1. Definition of Terms With Respect to Sedation:

In the previous VERSED label, terms such as conscious sedation and preoperative sedation were used to describe the pharmacological response to the administration of VERSED when in fact sedation, anxiolysis and amnesia are the targeted endpoints of VERSED administration. These terms were somewhat confusing to the medical community because a clear consensus on the definition of these terms does not exist. However sedation is viewed by medical professionals as a continuum where patients may move easily from light to deep sedation with the potential loss of protective reflexes. For this reason sedatives should be titrated and continuous monitoring of respiratory and cardiac function is required. In order to more clearly communicate the pharmacological effects of VERSED. the terms conscious sedation and preoperative sedation have been replaced with sedation/anxiolysis/amnesia and the need for continuous monitoring is reinforced throughout this revised label. A new MONITORING subsection was added to the DOSAGE AND ADMINISTRATION section which also includes a beginning paragraph discussing the definition of sedation.

2. Labeling VERSED for Use in Neonates

This label clearly attempts to present the risks of VERSED administration in this population so that the medical professional may assess the benefits versus the risks. The BOXED WARNING now includes a neonate subsection addressing the risks of rapid bolus administration and the potential for severe hypotension and seizures in this population. Other sections of the label which address the use of VERSED in neonates include CLINICAL PHARMACOLOGY: Pharmacokinetic subsection; WARNINGS: Usage in Preterm Infants and Neonates subsection; PRECAUTIONS: Pediatric Use subsection; ADVERSE REACTIONS: Neonates subsection and DOSAGE AND ADMINISTRATION: Usual Neonatal Dose subsection.

The CONTRAINDICATIONS section also now includes a contraindication concerning rapid bolus injection in all populations.

In addition the Agency previously requested if the dosing recommendations for neonates was based on a limited number of patients (24) included in an article by Jacqz-Aigrain and if there were additional data such as population kinetics available in neonates. A response to these inquires prepared by Dr. Charles Cote and Dr. Helen Karl is presented in Appendix B.

3. Monitoring

This revised VERSED labeling reinforces the continuous monitoring of all patients. Specifically the BOXED WARNING includes a statement as per the "Practice Guidelines on Sedation and Analgesia for non-Anesthesiologists" by the American Society of Anesthesiologists Task Force published in Anesthesiology, Volume 8, Feb. 1996, page 459. In addition the WARNINGS, PRECAUTIONS and the DOSAGE AND ADMINISTRATION sections of the VERSED label also include monitoring recommendations for patients receiving VERSED. These latter monitoring recommendations are also in accord with the American Academy of Pediatrics "Guidelines for Monitoring and Management of Pediatric Patients During and After Sedation for Diagnostic and Therapeutic Procedures" published in Pediatrics Volume 89, June 1992. In the latter section of the VERSED label a MONITORING subsection has been added addressing continuous monitoring in all patients.

4. IV Access

The need for intravenous access is discussed in the OVERDOSAGE section of the VERSED label as well as in the new MONITORING subsection of the DOSAGE AND ADMINISTRATION section. These recommendations are also made in accordance with the American Academy of Pediatrics and their guideline entitled, "Guidelines for Monitoring and Management of Patients During and After Sedation for Diagnostic and Therapeutic Procedures" published in Pediatrics Volume 89, June 1992.

5. Dosing Guidelines for Pediatrics

The DOSAGE AND ADMINISTRATION section of the label have been revised with respect to the pediatric dosing guidelines. Specifically an upper limit for the IM dose of 10 mg is now included in the dosing guidelines. When VERSED is administered intravenously by intermittent injection to pediatric patients, doses based on the age and weight of the patient are presented in the label along with a maximum recommended dose. This maximum recommended dose is 6 mg for patients 6 mo. to 5 yrs. age group and 10 mg for pediatric patients 6 years of age and older.

It is the opinion of the sponsor that the revised label presented in Appendix A addresses all the concerns raised by the Agency during their review of Supplement 030 and will provide for the safe and effective use of VERSED in all targeted populations including pediatric and neonatal patients. Please note that the issue concerning benzodiazepines and glaucoma discussed at the October 10 meeting has not been resolved yet in the VERSED label. We are currently evaluating all the published and unpublished data available on this topic and will revise the applicable statements in the label at a later date.

We understand that the Advisory Committee meeting will be discussing pediatric labeling only and not Supplements 018 and 029. In addition we would like to remind the Agency that we are still awaiting the final approval of Supplement 029 which the Agency agreed to complete before the resolution of the labeling issues for the pediatric supplement.

If you have any questions concerning this submission, please contact the undersigned by phone at 201-812-3719 or via fax at 201-812-3700 or 3554.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs

MJJ/gsm
Attachments
HLR No. 1996-2226

Department of Health and Human Services
Food and Drug Administration

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

Title 21, Code of Federal Regulations, Parts 314 & 601.

FOR FDA USE ONLY

Application Number

APPLICANT INFORMATION

Name of Applicant	Date of Submission
Hoffmann-La Roche Inc.	November 18, 1996
Telephone Number (Include Area Code)	**Facsimile (FAX) Number (Include Area Code)**
(201) 812-3719	(201) 812-3700/3554

Applicant Address (Number, Street, State, Country, and Zip Code o Mail Code):
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

Authorized U.S. Agent, name & Address (Number, Street, State, and Zip Code telephone & FAX Number) if applicable
Margaret J. Jack
Hoffmann-La Roche Inc.
340 Kingsland Street, Bldg. 719/4
Nutley, NJ 07110-1199

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE NUMBER (if previously issued) 18-654

PRODUCT DESCRIPTION

Established Name (e.g., Proper name, USP/USAN name)	Proprietary Name (trade name) if any	Code Name (if any)
midazolam hydrochloride	VERSED	Ro 21-3981

Chemical/Biochemical Name (If any)	Dosage Form:	Strengths:	Route of Administration:
	vial	5 mg/ml and 1 mg/ml	I.V. and I.M.

Proposed Indications for Use:
Sedation via continuous infusion and sedation of pediatric patients

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGIC APPLICATION (21 CFR part 601)

IF A NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2) ☐ 507

IF AN ANDA, or AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ Original Application ☒ Amendment to a Pending Application ☐ Resubmission
☐ Presubmission ☐ Notification ☐ Establishment Description Supplement
☐ SUPAC Supplement ☐ Efficacy Supplement ☐ Labeling Supplement ☐ Chemistry, Manufacturing & Controls Supplement

REASON FOR SUBMISSION
Provide revised draft labeling for Supplement 030

PROPOSED MARKETING STATUS (Check one) ☐ Prescription Product (Rx) ☐ Over-The-Counter Product (OTC)

Letter	
Number of Volumes Submitted	This application is ☒ Paper ☐ Paper and Electronic

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs ,510(k)s, IDEs, BMFs and DMFs referenced in the current application)

MJJ/gsm
HLR No. 1996-2226

This submission contains the following items (check all that apply)	
	1. Index
x	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (e.g. 21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing and control information (e.g. 21 CFR 314.50 (d)(1))
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i))
	5. Nonclinical pharmacology and toxicology section (e.g 21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (e.g 21 CFR 314.50 (d) (3))
	7. Clinical Microbiology (e.g 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g 21 CFR 314.50 (d) (5))
	9. Safety update report (e.g 21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (e.g 21 CFR 314.50 (d) (6))
	11. Case report tabulations (e.g 21 CFR 314.50 (f) (1))
	12. Case report forms (e.g 21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification
	17. Field copy certification
	18. User Fee Cover Sheet (Form FDA 3397)
x	19. Other (Specify) Provide revised labeling as requested by the Division

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to, the following:

1. Good manufacturing practice regulations in 21 CFR 210, 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610 and/or 809.
4. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substance act, I agree not to market the product until the drug enforcement administration makes a final scheduling decision.

The data and information in this submission have been reviewed and are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

Signature of responsible official or agent	Typed name and title	Date
Margaret Jack	Margaret J. Jack Program Director Drug Regulatory Affairs	November 18, 1996

Midazolam HCl Injection

PACKAGE INSERT

MIDAZOLAM HCl INJECTION

Rx only

WARNING

Adult and Pediatrics

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 and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous midazolam should be used only in hospital or ambulatory care settings, including physicians' and dental offices, that provide for continuous monitoring of respiratory and cardiac function, ie, pulse oximetry. Immediate availability of resuscitative drugs and age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and personnel trained in their use and skilled in airway management should be assured (see WARNINGS). For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the 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/anxiolysis/amnesia is age, procedure, and route dependent (see* DOSAGE AND ADMINISTRATION, PEDIATRIC PATIENTS for complete dosing information).

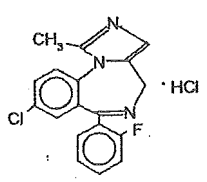
Neonates

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

DESCRIPTION

Midazolam 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 compounded with 0.8% sodium chloride and 0.01% edetate disodium with 1% benzyl alcohol as preservative, and *sodium hydroxide and/or hydrochloric acid for pH adjustment. pH 2.9-3.7.*

Midazolam is a white to light yellow crystalline compound, insoluble in water. The hydrochloride salt of midazolam, which is formed *in situ*, is soluble in aqueous solutions. Chemically, midazolam HCl is 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-a] [1,4] benzodiazepine hydrochloride. Midazolam hydrochloride has the molecular formula $C_{18}H_{13}ClFN_3 \cdot HCl$, a calculated molecular weight of 362.25 and the following structural formula:



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 following injection. In one adult study, when tested the following day, 73% of the patients who received midazolam intramuscularly had no recall of memory cards shown 30 minutes following drug *administration; 40% had no recall of the memory cards shown 60 minutes following drug administration.* Onset time of sedative effects in the pediatric population begins within 5 minutes and peaks at 15 to 30 minutes depending upon the dose administered. In pediatric patients, up to 85% had no recall of pictures shown after receiving intramuscular midazolam compared with 5% of the placebo controls.

Sedation in adult and pediatric patients is achieved within 3 to 5 minutes after intravenous (IV) injection; the time of onset is affected by total dose administered and the concurrent administration of narcotic premedication. Seventy-one percent of the patients in endoscopy studies had no recall of introduction of the endoscope; 82% of the patients had no recall of withdrawal of the endoscope. In one study of pediatric patients undergoing lumbar puncture or bone marrow aspiration, 88% *of patients had impaired recall vs* 9% of the placebo controls. In another pediatric oncology study, 91% of midazolam treated patients were amnestic compared with 35% of patients who had received fentanyl alone.

When midazolam is given IV as an anesthetic induction agent, induction of anesthesia occurs in approximately 1.5 minutes when narcotic premedication has been administered and in 2 to 2.5 minutes without narcotic premedication or other sedative premedication. Some impairment in a test of memory was noted in 90% *of the patients studied.* A dose response study of pediatric patients premedicated with 1.0 mg/kg intramuscular (IM) meperidine found that only 4 out of 6 pediatric patients who received 600 mcg/kg IV midazolam lost consciousness, with eye closing at 108 ± 140 seconds. This group was compared with pediatric patients who were given thiopental 5 mg/kg IV; 6 out of 6 closed their eyes at 20 ± 3.2 seconds. *Midazolam did not dependably induce anesthesia at this dose despite concomitant opioid administration* in pediatric patients.

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

In patients without intracranial lesions, induction of general anesthesia with IV midazolam is associated with a moderate decrease in cerebrospinal fluid pressure (lumbar puncture measurements), similar to that observed following IV thiopental. Preliminary data in neurosurgical patients with normal intracranial pressure but decreased 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 premedicating doses of midazolam do not depress the ventilatory response to *carbon dioxide stimulation to a clinically significant extent in adults. Intravenous induction doses of midazolam* depress the ventilatory response to carbon dioxide stimulation for 15 minutes or more beyond the duration of ventilatory depression following administration of thiopental in adults. Impairment of ventilatory response to carbon dioxide is more marked in adult patients with chronic obstructive pulmonary disease (COPD). Sedation with IV midazolam does not adversely affect the mechanics of respiration (resistance, static recoil, most lung volume measurements); total lung capacity and peak expiratory flow decrease significantly but static compliance and maximum expiratory flow at 50% of awake total lung capacity (V_{max}) increase. In one study of pediatric patients under general anesthesia, intramuscular midazolam (100 or 200 mcg/kg) was shown to depress the response to carbon dioxide in a dose-related manner.

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

Pharmacokinetics

Midazolam's activity is primarily due to the parent drug. Elimination of the parent drug takes place via hepatic *metabolism of midazolam to hydroxylated metabolites that are conjugated and excreted in the urine. Six single-dose* pharmacokinetic studies involving healthy adults yield pharmacokinetic parameters for midazolam in the following ranges: volume of distribution (Vd), 1.0 to 3.1 L/kg; elimination half-life, 1.8 to 6.4 hours (mean approximately 3 hours); total clearance (Cl), 0.25 to 0.54 L/hr/kg. In a parallel group study, there was no difference in the clearance in subjects administered 0.15 mg/kg (n=4) and 0.30 mg/kg (n=4) IV doses indicating linear kinetics. The clearance was successively reduced by approximately 30% at doses of 0.45 mg/kg (n=4) and 0.6 mg/kg (n=5) 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 (Cmax) 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 6 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 (Vd) determined from six single-dose pharmacokinetic studies involving healthy adults ranged from 1.0 to 3.1 L/kg. Female gender, old age, and obesity are associated with increased values of midazolam Vd. In humans, midazolam has been shown to cross the placenta and enter into fetal circulation and has been detected in human milk and CSF (see Special Populations).

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

Metabolism: In vitro studies with human liver microsomes indicate that the biotransformation of midazolam is mediated by cytochrome P450 3A4. This cytochrome also appears to be present in gastrointestinal tract mucosa as well as liver. Sixty to seventy percent of the biotransformation products is 1-hydroxy-midazolam (also termed alpha-hydroxy-midazolam) while 4-hydroxy-midazolam constitutes 5% or less. Small amounts of a dihydroxy derivative have also been detected but not quantified. The principal urinary excretion products are glucuronide conjugates of the hydroxylated derivatives

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

Studies of the intravenous administration of 1-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 0.5% (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.

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

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

Patients with renal impairment may have longer elimination half-lives for midazolam (see 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 (0.19 to 0.60 L/hr/kg) than in adults and the terminal elimination half-life (0.78 to 3.3 hours) is similar to or shorter than in adults. The pharmacokinetic properties during and following continuous intravenous infusion in pediatric patients in the operating room as an adjunct to general anesthesia and in the intensive care environment are similar to those in adults.

In seriously ill neonates, however, the terminal elimination half-life of midazolam is substantially prolonged (6.5 to 12.0 hours) and the clearance reduced (0.07 to 0.12 L/hr/kg) compared to healthy adults or other groups of pediatric patients.

It cannot be determined if these differences are due to age, immature organ function or metabolic pathways, underlying illness or debility.

Obese: In a study comparing normals (n=20) and obese patients (n=20) the mean half-life was greater in the obese group (5.9 vs 2.3 hours). This was due to an increase of approximately 50% in the Vd corrected for total body weight. The clearance was not significantly different between groups.

Geriatric: In three parallel group studies, the pharmacokinetics of midazolam administered IV or IM were compared in young (mean age 29, n=52) and healthy elderly subjects (mean age 73, n=53). Plasma half-life was approximately two-fold higher in the elderly. The mean Vd based on total body weight increased consistently between 15% to 100% in the elderly. The mean 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 Vd 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 6 ICU patients who developed acute renal failure (ARF) were compared with a normal renal function control group. Midazolam was administered as an infusion (5 to 15 mg/hr). Midazolam clearance was reduced (1.9 vs 2.8 mL/min/kg) and the half-life was prolonged (7.6 vs 13 hours) in the ARF patients. The renal clearance of the 1-hydroxy-midazolam glucuronide was prolonged in the ARF group (4 vs 136 mL/min) and the half-life was prolonged (12 vs>25 hours). Plasma levels accumulated in all ARF patients to about ten times that of the parent drug. The relationship between accumulating metabolite levels and prolonged sedation is unclear.

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

Plasma Concentration-Effect Relationship: Concentration-effect relationships (after an IV dose) have been demonstrated for a variety of pharmacodynamic measures (eg, 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, Drug Interactions.)

INDICATIONS AND USAGE

Midazolam Injection is indicated —

- intramuscularly or intravenously for preoperative sedation/anxiolysis/amnesia;
- intravenously as an agent for sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography and 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 supplementation of nitrous oxide and oxygen (balanced anesthesia);
- continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.

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

CONTRAINDICATIONS

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

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

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 ensured. Patients should be continuously monitored with some means of detection for early signs of hypoventilation, airway obstruction, or apnea, ie, pulse oximetry. Hypoventilation, airway obstruction, and apnea can lead to hypoxia and/or cardiac arrest unless effective countermeasures are taken immediately. The immediate availability of specific reversal agents (flumazenil) is highly recommended. Vital signs should continue to be monitored during the recovery period. Because intravenous midazolam depresses respiration (see CLINICAL PHARMACOLOGY) and because opioid agonists and other sedatives can add to this depression, midazolam should be administered as an induction agent only by a person trained in general anesthesia and should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintaining a patent airway and supporting ventilation. When used for sedation/anxiolysis/amnesia, midazolam should always be titrated slowly in adult or pediatric patients. Adverse hemodynamic events have been reported in pediatric patients with cardiovascular instability; rapid intravenous administration should also be avoided in this population (see DOSAGE AND ADMINISTRATION, PEDIATRIC PATIENTS for complete information).

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

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

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

Higher risk adult and pediatric surgical patients, elderly patients and debilitated adult and pediatric patients require lower dosages, whether or not concomitant sedating medications have been administered. Adult or pediatric patients with COPD are unusually sensitive to the respiratory depressant effect of midazolam. Pediatric and adult patients undergoing procedures involving the upper airway such as upper endoscopy or dental care, are particularly vulnerable to episodes of desaturation and hypoventilation due to partial airway obstruction. Adult and pediatric patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly (See CLINICAL PHARMACOLOGY). Because elderly patients frequently have inefficient function of one or more organ systems and because dosage requirements have been shown to decrease with age, reduced initial dosage of midazolam 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 tests of recovery from the effects of midazolam (see CLINICAL PHARMACOLOGY) cannot be relied upon to predict reaction time under stress. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until one full day after anesthesia and surgery, whichever is longer. For pediatric patients, particular care should be taken to assure safe ambulation.

Usage in Pregnancy

An increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chlordiazepoxide) 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 discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE section).

Usage 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. Seizures have been reported in several neonates following rapid intravenous administration.

The neonate also has reduced and/or 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 deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications (including midazolam) containing this preservative must take into account the total amount of benzyl alcohol administered. The recommended dosage range of midazolam for preterm and term infants includes amounts of 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 DOSAGE AND ADMINISTRATION, USUAL ADULT DOSAGE.) 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 peak CNS effects of both midazolam and concomitant medications, and have the personnel and size-appropriate equipment and facilities available for monitoring and intervention (see Boxed WARNING, WARNINGS and DOSAGE AND ADMINISTRATION, Monitoring.) 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.

Information for Patients

To assure safe and effective use of benzodiazepines, the following information and instructions should be communicated to the patient when appropriate:

Midazolam HCl Injection

PACKAGE INSERT

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 (eg, morphine, meperidine and fentanyl) and also secobarbital and droperidol. Consequently, the dosage of midazolam should be adjusted according to the type and amount of concomitant medications administered and the desired clinical response (see DOSAGE AND ADMINISTRATION.)

Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit the P450 3A4 enzyme system such as cimetidine (not ranitidine), erythromycin, 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 800 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 62 ng/mL. No change in *choice reaction time or sedation index was detected after dosing with the H2 receptor antagonists.*

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

The effects of diltiazem (60 mg tid) and verapamil (80 mg tid) on the pharmacokinetics and pharmacodynamics of midazolam were investigated in a three-way cross-over 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 induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular midazolam for premedication in adults.

The intravenous administration of midazolam decreases the minimum alveolar 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 minor interactive effects has not been fully studied, midazolam and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration in adults. Midazolam does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium and does not protect against the increased 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, dyclonine HCl and benzocaine) have been observed in adults or pediatric patients. In neonates, however, severe hypotension has been reported with concomitant administration of fentanyl. This effect has been observed in neonates on an infusion of midazolam who *received a rapid injection of fentanyl and in patients on an infusion of fentanyl who have received a rapid injection of* midazolam.

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

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Carcinogenesis: Midazolam maleate was administered with diet in mice and rats for 2 years at dosages of 1, 9 and 80 mg/kg/day. In female mice in the highest dose group there was a marked increase in the incidence of hepatic tumors. In high-dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumors. Dosages of 9 mg/kg/day of midazolam maleate (25 times a human dose of 0.35 mg/kg) do not increase the incidence of tumors. The pathogenesis of induction of these tumors is not known. These tumors were found after chronic administration, whereas human use will ordinarily be of single or several doses.

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

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

Pregnancy
Teratogenic Effects: Pregnancy Category D. (See WARNINGS).

Segment II teratology studies, performed with midazolam maleate injectable in rabbits and rats at 5 and 10 times the human dose of 0.35 mg/kg, did not show evidence of teratogenicity.

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

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

The use of injectable 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.

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

Pediatric Use
The safety and efficacy of midazolam for sedation/anxiolysis/amnesia following single dose intramuscular administration, intravenously by intermittent injections and continuous infusion have been established in pediatric and neonatal patients. For specific safety monitoring and dosage guidelines see Boxed WARNING, CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, OVERDOSAGE and DOSAGE AND ADMINISTRATION. UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE INCREMENTS OF MIDAZOLAM ON A MG/KG BASIS. As a group, pediatric patients generally require higher dosages of midazolam (mg/kg) than 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.*

Geriatric Use
Because geriatric patients may have altered drug distribution and diminished hepatic and/or renal function, reduced doses of midazolam are recommended. Intravenous and intramuscular doses of midazolam should be decreased for elderly and for debilitated patients (see WARNINGS and DOSAGE AND ADMINISTRATION) and subjects over 70 years of age may be particularly sensitive. These patients will also probably take longer to recover completely after midazolam administration for the induction of anesthesia. Administration of IM and IV midazolam to elderly and/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 geriatric patients are provided in the DOSAGE AND ADMINISTRATION section for premedicated patients for sedation/anxiolysis/amnesia following IV and IM administration for induction of anesthesia following IV administration and for continuous infusion.

ADVERSE REACTIONS

See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs were the most frequently seen findings following parenteral administration of midazolam in adults and included decreased tidal volume and/or respiratory rate decrease (23.3% 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 (eg, upper endoscopy and dental procedures).

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

headache (1.3%)

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

Administration of IM midazolam to elderly and/or higher risk surgical patients has been associated with rare reports of death under circumstances compatible with 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).

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

hiccoughs (3.9%) *Local effects at the IV site*

nausea (2.8%)	tenderness (5.6%)
vomiting (2.6%)	pain during injection (5.0%)
coughing (1.3%)	redness (2.6%)
"oversedation" (1.6%)	induration (1.7%)
headache (1.5%)	phlebitis (0.4%)
drowsiness (1.2%)	

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

Neonates
For information concerning hypotensive episodes and seizures following the administration of midazolam to neonates (see Boxed WARNING, CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

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

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

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

Gastrointestinal: Acid taste, excessive salivation, retching.

Midazolam HCl Injection

PACKAGE INSERT

CNS/Neuromuscular: Retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia.

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

Integumentary: Hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site.

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

Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

DRUG ABUSE AND DEPENDENCE

Midazolam is subject to Schedule IV control under the Controlled Substances Act of 1970.

Midazolam was actively self-administered in primate models used to assess the positive reinforcing effects of psychoactive drugs.

Midazolam produced physical dependence of a mild to moderate intensity in cynomolgus monkeys after 5 to 10 weeks of administration. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

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

OVERDOSAGE

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

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. There are anecdotal reports of reversal of adverse hemodynamic responses associated with midazolam following administration of flumazenil to pediatric patients. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, assure adequate ventilation, and establish adequate intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for 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

Midazolam is a potent sedative agent that requires slow administration and individualization of dosage. Clinical experience has shown midazolam to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM MIDAZOLAM INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excessive single doses or rapid or 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 Boxed WARNING and WARNINGS).

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

Midazolam should only be administered IM or IV (see WARNINGS).

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

Midazolam injection may be mixed in the same syringe with the following frequently used premedications: morphine sulfate, meperidine, atropine sulfate or scopolamine. Midazolam, at a concentration of 0.5 mg/mL, is compatible with 5% dextrose in water and 0.9% sodium chloride for up to 24 hours and with lactated Ringer's solution for up to 4 hours. Both the 1 mg/mL and 5 mg/mL formulations of midazolam may be diluted with 0.9% sodium chloride or 5% dextrose in water.

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

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

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

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

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

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

USUAL ADULT DOSE

Intramuscularly
For preoperative sedation /anxiolysis/amnesia (induction 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 Mindent midazolam is administered to patients with chronic obstructive pulmonary disease, other higher risk surgical patients, patients 60 or more years of age, and patients who have received concomitant narcotics or other CNS depressants (see ADVERSE REACTIONS). In a study of patients 60 years or older, who did not receive concomitant administration of narcotics, 2 to 3 mg (0.02 to 0.05 mg/kg) of midazolam produced adequate sedation during the preoperative period. The dose of 1 mg IM midazolam may suffice for 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 hydrochloride and reduced doses of narcotics.

Intravenously
Sedation/anxiolysis/amnesia for procedures (see INDICATIONS AND USAGE): Narcotic premedication results in less variability in patient response and a reduction in dosage of midazolam. For peroral procedures, the use of an appropriate topical anesthetic is recommended. For bronchoscopic procedures, the use of narcotic premedication is recommended.

Midazolam 1 mg/mL formulation is recommended for sedation/anxiolysis/amnesia for procedures to facilitate slower injection. Both the 1 mg/mL and the 5 mg/mL formulations may be diluted with 0.9% sodium chloride or 5% dextrose in water.

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 response will vary with age, physical status and concomitant medications, but may also vary independent of these factors. (see WARNINGS concerning cardiac/respiratory arrest/airway obstruction/ hypoventilation).

1. *Healthy Adults Below the Age of 60:* Titrate slowly to the desired effect, (eg, the initiation of slurred speech). Some patients may respond to as little as 1 mg. No more than 2.5 mg should be given over a period of at least 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If further titration is necessary, continue to titrate, using small increments, to the appropriate level of sedation. Wait an additional 2 or more minutes after each increment to fully evaluate the sedative effect. A total dose greater than 5 mg is not usually necessary to reach the desired endpoint.

   If narcotic premedication or other CNS 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 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, (eg, the initiation of slurred speech). Some patients may respond to as little as 1 mg. No more than 1.5 mg should be given over a period of no less than 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If additional titration is necessary, it should be given at a rate of no more than 1 mg over a period of 2 minutes, waiting an additional 2 or more minutes each time to fully evaluate the sedative effect. Total doses greater than 3.5 mg are not usually necessary.

Midazolam HCl Injection

PACKAGE INSERT

If concomitant CNS depressant premedications are used in these patients, they will require at least 50% less midazolam than healthy young unpremedicated patients.

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

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

Individual response to the drug is variable, particularly when a narcotic premedication is not used. The dosage should be titrated to the desired effect according to the patient's age and clinical status.

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

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

Unpremedicated patients over the age of 55 years usually 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 IM), and meperidine (dosage individualized, up to 1 mg/kg IM). Sedative premedications were hydroxyzine pamoate (100 mg orally) and sodium secobarbital (200 mg orally). Except for intravenous fentanyl, administered 5 minutes before induction, all other premedications should be administered approximately 1 *hour prior to the time anticipated for midazolam induction.*

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 0.1 mg/kg/hr (1 to 7 mg/hr). Higher loading or maintenance infusion rates may occasionally be required in some patients. The lowest recommended doses should be used in patients with residual effects from anesthetic drugs, or in those concurrently receiving other sedatives or opioids.

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 infused at the lowest rate that produces the desired level of sedation. Assessment of sedation should be performed at *regular intervals and the midazolam infusion rate adjusted* up or down by 25% to 50% of the initial infusion rate so as to assure adequate titration of sedation level. Larger 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 find the minimum effective infusion rate. Finding the minimum effective infusion rate decreases the potential accumulation of midazolam and provides for the most rapid recovery once the infusion is terminated. Patients who exhibit agitation, hypertension, or tachycardia in response to noxious stimulation, but who are otherwise adequately sedated, may benefit from concurrent administration of an opioid analgesic. Addition of an opioid will generally reduce the minimum effective midazolam infusion rate.

PEDIATRIC PATIENTS

UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE INCREMENTS OF MIDAZOLAM ON A MG/KG BASIS. As a group, pediatric patients *generally require higher dosages of midazolam (mg/kg)* than do adults. Younger (less than six years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients, and may require close monitoring (see tables below). In obese **PEDIATRIC PATIENTS**, the dose should be calculated based on ideal body weight. When midazolam is given in conjunction with opioids or other sedatives, the potential for respiratory depression, airway obstruction, or hypoventilation is increased. For appropriate patient monitoring see Boxed **WARNING, WARNINGS, DOSAGE AND ADMINISTRATION,** Monitoring. The 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.

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

	Assessment Categories			
Responsiveness	Speech	Facial Expression	Eyes	Composite Score
Responds readily to name spoken in normal tone	normal	normal	clear, no ptosis	5 (alert)
Lethargic response to name spoken in normal tone	mild slowing or thickening	mild relaxation	glazed or mild ptosis (less than half the eye)	4
Responds only after slurring or name is called loudly and/or repeatedly	slurring 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 PEDIATRIC PATIENTS UNDERGOING *PROCEDURES WITH INTRAVENOUS MIDAZOLAM FOR SEDATION*

Age Range (years)	n	OAA/S Score				
		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%)	8 (36%)	0	0
>5-12	34	1 (3%)	6 (18%)	22 (65%)	5 (15%)	0
>12-17	18	0	4 (22%)	14 (78%)	0	0
Total (1-17)	90	16 (18%)	19 (21%)	47 (52%)	8 (9%)	0

Midazolam HCl Injection

PACKAGE INSERT

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

Usual Pediatric Dose (Non-Neonatal)
Sedation after intramuscular midazolam is age and dose dependent: higher doses may result in deeper and more prolonged sedation. Doses of 0.1 to 0.15 mg/kg are usually effective and do not prolong emergence from general anesthesia. For more anxious patients, doses up to 0.5 mg/kg have been used. Although not systematically studied, the total dose usually does not exceed 10 mg. If midazolam is given with an opioid, the initial dose of each must be reduced.

Intravenously by Intermittent Injection
For sedative/anxiolysis/amnesia prior to and during procedures or prior to anesthesia.

Usual Pediatric Dose (Non-Neonatal)
It should be recognized that the depth of sedation/anxiolysis needed for pediatric patients depends on the type of procedure to be performed. For example, simple light sedation/anxiolysis in the preoperative period is quite different from the deep sedation and analgesia required for an endoscopic procedure in a child. For this reason, there is a broad range of dosage. For all pediatric patients, regardless of the indications for sedation/anxiolysis, it is vital to titrate midazolam and other concomitant medications slowly to the desired clinical effect. The initial dose of midazolam should be administered over 2 to 3 minutes. Since midazolam is water soluble, it takes approximately three times longer than diazepam to achieve peak EEG effects, therefore one must wait an additional 2 to 3 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments until the appropriate level of sedation is achieved. If other medications capable of depressing the CNS are coadministered, the peak effect of those concomitant medications must be considered and the dose of midazolam adjusted. The importance of drug titration to effect is vital to the safe sedation/anxiolysis of the pediatric 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.

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

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

Continuous Intravenous Infusion
For sedation/anxiolysis/amnesia in critical care settings.

Usual Pediatric Dose (Non-Neonatal)
To initiate sedation, an intravenous loading dose of 0.05 to 0.2 mg/kg administered over at least 2 to 3 minutes can be used to establish the desired clinical effect 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 0.06 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 PRECAUTIONS: Drug Interactions) 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 opioids 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 (eg, 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 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 reassessed, 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 WARNINGS: Usage in 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.

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

HOW SUPPLIED

Package configurations for Midazolam Hydrochloride Injection containing midazolam hydrochloride equivalent to 5 mg midazolam/mL:

1 mL vials – unit pack of 10
2 mL vials – unit pack of 10
5 mL vials – unit pack of 10
10 mL vials – unit pack of 10

Package configurations for Midazolam Hydrochloride Injection containing midazolam hydrochloride equivalent to 1 mg midazolam/mL:

2 mL vials – unit pack of 10
5 mL vials – unit pack of 10
10 mL vials – unit pack of 10

Case packs containing 20 unit packs are also available for each vial size.

Store at controlled room temperature 15 to 30°C (59-86°F). [see USP]

Mfg by:
Novex Pharma
Richmond Hill, Ontario
Canada L4C 5H2

Mfg for:
Apotex Corp.
Weston, FL 33326

Revised: August 2000

的な観察が行える状況においてのみ使用する．具体的には心電図モニター，パルスオキシメーター，血圧計その他適切な方法でモニタリングを行うべきである．観察は患者が完全に回復するまで行う[18]．

(8) 原則として投与前には絶飲食時間をとる．小児における適切な絶飲食時間とは軽食及び粉ミルク6時間，母乳4時間，飲水2時間が目安である[23]．

5) 参考文献

1) Sorbo S, Hudson RJ, Loomis JC：The pharmacokinetics of thiopental in pediatric surgical patients. Anesthesiology 1984；61：666-670（II-c）
2) Jonmarker C, Westrin P, Larsson S, et al：Thiopental requirements for induction of anesthesia in children. Anesthesiology 1987；67：104-107（II-c）
3) Brett CM, Fisher DM：Thiopental dose-response relations in unpremedicated infants, children, and adults. Anesth Analg 1987；66：1024-1027（II-c）
4) Cote CJ, Goudsouzian NG, Liu LM, et al：The dose response of intravenous thiopental for the induction of general anesthesia in unpremedicated children. Anesthesiology 1981；55：703-705（II-c）
5) Westrin P, Jonmarker C, Werner O：Thiopental requirements for induction of anesthesia in neonates and in infants one to six months of age. Anesthesiology 1989；71：344-346（II-c）
6) Duncan BB, Zaimi F, Newman GB, et al：Effect of premedication on the induction dose of thiopentone in children. Anaesthesia 1984；39：426-428（II-a）
7) 大前禎毅，吉岡博：けいれん重積．小児科臨床2000；53：2069-2075（III）
8) 久佐賀晃，山岡俊彦，松石豊次郎：小児救急医療における薬物療法の基本-抗けいれん薬-．小児科診療2001；64：1670-1677（III）
9) 藤谷健，佐藤保之：頭部外傷のIntensive Care．小児内科1986；18巻臨増319-325（III）
10) 高橋義男，大井静雄：小児頭部外傷．小児内科2000；32巻増刊：183-191（III）
11) 村中秀樹，藤田浩史：頭蓋内圧亢進の管理．小児内科2000；32巻増刊：156-160（III）
12) Nordby HK, Nesbakken R：The effect of high dose barbiturate decompression after severe head injury. A controlled clinical trial. Acta Neurochir (Wien) 1984；72：157-166（II-c）
13) Reid RW, Warner DS：Arguments for use of barbiturates in infants and children undergoing deep hypothermic circulatory arrest. J Cardiothorac Vasc Anesth 1998；12：591-594（III）
14) Nguyen MT, Greenberg SB, Fitzhugh KR, et al：Pediatric imaging：sedation with an injection formulation modified for rectal administration. Radiology 2001；221：760-762（II-c）
15) Okutan V, Lenk MK, Sarici SU, et al：Efficacy and safety of rectal thiopental sedation in outpatient echocardiographic examination of children. Acta Paediatr 2000；89：1340-1343（II-c）
16) Alp H, Guler I, Orbak Z, et al：Efficacy and safety of rectal thiopental：sedation for children undergoing computed tomography and magnetic resonance imaging. Pediatr Int 1999；41：538-541（II-c）
17) Beekman RP, Hoorntje TM, Beek FJ, et al：Sedation for children undergoing magnetic resonance imaging：efficacy and safety of rectal thiopental. Eur J Pediatr 1996；155：820-822（II-c）
18) ラボナール添付文書(第2版)，1998年11月．田辺製薬，大阪
19) Cote CJ, Petkau AJ：Thiopental requirements may be increased in children reanesthetized at least one year after recovery from extensive thermal injury. Anesth Analg 1985；64：1156-1160（II-a）
20) Pentothal (thiopental sodium injection), Product information. Abbott Laboratories, Illinois, USA（III）
21) Pizov R, Brown RH, Weiss YS, et al：Wheezing during induction of general anesthesia in patients with and without asthma. A randomized, blinded trial. Anesthesiology 1995；82：1111-1116（II-a）
22) Kingston HG, Hirshman CA：Perioperative management of the patient with asthma. Anesth Analg 1984；63：844-855（III）
23) Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration：application to healthy patients undergoing elective procedures：a report by the American Society of Anesthesiologists Task Force on Preoperative Fasting. Anesthesiology 1999；90：896-905（III）

2)

ミダゾラム midazolam

1) 薬理作用（小児における特異性について）[1]

1歳以上の小児患者ではミダゾラム単回投与後の薬物動態は成人患者と同様の結果が報告されている．体重補正されたクリアランスは成人と同様もしくは高めである(0.19～0.8 L/時/kg)．排泄半減期は成人と同様か短い(0.78～3.3時間)．持続静注時の薬物動態も成人患者と同様とされている．重症新生児は成人や健康な小児患者とは異なった薬物動態を示し，排泄半減期は著明に延長

し(6.5～12時間)，クリアランスは減少している(0.07～0.12 L/時/kg)．

ECMO (Extracorporeal Membrane Oxygenation) 中の新生児では，薬物の回路への吸着によると思われる，分布容量の増加や半減期の延長など，異なる薬物動態をしめす[2]．

2) 適応

(1) 全身麻酔の導入，維持

(2) けいれんの治療，

(3) 検査や処置の鎮静

(4) 人工呼吸中の鎮静

3) 使用法

(1) 全身麻酔の導入，維持[3～5]

小児患者にはミダゾラム 0.075～0.6 mg/kg を静脈内に緩徐に投与する．必要に応じて初回量の半量ないし同量を患者の状態をみながら追加投与する．投与後，通常1分以内にすみやかに意識消失が得られる．なお，症例によってはミダゾラム 0.6 mg/kg の投与によっても適切な麻酔導入が得られない場合が報告されており[5]，その際にはチオペンタール，プロポフォールなどの他の麻酔導入薬を併用することが望ましい．

全身麻酔の維持に用いる場合には，初回投与量，もしくはその半量を患者の状態や手術の進行状況に応じて適宜追加投与する．小児患者では排泄半減期が成人患者に比して短い場合があることに留意する．

(2) けいれんの治療[6,7]

小児のけいれん重積発作の治療として，ミダゾラム 0.15 mg/kg を静脈内投与する．必要があれば初回投与に続けて 1～2 mcg/kg/分で持続投与する．

(3) 検査，処置のための鎮静[8]

小児患者にはミダゾラム 0.1～0.3 mg/kg を緩徐に静脈内投与する．長時間に渡る鎮静が必要な場合には初回量投与に続けて 0.5-2 mcg/kg/分で持続投与する．目的とする鎮静の程度，年齢，全身状態に応じて投与量を調節する．疼痛を伴う処置を行う場合には麻薬性鎮痛薬や局所麻酔などを適宜併用する．

(4) 人工呼吸中の鎮静[9][10]

小児患者の人工呼吸中の鎮静については，ミダゾラム 0.25 mg/kg を静脈内投与後，0.4～6 mcg/kg/分で持続投与する．手術後や外傷患者など疼痛を伴う状態の患者では，塩酸モルヒネ，フェンタニルなどの麻薬性鎮痛薬の併用を考慮する．ミダゾラム投与量は鎮静の程度，全身状態，併用薬物などにより適宜増減する．

4) 注意点

(1) ミダゾラムの作用には個人差があるので，患者の状態をみながら投与量を調節する[12]．

(2) 他の鎮痛剤，鎮静剤などを併用している患者ではミダゾラムの作用が増強される場合があるので投与量を減弱する[11]．

(3) ミダゾラムの投与により呼吸抑制，循環抑制があらわれることがあるので，呼吸及び循環動態の連続的な観察が行える状況においてのみ使用する．具体的には心電図モニター，パルスオキシメーター，血圧計その他適切な方法でモニタリングを行うべきである．観察は患者が完全に回復するまで行う[11]．

(4) 小児の基本的蘇生措置に精通した医師の監視下にて使用する．蘇生措置に必要な気道確保器具，救急薬品などはあらかじめ用意しておく[11]．

(5) 小児患者にミダゾラムを静注投与した際におこる比較的頻度の高い副作用は次の通りである：酸素飽和度低下：4.6%，無呼吸：2.8%，低血圧：2.7%，脱抑制：2.0%，しゃっくり：1.2%，けいれん様発作：1.1%，眼振：1.1%.気道に関連した副作用がみられた患者のうち多くは他の中枢神経系抑制剤の併用投与を受けていた[1]．

(6) 新生児に対して急速静脈投与を行った際に高度の低血圧がみられた症例が報告されている[1]．特に未熟児，全身状態の不良な新生児，フェンタニルが投与されている新生児では十分に注意して使用する．逆にミダゾラムが持続静脈投与されている新生児に対してフェンタニルを静注した際に高度の低血圧がみられた症例も報告されている．

(7) 新生児に対して急速静脈投与を行った後にけいれん発作が見られた症例が報告されている[1]．

(8) 日本で発売されているミダゾラム製剤（ドルミカム）にはベンジルアルコールは添加されていない．米国で発売されているミダゾラム製剤 (Versed) にはベンジルアルコールが添加されており，未熟児，新生児に対してミダゾラムを大量かつ長時間に渡り投与した場合には，ベンジルアルコールによる毒性により低血圧，代謝性アシドーシス，核黄疸の頻度の上昇などが起こりうる[1]．

(9) 肥満した小児患者では体重当たりの投与量は理想体重で計算する[1]．

(10) ミダゾラムは肝臓のシトクロムP 450-3 A 4 にて代謝される．同酵素で代謝される他の薬物（シメチジン，エリスロマイシン，ジルチアゼム，ベラパミル，ケトコナゾール，イトラコナゾールなど）を投与されてい

る患者では，ミダゾラムの作用が遷延する場合がある[1]．

(11) 他のベンゾジアゼピン系鎮静剤と同様に，閉塞隅角緑内障の患者に対しては禁忌である[1]．

(12) ミダゾラムの過量に対してはフルマゼニル投与で対処できる．フルマゼニル投与の前には適切な気道確保は必須である．けいれんの既往がある小児患者ではフルマゼニル投与後にけいれんを発症する場合もある[1]．フルマゼニル投与後の再鎮静に対しても注意を要する．

(13) 集中治療領域で長期間に渡り大量のミダゾラムを投与されていた小児患者において，急激な投与中止後に興奮状態，幻覚，けいれんなどの離脱症状を示した症例が報告されている[12]．

(14) 集中治療領域での鎮静目的に長期間の投与ではミダゾラムに対する耐性が出現し，鎮静を得るための投与量が多くなることがある．その際には，他の鎮静剤の併用を考慮する．

(15) 鎮静目的であっても原則として投与前には絶飲食時間をとる．小児における適切な絶飲食時間とは軽食及び粉ミルク6時間，母乳4時間，飲水2時間が目安である[13]．

5) 参考文献

1) VERSED (midazolam HCl) INJECTION, Product Information revised 6/2000. Roche Laboratories Inc. New Jersey, USA
2) Mulla H, McCormack P, Lawson G, et al : Pharmacokinetics of midazolam in neonates undergoing extracorporeal membrane oxygenation. Anesthesiology 2003 ; 99 : 275-282 (I)
3) Cole WH : Midazolam in paediatric anaesthesia. Anaesth Intensive Care 1982 ; 10 : 36-39 (II-a)
4) Jones RD, Visram AR, Chan MM, et al : A comparison of three induction agents in paediatric anaesthesia-cardiovascular effects and recovery. Anaesth Intensive Care 1994 ; 22 : 545-555 (II-a)
5) Salonen M, Kanto J, Iisalo E, et al : Midazolam as an induction agent in children : a pharmacokinetic and clinical study. Anesth Analg 1987 ; 66 : 625-628 (II-a)
6) Rivera R, Segnini M, Baltodano A, et al : Midazolam in the treatment of status epilepticus in children. Crit Care Med 1993 ; 21 : 991-994 (II-c)
7) Pellock JM : Use of midazolam for refractory status epilepticus in pediatric patients. J Child Neurol 1998 ; 13 : 581-587 (III)
8) Rosen DA, Rosen KR : Intravenous conscious sedation with midazolam in paediatric patients. Int J Clin Pract 1998 ; 52 : 46-50 (III)
9) Booker PD, Beechey A, Lloyd-Thomas AR : Sedation of children requiring artificial ventilation using an infusion of midazolam. Br J Anaesth 1986 ; 58 : 1104-1108 (II-c)
10) Rosen DA, Rosen KR : Midazolam for sedation in the paediatric intensive care unit. Intensive Care Med 1991 ; 17 : S 15-S 19 (II-c)
11) ドルミカム注添付文書(第4版)，2002年3月．山之内製薬．東京
12) Sury MR, Billingham I, Russell GN, et al : Acute benzodiazepine withdrawal syndrome after midazolam infusions in children. Crit Care Med 1989 ; 17 : 301-302 (III)
13) Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration : application to healthy patients undergoing elective procedures : a report by the American Society of Anesthesiologists Task Force on Preoperative Fasting. Anesthesiology 1999 ; 90 : 896-905 (III)

3)

プロポフォール propofol

1) 薬理作用

1～3歳児に4 mg/kgを単回静脈内投与した時の中央コンパートメント容量は成人に比べて約3倍，クリアランスは約1.5倍，定常状態時の体重当たりの分布容量は約3.5倍と大きいことが報告されている[1]．3～11歳までの小児に3 mg/kg単回静注時の中央コンパートメント容量は成人と比べて約1.5倍，クリアランスはほぼ同等，定常状態時の体重当たりの分布容積は4.2倍と大きかった[2]．これらI～11歳までの小児でのデータから，単回投与で成人と同じ血中濃度を得るには成人と比べて多量が必要となるが，クリアランスも大きいことからそれほど蓄積作用は考えられない．しかし半減期はプロポフォールの持続投与に比例し延長するとの報告もあり[3]，長時間投与では薬物が残存し，覚醒を遅らせる．

2) 適 応

(1) 全身麻酔の導入及び維持
(2) 検査時の鎮静

「厚生労働省医薬品等適正使用推進施行事業−
麻酔薬および麻酔関連薬使用ガイドライン−
改訂第２版（2004年５月　社団法人　日本麻酔科学会）」

総責任者は　与五沢　利夫
ミダゾラム担当　蔵谷　紀文（国立療養所香川小児病院　麻酔科）

■名称　社団法人 日本麻酔科学会
■住所　〒 113-0033
東京都文京区本郷３丁目18番11号 TY ビル6F
■電話番号　　03-3815-0590
■FAX 番号　　03-3813-0464
http://www.anesth.or.jp/common/location.html

学会名：　日本小児神経学会

医薬品名：　プレドニゾロン

要約表　（様式）

1．小児医療を行うにあたり必要と考えられる処方等に関する概要 ※現在の国内承認内容と異なる部分には下線を付して下さい。	販売名 （一般名）	販売名：プレドニン、プレドニゾロン、プレドハン、プレロン （一般名：プレドニゾロン predonisolone）
	関係企業	プレドニン錠：武州-塩野義 プレドニゾロン散、剤：武田薬品 プレドニゾロン錠：(1)旭化成(2)イセイ(3)三恵薬品、三和化学、純生薬品、竹島、日本ガレン、東洋ファルマー、東和薬品、ニプロファーマ、陽進堂(4)メルクホエイ プレドニゾロン末、散：丸石 プレドハン錠：ニプロファーマ プレロン錠：大洋薬品
	剤型・規格	白色結晶性の粉末 末 97～102% 散剤：1%（武田薬品：1g 中にプレドニゾロン 10mg 含有する白色粉末、無臭、苦い） 錠剤：1mg、2.5mg、5mg （塩野義プレドニン錠剤：うすい橙色の素錠、無臭 武田薬品プレドニゾロン錠剤：白色の素錠　）
	効能・効果	プレドニゾロンは主として抗炎症作用、抗アレルギー作用、他に生体における諸種の代謝作用、生体免疫反応への作用がある。 Duchenne 型筋ジストロフィー患者においては、筋量増加、筋力増強、運動機能長期保持が得られる。その理由として、筋ジストロフィーモデルマウスにおける実験で証明された、以下の効果が上げられる。 (1) 信号伝達、免疫応答等に関する遺伝子の mRNA 量の調整 (2) 細胞障害性 T リンパ球の減少 (3) 細胞内カルシウム流入、濃度の低下 (4) ラミニンの増加、再生筋増加 (5) 筋アポトーシス、細胞浸潤の抑制 (6) ジストロフィン発現の増加 (7) 神経筋伝達への作用 (8) 筋繊維損傷の防御 (9) 筋壊死の抑制 (10) 骨格筋崩壊の速度低下 (11) 筋内タウリン、クレアチン値の増加

学会名：　日本小児神経学会

医薬品名：　プレドニゾロン

	用法・用量	米国においては、米国神経学アカデミー(AAN)、小児神経学会(CNS)のガイドラインにてプレドニゾン（predonisone）0.75mg/kg/日内服、体重増加、尿糖などの副作用出現時には0.30mg/kg/日へ減量する方針が推奨されている。 英国においても副作用が少なく、効果が得られる量としてプレドニゾロン（predonisolon）0.75mg/kg/日投与が推奨されている。 本邦では、プレドニゾロン 0.5mg/kg の隔日投与がされているが、その量でも有効であり、副作用が少ない。
	対象年齢	基本的に全年齢で対象となるが、5歳以下での経験は非常に少ない。
	その他	
	別添１の類型	2)国内に同一有効成分および同一剤型の医薬品はあるが、小児（あるいは特定の年齢群）の必要な適応（以下「新規適応」という。）が無いもの。 (ア)　　小児（あるいか特定の年齢群）の他の適応はある （用量や安全性の評価がある程度されている） (1)成人や他年齢群でも新規適応がない。
2．欧米での承認状況	承認取得国及び承認年月日	欧米では治療法の一つとして肯定的である。 米国では米国神経学アカデミー(AAN)、小児神経学会(CNS)でも Duchenne 型筋ジストロフィー患者へのプレドゾン（predonisone）投与ガイドラインも作成されている。
	販売名	ORAPRED(一般名：predonisolone sodium phosphate oral solution)など
	関係企業名	Biomarin など
	剤型・規格	
	効能・効果	Duchenne 型筋ジストロフィー患者における筋量増加、筋力増強、運動機能長期保持の獲得。

学会名：　日本小児神経学会

医薬品名：　プレドニゾロン

	用法・用量	米国神経学アカデミー(AAN)、小児神経学会(CNS)のガイドラインにて、プレドニゾン（predonisone）として0.75mg/kg/日内服、副作用出現時には0.30mg/kg/日へ減量する方針が推奨されている。 英国では一般的にプレドニゾロン(predonisolone)として0.75mg/kg/日投与が推奨。
	対象年齢	一般的に6歳以上
	その他	米国神経学アカデミー(AAN)、小児神経学会(CNS)のガイドラインでは糖質コルチコイド薬としてプレドニゾン（predonisone）が記載されている。英国ではプレドニゾロン(predonisolone)である。
3．有用性を示すエビデンスについて	別添2（ア）①の該当性について	
	別添2（ア）②の該当性について	Duchenne 型筋ジストロフィー(DMD)患者に対する糖質コルチコイド投与による治療に関してはこれまでに約30の報告がある。 中でも以下の5編は症例数も多く、全無作為二重盲検法を使用しており、強力なエビデンスであると考えられる。 (1) Mendell Jr et al.N.Engl J Med 1989;320:1592-1597 (2) Griggs RC et al. Arch Neurol 1991;48:383-388 (3) Angelini C et al. Muscle Nerve 1994;17:386-391 (4) Backman E et al. Neuromusc Disord 1995;5:233-241 (5) Rahman MM et al. Bangladesh Med Res Couns Bull 2001;27:38-42

現時点まで得られているエビデンスについて

中でも(1)Neurology. 2005 Jan 11;64(1):13-20.に掲載されたMoxley RT 3rd等の報告(Practice parameter: corticosteroid treatment of Duchenne dystrophy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Societ)は前述した米国神経学アカデミー(AAN)、小児神経学会(CNS)のガイドラインの根拠となっている。この報告は1966年から2004年までのDMDと糖質コルチコイド治療に関する25の報告を、治療、経過観察期間とプレドニゾン(predonison)の投与量によりいくつかのグループに分け評価を行った。評価は筋力、尿中クレアチン量（筋量)、階段昇降、走行、起立にかかる時間による運動機能評価、肺機能検査により行われた。いずれのグループも糖質コルチコイド（プレドニゾン、プレドニゾロン）投与群の方がプラセボ群に比較して、明らかな有意差をもって改善が認められた。高用量群の方が低用量軍より、有為差のある効果を認めたが、一方で副作用の出現率（体重増加、尿糖、白内障など）が有意に認められた。結論として0.75mg/kg/日投与が最も副作用が少なく効果的な結果が得られる投与量として推奨された。
また(2) Cochrane Database Syst Rev.に2004年に発表され、以後も継続して亢進されているManzur AY等によるレビュー（Glucocorticoid corticosteroids for Duchenne muscular dystrophy）においても同様にCochran Neuromuscular disease group registerと1966年以後の報告の中から十分な経過観察期間があり、且つ無作為試験を行っている研究を抽出し、評価を行っている。評価内容は6ヶ月から2年内の筋力、運動機能により行われた。(1)と同様に、有意差をもって、糖質コルチコイド（Predonisolone, predonisone, deflazacort）投与群に効果が認められた。

(3)我が国でも平成8から13年の厚生労働省精神・神経疾患研究委託費による研究報告書、筋ジストロフィーの遺伝相談法及び病態に基づく治療法の開発に関する研究において、姜ら、大澤等が歩行可能時期の延長等の臨床効果に関して報告をしている。

学会名：　日本小児神経学会

医薬品名：　プレドニゾロン

	根拠となる論文・試験については、別表に記載願います。	
4．（1）適応疾病の重篤度等	別添2（イ）①の該当性について	
	別添2（イ）②の該当性について	適応疾患が重篤であり、病気の進行が不可逆及び日常生活に著しい影響を及ぼす疾患
	別添2（イ）③の該当性について	
	評価理由 Duchenne 型筋ジストロフィーは 5 歳前に発症し、7ー12 歳に歩行不能となり、20 代で呼吸不全などから死に至る不可逆性の重篤な疾患である。 歩行不能となってからは、症状が進行し、寝返り不可、完全に介護を必要とする。また 10 代後半から呼吸機能の低下が認められ、人工呼吸器を必要となるケースが多い。	
	根拠となる論文・試験については、別表に記載願います。	
4．（2）小児科領域における	別添2（ウ）①の該当性について	（ウ）既存の治療法、予防法がない。

学会名：　日本小児神経学会

医薬品名：　プレドニゾロン

医療上の有用性	別添2（ウ）②の該当性について	
	別添2（ウ）③の該当性について	
	評価理由 Duchenne 型筋ジストロフィーに関しては、骨格筋細胞膜のジストロフィンの欠損が理由とされ、その遺伝子解析も進み、実験動物においては遺伝子治療の試みもなされている。しかし、遺伝子治療、筋芽細胞移植などの治療法に関しても、あくまでも動物実験の段階である。有効な治療法、予防法が存在しない段階で、筋力を保ち、歩行可能時間延長などの効果のある糖質コルチコイド療法の導入は非常に有用であると考える。	
	根拠となる論文・試験については、別表に記載願います。	
5．優先度	有効成分中の3位	