WARNING**, **WARNINGS** and **DOSSAGE AND ADMINISTRATION** sections.) Practitioners administering midazolam 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** section.

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, 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 secobarbital and chloral hydrate. Consequently, the dosage of midazolam should be adjusted according to the type and amount of concomitant medications administered and the desired clinical response (see **DOSSAGE AND ADMINISTRATION**).

Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit the P450-3A4 enzyme system such as clarithromycin, erythromycin, diltiazem, verapamil, ketoconazole and itraconazole. These drug interactions may result in prolonged sedation due to a decrease in plasma clearance of midazolam.

The effect of single oral doses of 400 mg cimetidine and 300 mg ranitidine on steady-state concentrations 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 oral dose, bid, for 1 week (n=16), 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 diltiazem (60 mg bid) and verapamil (80 mg tid) on the pharmacokinetics and pharmacodynamics of midazolam were investigated in a 3-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.

A moderate reduction in reduction 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 concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of midazolam 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 additive 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 intracranial pressure noted following administration of succinylcholine. Midazolam does not cause a clinically significant change in dosage, onset or duration of a single intubating 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, diazepam, hydroxyzine, d-tubocurarine, succinylcholine, and other nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, tetracaine, articaine and bupivacaine) have been observed in adult 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, 5 and 25 mg/kg/day. In female mice 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. Doses 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 in rabbits and rats at 5 and 10 times the human dose of 0.35 mg/kg, did not show evidence of teratogenicity.

Lactation: Pharmacokinetics—Studies in rats showed no adverse effects on reproductive parameters during gestation and lactation. Doses tested were approximately 10 times the human dose of 0.35 mg/kg.

Placental Transfer: In humans, measurable levels of midazolam were found in maternal venous serum, umbilical venous and arterial serum and meconium, indicating placental transfer of the drug. Following intramuscular administration of 0.05 mg/kg of midazolam, both the venous and the umbilical arterial serum concentrations were lower than maternal concentrations.

Use in Obstetrics: The safety and efficacy of 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 obstetrical use.

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

Indications: The safety and efficacy of midazolam for sedation/anxiolysis/analgesia 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 **BOX WARNING, CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, OVERDOSAGE AND DOSAGE AND ADMINISTRATION** sections. **UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE INCREMENTS OF MIDAZOLAM ON A WEIGHT 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 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 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.

Pediatric Use: Because pediatric 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/or high-risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiration, especially narcotics (see **DOSAGE AND ADMINISTRATION**).

Specific dosing and monitoring guidelines for pediatric patients are provided in the **DOSAGE AND ADMINISTRATION** section for premedicated patients for sedation/anxiolysis/analgesia 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 (injected) midazolam. Increased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.6% 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 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.

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

headache (1.3%)

Local effects at IM injection site

pain (3.7%)

injection (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 cardiorespiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiratory capability (see **DRUG ABUSE AND DEPENDENCE**).

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

Nausea (3.0%)

nausea (2.8%)

vomiting (2.6%)

coughing (1.3%)

oversedation (1.0%)

headache (1.2%)

drowsiness (1.2%)

Local effects at the IV site

itchiness (5.6%)

pain during injection (5.0%)

redness (2.6%)

injection (1.7%)

phlebitis (1.4%)

Pediatric Patients: The following adverse events related to the use of IV midazolam in pediatric patients were reported in the medical literature: desaturation 4.5%, apnea 2.5%, hypotension 2.7%, paradoxical reactions 2.9%, nausea 1.2%, seizure-like activity 1.1% and myalgias 1.1%. The majority of adverse events occurred in patients receiving other CNS depressing medications and in patients where midazolam was not used as a single sedating agent.

Warnings: For information concerning hypotensive episodes and seizures following the administration of midazolam to neonates, see **BOX WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS** sections.

Other adverse experiences, observed mainly following IV injection as a single sedative/anxiolytic 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: Dizziness, 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, progression, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, arousal during emergence, sleep disturbance, zitterbewegungen, myoclonus, myoclonic movements, severe muscle activity, ataxia, dizziness, cyphoptosis, strabismic squint, dysphoria, parosmia.

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

Idiosyncrasy: Hypo-sensitivity at injection site, swelling or feeling of burning, warmth or coldness at injection site.

Hypersensitivity: Allergic reactions including anaphylactic reactions, hives, rash, pruritus.

Neuroleptanesthesia: Yawning, lethargy, chills, weakness, lachrymation, taste feeling, heat/cold.

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 other benzodiazepines, including 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 mild 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.

OVERDOSAGE

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 overdosage has been reported.

Treatment of Overdosage: Treatment of intractable 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 following administration of flumazenil to pediatric patients. Prior to the administration of flumazenil, necessary measures should be instituted to secure the airway, ensure 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 resedation, 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 medications. The reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk patients. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. The complete flumazenil package insert, including **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS**, should be consulted prior to use.

DOSAGE AND ADMINISTRATION

The 1 mL and 2 mL Midazolam Injection vials include a cautionary label that extends above the main label and highlights the drug name and strength per total volume. The purpose of the extended label is to prevent medication errors due to the different strengths of Midazolam Injection. Read the label and confirm you have selected the correct medication and strength. Then locate the "See Here" point on the label, and remove this cautionary label prior to removing the flip-off cap.

Midazolam is a potent sedative agent that requires slow administration and individualization of dosage. Clinical experience has shown midazolam to be 2 to 4 times as potent per mg as diazepam. **BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROFOUND 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 undergoing a procedure involving the upper airway such as endoscopy or dental (see **BOX WARNING AND WARNINGS**).

Reactions such as agitation, involuntary movements, hyperreflexia and convulsions 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 analgesics: morphine sulfate, meperidine, atropine sulfate or scopolamine hydrobromide, at a concentration of 0.5 mg/mL, compatible with 5% dextrose in water and 0.9% sodium chloride. 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.

Warnings: 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 concurrent use of other CNS depressants. Continuous monitoring of respiratory and cardiac function is required (i.e., pulse oximetry).

Adults and Pediatric: Sedation guidelines recommend a careful preadministration 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 preoxygenation procedures.

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 (2 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**).

Precautions: 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.

Use in Adult Dose

INTRAMUSCULARLY

Sedation/anxiolysis/amnesia for procedures (See **INDICATIONS AND USAGE**): For preoperative sedation/anxiolysis/amnesia (reduction of sleepiness or drowsiness and relief of apprehension and to impair memory of perioperative events).

For intramuscular use, midazolam 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.

The dose must be individualized and reduced when IM midazolam is administered to patients with chronic obstructive pulmonary disease or 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 of age 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 time to 1 mg midazolam may vary in some older 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.

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

INTRAVENOUSLY

Sedation/anxiolysis/amnesia for procedures (See **INDICATIONS AND USAGE**): For preoperative sedation/anxiolysis/amnesia (reduction of sleepiness or drowsiness and relief of apprehension and to impair memory of perioperative events).

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

When used for sedation/anxiolysis/amnesia for a procedure, dosage must be individualized and titrated. Midazolam 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. Individual responses will vary with age, physical status and concomitant medications, but may also vary independent of these factors. (See **WARNINGS** concerning cardiorespiratory arrest/airway obstruction/hyperventilation.)

1. **Healthy Adults Below the Age of 60:** Titrate slowly to the desired effect, e.g., the initiation of stirred speech. Some patients may require up to 10 mg. No more than 0.5 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 depressants are used, patients will require approximately 30% less midazolam than unpremedicated patients.

2. **Patients Age 60 or Older, and Debilitated or Chronically Ill Patients:** Because the danger of hypoventilation, airway obstruction, or arrest is greater in elderly patients and those with chronic

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

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 3.9 mg are not usually necessary. If concurrent 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 patient. These additional doses should be given only after a thorough clinical evaluation clearly indicates the need for additional sedation. 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 65 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 65 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 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 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 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, administered 5 minutes before induction), morphine (dosage individualized, up to 0.15 mg/kg IV), and propofol (dosage individualized up to 1 mg/kg IV). 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.

Incremental injections of approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary.

Injectable midazolam 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.

CONTINUOUS INFUSION
For continuous infusion, midazolam 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.

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 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.

Individual response to midazolam is variable. The infusion 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 initiated 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 adjustments 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 limit 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 terminated. Patients who exhibit agitation, hypertension or tachycardia in sedation, 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 infusion rate.

USUAL ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE INCREMENTS OF MIDAZOLAM ON A KG/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 hyperventilation is increased. For optimal patient monitoring, see **BOX WARNING, WARNINGS, Monitoring subsection of DOSAGE AND ADMINISTRATION**. 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.

Pediatric Patients

OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (OAA/S)

Responsiveness	Assessment Categories			Composite Score (5 alert)
	Speech	Facial Expression	Eyes	
Responds readily to name spoken in normal tone	normal	normal	clear, no ptosis	5
Lethargic; responds to name spoken in normal tone	mild slowing or fluctuating	mild relaxation	glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	staring or prominent slowing	marked relaxation (slack jaw)	glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	few recognizable words	—	—	2
Does not respond to mild prodding or shaking	—	—	—	1 (deep sleep)

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

Age Range (years)	n	1 (deep sleep)	2	3	4	5 (alert)
1-2	16	6 (38%)	4 (25%)	3 (19%)	3 (19%)	0
>2-5	22	9 (41%)	5 (23%)	6 (28%)	0	0
>5-12	34	1 (3%)	6 (18%)	22 (65%)	3 (9%)	0
>12-17	16	0	4 (25%)	14 (88%)	0	0
Total (1-17)	90	16 (18%)	19 (21%)	47 (52%)	6 (7%)	0

INTRAMUSCULARLY
For sedation/analgesia/immobility 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 prevent 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/analgesia/immobility prior to and during procedures or prior to anesthesia.

USUAL PEDIATRIC DOSE (NON-NEONATAL)
It should be recognized that the depth of sedation/analgesia needed for pediatric patients depends on the type of procedure to be performed. For example, simple light sedation/analgesia in the preoperative period is quite different from 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/analgesia, 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 longer than diazepam to achieve peak effect; 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 peak effect of those concomitant medications must be considered and the dose of midazolam adjusted. The importance of drug titration is vital to the safe sedation/analgesia of the pediatric patient. The total dose of midazolam will depend on patient response, 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 hyperventilation; therefore, titration with small increments to clinical effect and careful monitoring are essential.
- Pediatric patients 6 months to 5 years of age:** Initial dose 0.05 to 0.1 mg/kg. A total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint but usually does not exceed 6 mg. Prolonged sedation and risk of hyperventilation may be associated with the higher doses.
- 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 endpoint but usually does not exceed 10 mg. Prolonged sedation and risk of hyperventilation may be associated with the higher doses.
- 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 0.2 mg/kg administered over 2 to 3 minutes can be used to establish the desired clinical effect in **PATIENTS WHOSE TRACHEA IS INTUBATED**. (Midazolam should not be administered as a rapid intravenous dose.) This loading dose may be followed by a continuous intravenous 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 depressant medications such as opioids. Based on pharmacokinetic parameters and reported clinical experience, continuous intravenous infusions of midazolam should be initiated at a rate of 0.05 to 0.12 mg/kg/hr (1 to 2 mcg/kg/min). The rate of infusion can be increased or decreased (generally by 25% of the initial or subsequent 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 erythromycin and/or other P450-3A4 enzyme inhibitors (see **Drug Interactions** section) and in patients with liver dysfunction. Low cardiac output (especially those requiring inotropic support), and in neonates. Hypotension may be observed in patients who are critically ill, particularly those receiving midazolam and/or when midazolam is rapidly administered.

When initiating an infusion with midazolam in hemodynamically compromised patients, the usual loading dose of midazolam should be titrated in small increments and the patient monitored for hemodynamic instability, i.e., hypotension. These patients are also vulnerable to the respiratory depressant effects of midazolam and require careful monitoring of respiratory rate and oxygen saturation.

CONTINUOUS INTRAVENOUS INFUSION
For sedation in critical care settings.

USUAL NEONATAL DOSE
Based on pharmacokinetic parameters and reported clinical experience in preterm and term neonates **WHOSE TRACHEA WAS INTUBATED**, continuous intravenous infusions of midazolam injection should be initiated at a rate of 0.03 mg/kg/hr (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 assessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation. This is particularly important because of the potential for adverse effects related to metabolism of the benzyl alcohol (see **Dosage at Preterm Infants and Neonates**). Hypotension may be observed in patients who are critically ill and in preterm and term infants, particularly those receiving fentanyl and/or when midazolam is administered rapidly. Due to an increased risk of apnea, extreme caution is advised when sedating preterm and former preterm patients whose trachea is not intubated.

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

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

HOW SUPPLIED

Midazolam Injection, USP is available in the following:

- 1 mg/ml midazolam hydrochloride equivalent to 1 mg midazolam/ml.
2 ml Vial packaged in 10s [redacted] and in 25s [redacted]
5 ml Vial packaged in 10s [redacted]
- 5 mg/ml midazolam hydrochloride equivalent to 5 mg midazolam/ml.
1 ml Vial packaged in 10s [redacted] and in 25s [redacted]
2 ml Vial packaged in 10s [redacted] and in 25s [redacted]
10 ml Vial packaged in 10s [redacted]

STORAGE

Store at 20°-25°C (68°-77°F), excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

IN THE ARKANSAS SUPREME COURT

State of Arkansas *et al.*

Appellants

v.

Case No. CV-17-317

McKesson Medical-Surgical, Inc.

Appellee

***Amicus* Brief of Fresenius Kabi USA, LLC, and
West-Ward Pharmaceuticals Corp.**

Fresenius Kabi USA, LLC, and West-Ward Pharmaceuticals Corp. (the Manufacturers), for their *amicus* brief, state:

Similar to McKesson, the Manufacturers recently learned of information suggesting that medicines they manufactured might be used in lethal injections in Arkansas. The use of their medicines for lethal injections violates contractual supply-chain controls that the Manufacturers have implemented. It also creates a public-health risk because it could result in the denial of medicines from patients who need them most.

Exhibit C

1. The use of the medicines for lethal injections violates contractual supply-chain controls.

In recent years, more than 30 U.S. and international pharmaceutical companies, including the Manufacturers (and McKesson, according to its court filings), have instituted supply-chain controls to prevent the sale of their medicines for use in capital punishment. Ty Alper, *Why the execution drug shortage won't go away*, Los Angeles Times, April 13, 2015, available at <http://www.latimes.com/nation/la-oe-alper-lethal-injection-shortages-20150414-story.html> (last visited on April 20, 2017).

For example, the Manufacturers sell only to wholesalers and distributors who agree to resell only to acute-care hospitals, clinics, and healthcare facilities where the medicine's use is medically necessary within those facilities. The Manufacturers also instruct wholesalers and distributors (1) to reject sales or delivery of medicines such as those here to any correctional facilities and (2) to exclude delivery (directly or indirectly) other than to own-use customers, including other wholesalers and distributors and retail pharmacies, to reduce the possibility of the

medicine reaching correctional facilities. These controls are similar to the controls under which McKesson was operating at the time the Arkansas Department of Correction acquired product from McKesson.

The Manufacturers have legitimate interests in implementing these controls. The use of the medicines in lethal injections runs counter to the Manufacturers' mission to save and enhance patients' lives, and carries with it not only a public-health risk, but also reputational, fiscal, and legal risks. The Manufacturers therefore renegotiated contracts, remodeled distribution networks, and instituted supply-chain controls to prevent the use of the medicines in lethal injections.

It appears that these controls have been bypassed. The Manufacturers' records indicate no direct or indirect sales of the medicines to the Arkansas Department of Correction. The only conclusion is that these medicines were acquired from an unauthorized seller in violation of important contractual terms that the Manufacturers relied on when selling the medicines.

2. Using the medicines for lethal injections poses a public-health risk.

More significantly, the use of the medicines for lethal injections creates a public-health risk by undermining the safety and supply of lifesaving medicines. Improperly procured medicines from unauthorized sellers are at risk of adulteration or chemical change due to improper handling, for example, the failure to maintain proper temperature levels during storage and transport.

Diverting the medicines to executions and away from healthcare creates unnecessary shortages for patients who need them most. Medicines that could be used to protect life are instead being used to end it. The unintended consequence could be to undermine the supply and to place patients in Arkansas and across the country at risk.

Yet another public-health factor is European Union regulation 1352/2011, which prevents trade in products that could be used for capital punishment or torture. The regulation has already reduced the supply to patients and physicians of

medicines that have been used in the past in lethal-injection programs. Arkansas's plan to administer capital punishment using these medicines could similarly decrease the supply in the future.

Although *amici curiae* take no position on the merits of capital punishment, they ask the Court to consider (1) the troubling circumstances under which it appears the Manufacturers' and McKesson's medicines were obtained and (2) the Manufacturers' unique knowledge and perspective on the public-health risks of using these medicines as part of a lethal-injection program. For those reasons and the reasons McKesson has outlined, this Court should affirm the temporary restraining order.

Respectfully submitted,

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By: /s/ Brett D. Watson
Brett D. Watson
Ark. Bar No. 2002182

Certificate of Service

A copy of the foregoing has been conventionally filed and notice of filing has been sent to all counsel of record on April 20, 2017, via the CM/ECF system.

/s/ Brett D. Watson
Brett D. Watson

**CERTIFICATE OF COMPLIANCE AND
IDENTIFICATION OF PAPER DOCUMENTS NOT IN
PDF FORMAT**

Certification:

I hereby certify that I have submitted and served on opposing counsel an unredacted document and, if required, a redacted PDF document that comply with the Rules of the Supreme and the Court of Appeals. The PDF documents are identical to the corresponding parts of the paper documents from which they were created as filed with the Court. To the best of my knowledge, information, and belief formed after scanning the PDF documents for viruses with an antivirus program, the PDF documents are free of computer viruses. A copy of this certificate has been submitted with the paper copies filed with the Court and has been served on all opposing parties.

Identification of paper documents not in PDF format:

The following original paper documents are not in PDF format and are not included in the PDF document(s): None.

/s/ Brett D. Watson
Brett D. Watson