Versed advertisement.

[s.l.]: [s.n.], 1999-10-10

ALL IS FORGOTTEN.

NEW PEDIATRIC INDICATION

- **The only injectable sedative indicated for premedication in children and continuous infusion in mechanically ventilated children and neonates**
- **For IM or IV premedication in children 6 months and older...may ease separation from parents[1]**
- **Most children do not remember painful procedures[2]**
- **Smooth, steady control of sedation in critical care settings with continuous infusion[3-5]**
- **Administered safely in over 24 million pediatric patients[6]**

VERSED®
midazolam HCl (IV)
INJECTION
VERSED is available in 1 mg/mL and 5 mg/mL strengths.

Calms the Child, Reduces the Recall

VERSED (midazolam HCl) should be titrated slowly, never given as a bolus. Respiratory depression and/or arrest may result from excess doses or rapid or single bolus. VERSED is 3 to 4 times as potent per mg as diazepam.

Drug elimination may be delayed in patients receiving erythromycin and/or other P450-3A4 enzyme inhibitors 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, and in preterm and term infants, particularly those receiving opioids and/or when VERSED is rapidly administered.

When VERSED is given in conjunction with opioids or other sedatives, the potential for respiratory depression/airway obstruction is increased, and the minimum effective VERSED dose is generally reduced.

References: 1. Klein RL, Kingston HGG, Childs D. Refinements in the use of intramuscular midazolam premedication in pediatric day surgery patients. *Anesth Analg.* 1989;68:S148. Abstract. **2.** Friedman AG, et al. Midazolam premedication for pediatric bone marrow aspiration and lumbar puncture. *Med Pediatr Oncol.* 1991;19:499-504. **3.** Rosen DA, Rosen KR. Midazolam for sedation in the paediatric intensive care unit. *Intensive Care Med.* 1991;17:S15-S19. **4.** Hartwig S, Roth B, Theisohn M. Clinical experience with continuous intravenous sedation using midazolam and fentanyl in the paediatric intensive care unit. *Eur J Pediatr.* 1991;150:784-788. **5.** 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. **6.** Data on file (Abs. 069-032), Hoffmann-La Roche Inc., Nutley, New Jersey.

VERSED®
(midazolam HCl) Ⓥ
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

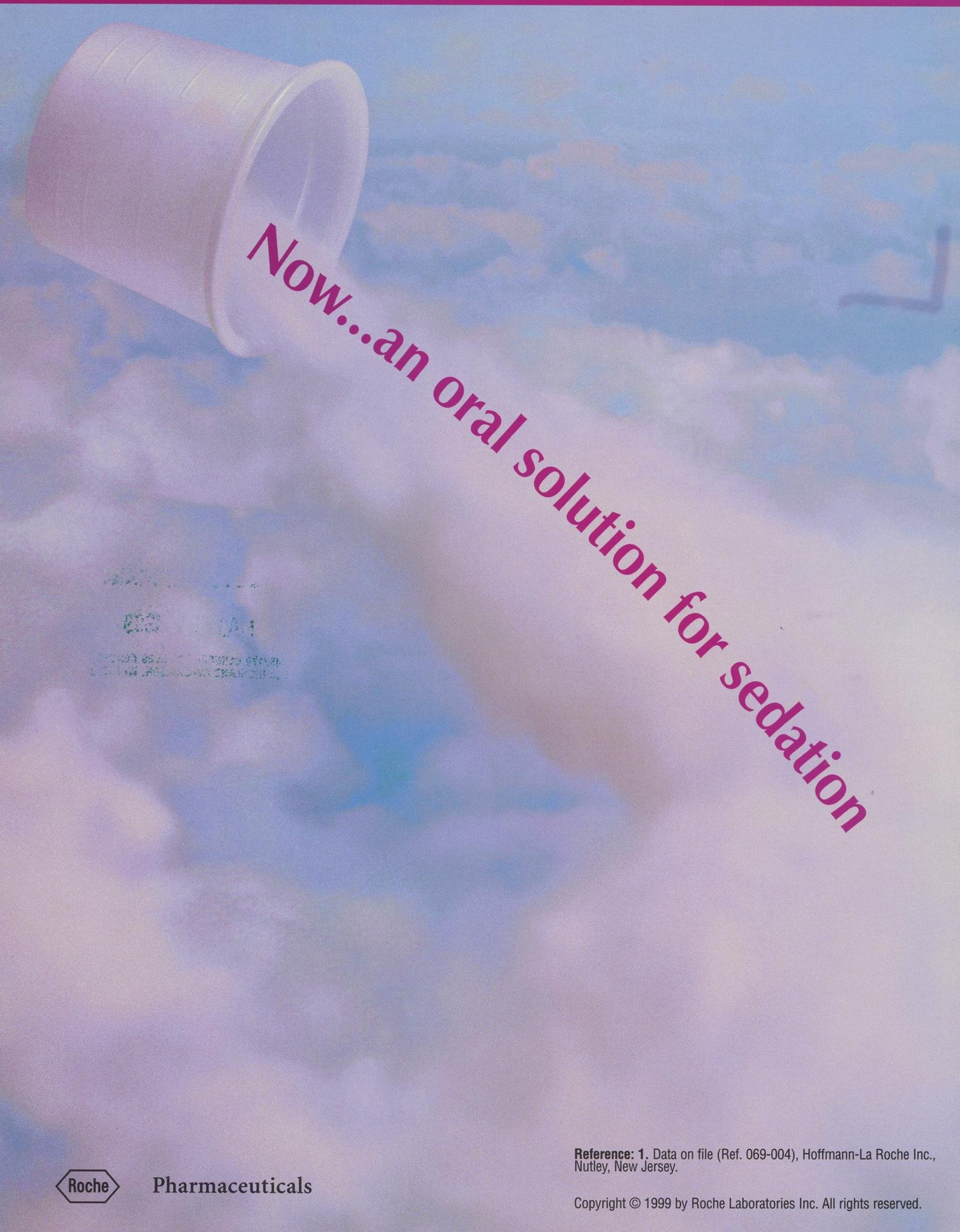
Adult and Pediatric: Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED 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. 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 VERSED for sedation/anxiolysis/amnesia is age, procedure, and route dependent.
Neonates: VERSED 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.

CONTRAINDICATIONS: Injectable VERSED 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 VERSED; patients with glaucoma have not been studied.
VERSED is not intended for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol in the dosage form.
WARNINGS: VERSED 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 VERSED 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 VERSED depresses respiration and because opioid agonists and other sedatives can add to this depression, VERSED 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, VERSED 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.
Serious cardiorespiratory adverse events have occurred after administration of VERSED. 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 VERSED; 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 VERSED 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 VERSED. 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. 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 VERSED is recommended, and the possibility of profound and/or prolonged effect should be considered.
Injectable VERSED 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 VERSED 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 VERSED. 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 VERSED following nonintravenous and nonintramuscular routes of administration have not been established. VERSED should only be administered intramuscularly or intravenously.
The decision as to when patients who have received injectable VERSED, 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 VERSED 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.
Usage In Preterm Infants And Neonates: Rapid injection should be avoided in the neonatal population. VERSED 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 VERSED.

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 VERSED) containing this preservative must take into account the total amount of benzyl alcohol administered. The recommended dosage range of VERSED 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 VERSED should be decreased for elderly and for debilitated patients. These patients will also probably take longer to recover completely after VERSED administration for the induction of anesthesia.VERSED 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 VERSED 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 VERSED 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 VERSED and concomitant medications, and have the personnel and size-appropriate equipment and facilities available for monitoring and intervention. Practitioners administering VERSED must have the skills necessary to manage reasonably foreseeable adverse effects, particularly skills in airway management. For information regarding withdrawal see DRUG ABUSE AND DEPENDENCE section.
Information for Patients: To assure safe and effective use of benzodiazepines, the following information and instructions should be communicated to the patient when appropriate:
1. Inform your physician about any alcohol consumption and medicine you are now taking, especially blood pressure medication and antibiotics, including drugs you buy without a prescription. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol during benzodiazepine treatment.
2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.
4. Patients should be informed of the pharmacological effects of VERSED, such as sedation and amnesia, which in some patients may be profound. The decision as to when patients who have received injectable VERSED, 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 VERSED 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 VERSED should be adjusted according to the type and amount of concomitant medications administered and the desired clinical response.
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.
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 VERSED for premedication in adults.
The intravenous administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED 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, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration in adults. VERSED 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. VERSED 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, succinylcholine, d-tubocurarine and other nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed in adults or pediatric patients. In neonates, however, severe hypotension has been reported with concomitant administration of fentanyl. This effect has been observed in neonates on an infusion of midazolam who received a rapid injection of fentanyl and in patients on an infusion of fentanyl who have received a rapid injection of midazolam.
Drug/Laboratory Test Interactions: Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.
Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:* Midazolam maleate was administered with diet in mice and rats for 2 years at dosages of 1, 9 and 80 mg/kg/day. In female mice in the highest dose group there was a marked increase in the incidence of 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.
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 VERSED 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, VERSED is not recommended for obstetrical use.
Nursing Mothers: Midazolam is excreted in human milk. Caution should be exercised when VERSED is administered to a nursing woman.
Pediatric Use: The safety and efficacy of VERSED for sedation/anxiolysis/amnesia following single dose intramuscular administration, intravenously by intermittent injections and continuous infusion have been established in pediatric and neonatal patients. UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE INCREMENTS OF VERSED ON A MG/KG BASIS. As a group, pediatric patients generally require higher dosages of VERSED (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 VERSED 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.
VERSED 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.
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 VERSED in adults and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and

NEW ORAL



Reference: 1. Data on file (Ref. 069-004), Hoffmann-La Roche Inc., Nutley, New Jersey.

Roche Pharmaceuticals

For premedication sedation, anxiolysis and amnesia in pediatric patients

Reliable Sedation for a Smooth Procedure

- Accepted by 95% of patients, cherry-flavored VERSED SYRUP eases separation from parents and facilitates cooperation at induction of anesthesia.[1] And that can mean a procedure that's easy on patients and their parents.

The Oral Solution for Premedication

- Needle-free, premixed and ready to use, VERSED SYRUP provides prompt, satisfactory sedation—within 10 minutes for >70% of patients.[1] Sedative/anxiolytic effects last up to 45 minutes.[1]

Adverse Events Profile

- In clinical trials, adverse events prior to mask induction in all body systems combined were reported in 1.8% of patients. During the entire monitoring period, which included premedication, anesthesia and recovery, adverse events in all body systems were reported in 21% of patients. Respiratory depression was reported in 1% of patients.

New

VERSED® SYRUP

midazolam HCl IV

2mg/mL

The solution for pediatrics

Important Safety Considerations

VERSED SYRUP has been associated with respiratory depression and respiratory arrest, especially when used for sedation in non-critical care settings. VERSED SYRUP has been associated with reports of respiratory depression, airway obstruction, desaturation, hypoxia and apnea, most often when used concomitantly with other central nervous system depressants (eg, opioids). When VERSED SYRUP is given as the sole agent at recommended dosages, these adverse respiratory events occur infrequently.

VERSED SYRUP should be used only in hospital or ambulatory care settings (including physicians' and dentists' offices) that can provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and age- and size-appropriate equipment for ventilation and intubation, and personnel trained in their use and skilled in airway management, should be assured. For deeply sedated patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

VERSED SYRUP should only be used with itraconazole or ketoconazole if absolutely necessary, due to the potential for intense and prolonged sedation as well as respiratory depression. VERSED SYRUP should be used with caution in conjunction with any medications known to inhibit or induce the cytochrome P450 3A4 enzyme system.

The dose of VERSED SYRUP in pediatric patients is based on body weight and must be individualized. When used in high-risk patients, or in conjunction with narcotics or other CNS depressants, the minimum effective dose should be considered.

VERSED SYRUP must be given to patients only if they will be monitored by direct visual observation by a healthcare professional. VERSED SYRUP has not been studied in patients less than 6 months of age.

Please see adjacent page for boxed warning and summary of product information.

VERSED®
(midazolam HCl) Ⓥ
SYRUP

Before prescribing, please consult complete product information, a summary of which follows:

VERSED Syrup has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. VERSED Syrup has been associated with reports of respiratory depression, airway obstruction, desaturation, hypoxia, and apnea, most often when used concomitantly with other central nervous system depressants (eg, opioids). VERSED Syrup should be used only in hospital or ambulatory care settings, including physicians' and dentists' offices, THAT CAN PROVIDE FOR CONTINUOUS MONITORING OF RESPIRATORY AND CARDIAC FUNCTION. IMMEDIATE AVAILABILITY OF RESUSCITATIVE DRUGS AND AGE- AND SIZE-APPROPRIATE EQUIPMENT FOR VENTILATION AND INTUBATION, AND PERSONNEL TRAINED IN THEIR USE AND SKILLED IN AIRWAY MANAGEMENT SHOULD BE ASSURED (see WARNINGS). For deeply sedated patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

INDICATIONS AND USAGE: VERSED Syrup is indicated for use in pediatric patients for sedation, anxiolysis and amnesia prior to diagnostic, therapeutic or endoscopic procedures or before induction of anesthesia. VERSED Syrup is intended for use in monitored settings only and not for chronic or home use (see WARNINGS). **VERSED SYRUP MUST BE USED AS SPECIFIED IN THE LABEL.**

CONTRAINDICATIONS: Patients with a known hypersensitivity to the drug or allergies to cherries or formulation excipients. Patients with acute narrow-angle glaucoma. 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 of general anesthesia with injectable VERSED; patients with glaucoma have not been studied.

WARNINGS: Serious respiratory adverse events have occurred after administration of oral VERSED, most often when used in combination with other central nervous system depressants. These adverse events have included respiratory depression, airway obstruction, oxygen desaturation, apnea, and rarely, respiratory and/or cardiac arrest (see box WARNING). When oral midazolam is administered as the sole agent at recommended doses these respiratory events occur infrequently. These events are also markedly increased in patients with abnormal airway anatomy, cyanotic congenital heart disease, sepsis or severe pulmonary disease.

Prior to administration in any dose, ensure 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. VERSED Syrup must never be used without individualization of dosage, particularly when used with other medications capable of producing central nervous system depression.

VERSED Syrup should be used only in hospital or ambulatory care settings, including physicians' and dentists' offices, that are equipped to provide continuous monitoring of respiratory and cardiac function. VERSED Syrup must only be administered to patients if they will be monitored by direct visual observation by a health care professional. If VERSED Syrup will be administered in combination with other anesthetic drugs or drugs which depress the central nervous system, patients must be monitored by persons specifically trained in the use of these drugs and, in particular, in the management of respiratory effects of these drugs, including respiratory and cardiac resuscitation of patients in the age group being treated.

For deeply sedated patients, a dedicated individual whose sole responsibility is to observe the patient, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

Patients should be continuously monitored for early signs of hypoventilation, airway obstruction, or apnea with means for detection readily available (eg, 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.

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. Consideration should be given to the possibility of paradoxical reaction. Should such reactions occur, the response to each dose of VERSED and all other drugs, including local anesthetics, should be evaluated before proceeding. Reversal of such responses with flumazenil has been reported in pediatric and adult patients.

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

Coadministration with ketoconazole and itraconazole has been shown to result in large increases in C_{max} and AUC of midazolam due to a decrease in plasma clearance of midazolam (see PRECAUTIONS). Due to the potential for intense and prolonged sedation and respiratory depression, VERSED Syrup should only be coadministered with these medications if absolutely necessary and with appropriate equipment and personnel available to respond to respiratory insufficiency.

Higher risk pediatric surgical patients may require lower doses, whether or not concomitant sedating medications have been administered. Pediatric patients with cardiac or respiratory compromise may be unusually sensitive to the respiratory depressant effect of VERSED. Pediatric 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. Patients with chronic renal failure or congestive heart failure eliminate midazolam more slowly.

The decision as to when patients, particularly outpatients, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized. Gross tests of recovery 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. Particular care should be taken to assure safe ambulation.

Usage in Pregnancy: Although not studied in pregnant patients, an increased risk of congenital malformations associated with benzodiazepine drugs (diazepam and chlordiazepoxide) have been suggested in several studies. If pregnant, the patient should be apprised of the potential hazard to the fetus. ***Usage in Preterm Infants and Neonates:*** Not studied in patients less than 6 months of age.

PRECAUTIONS: See WARNINGS and *Drug Interactions.* Efficacy and safety are functions of the dose administered, the clinical status of the patient and the **concomitant use of CNS depressants or inhibitors of CYP3A4 isozymes.** See WARNINGS and *Drug Interactions.* ***Information for Patients:*** To assure safe and effective use, the following should be communicated to the patient when appropriate:

1. Inform your physician about any alcohol consumption and medicine you are now taking, especially blood pressure medication and antibiotics, including drugs you buy without a prescription. Alcohol has an increased effect when consumed with benzodiazepines. 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 VERSED Syrup, such as sedation and amnesia, which in some patients may be profound. The decision as to when patients may engage in activities requiring complete mental alertness must be individualized. 5. VERSED Syrup should not be taken in conjunction with grapefruit juice. 6. For pediatric patients, particular care should be taken to assure safe ambulation.

Drug Interactions: *Inhibitors of CYP3A4 Isozymes:* Oral midazolam should be used with caution in patients treated with drugs known to inhibit CYP3A4 (ie, some azole antimycotics, protease inhibitors, calcium channel antagonists, and macrolide antibiotics) because inhibition of metabolism may lead to more intense and prolonged sedation. Patients being treated with such medications should receive lower than recommended doses of VERSED Syrup and the clinician should expect a more prolonged effect. Drugs such as erythromycin, diltiazem, verapamil, ketoconazole, fluconazole and itraconazole were shown to significantly increase the C_{max} and AUC of orally administered midazolam. Although not studied, the potent cytochrome P450 3A4 inhibitors ritanovir and nelfinavir may cause intense and prolonged sedation and respiratory depression. *Inducers of CYP3A4 Isozymes:* Cytochrome P450 inducers, such as rifampin, carbamazepine, and phenytoin, induce metabolism and caused a markedly decreased C_{max} and AUC of oral midazolam. Although not studied, phenobarbital is expected to have the same effect. Caution is advised in patients receiving these medications; dose adjustments should be considered. *CNS Depressants:* In one reported case, difficulty in achieving adequate sedation may have been due to both the gastrointestinal effects and stimulant effects of methylphenidate. The sedative effect of VERSED Syrup is accentuated by any concomitantly administered medication which depresses the central nervous system, particularly narcotics (eg, morphine, meperidine and fentanyl), propofol, ketamine, nitrous oxide, secobarbital and droperidol. Consequently, the dose of VERSED Syrup should be adjusted according to the type and amount of concomitant medications administered and the desired clinical response. No significant adverse interactions with common premedications (such as atropine, scopolamine, glycopyrrrolate, diazepam, hydroxyzine, and other muscle relaxants) or local anesthetics have been observed.

Drug/Laboratory Test Interactions: Midazolam has not been shown to interfere with test results. ***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 (10 times the highest oral dose of 1.0 mg/kg for a pediatric patient, on a mg/m^2 basis) group there was a marked increase in the incidence of hepatic tumors. In high-dose (19 times the pediatric 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 (1 to 2 times the pediatric dose) did not increase the incidence of tumors in mice or rats. The pathogenesis of induction of these tumors is not known. These tumors were found after chronic administration, whereas human use will ordinarily be single or intermittent 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 16 mg/kg/day PO (3 times the human dose of 1.0 mg/kg, on a mg/m^2 basis).

Pregnancy: *Teratogenic Effects:* Pregnancy Category D (see WARNINGS). ***Labor and Delivery:*** The use of VERSED Syrup 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, VERSED Syrup is not recommended for obstetrical use. ***Nursing Mothers:*** Midazolam is excreted in human milk. Caution should be exercised when administered to a nursing woman. ***Geriatric Use:*** Safety and efficacy have not been fully studied in geriatrics. One study noted a 60% incidence of hypoxemia in premedicated patients versus 15% in the nonpremedicated group. It is recommended that this product not be used in geriatrics. ***Use in Patients With Heart Disease:*** Following oral administration of 7.5 mg of midazolam to adult patients with congestive heart failure, the half-life of midazolam was 43% higher than in control subjects. One study suggests that hypercarbia or hypoxia following premedication with oral midazolam might pose a risk to children with congenital heart disease and pulmonary hypertension, although there are no known reports of pulmonary hypertensive crises that had been triggered by premedication. In the study, 22 children were premedicated with oral midazolam (0.75 mg/kg) or IM morphine plus scopolamine prior to elective repair of congenital cardiac defects. Both premedication regimens increased $PtcCO_2$ and decreased SpO_2 and respiratory rates preferentially in patients with pulmonary hypertension.

ADVERSE REACTIONS: Observed in a randomized, double-blind, parallel-group trial (n=397) conducted at doses of 0.25, 0.50 and 1.0 mg. ***Adverse Events occurring during the premedication period before mask induction:*** Occurred in 0.8% to 3.8% of patients depending on dose (1.8% overall); these were emesis, nausea, laryngospasm (at the moment of induction), and sneezing/rhinorrhea, each occurring in ≤1.5% of patients. ***Adverse Events (≥1%) occurring during the entire monitoring period (premedication, anesthesia, recovery):*** The highest incidences at any dose were as follows, with overall incidence generally lower: Emesis 11%, nausea 5%, hypoxia 4%, laryngospasm 4%, respiratory depression 2%, rhonchi 2%, airway obstruction 2%, upper airway congestion 2%, agitated 2%, bradycardia 2%, bigeminy 2%, prolonged sedation 2%, rash 2%. *All body systems:* 21%. For the respiratory system overall, adverse events increased in frequency as dosage was increased: 7/132 (5%) patients in the 0.25 mg/kg dose group, 9/132 (7%) patients in the 0.5 mg/kg dose group, and 15/133 (11%) patients in the 1.0 mg/kg dose group. Although many of the respiratory complications occurred in settings of upper airway procedures or concurrently administered opioids, a number of these events occurred outside of these settings as well. Administration of VERSED Syrup was generally accompanied by a slight decrease in both systolic and diastolic blood pressures, as well as a slight increase in heart rate. There were no deaths during the study and no patient withdrew from the study due to adverse events. Serious adverse events (both respiratory disorders) were experienced postoperatively by two patients: one case of airway obstruction and desaturation (SpO_2 of 33%) in a patient given VERSED Syrup 0.25 mg/kg, and one case of upper airway obstruction and respiratory depression following 0.5 mg/kg. Both patients had received intravenous morphine sulfate (1.5 mg total for both patients). Other adverse events that have been reported in the literature with the oral administration of midazolam (not necessarily VERSED Syrup), are listed below. The incidence rate for these events was generally <1%. *Respiratory:* apnea, hypercarbia, desaturation, stridor. *Cardiovascular:* decreased systolic and diastolic blood pressure, increased heart rate. *Gastrointestinal:* nausea, vomiting, hiccoughs, gagging, salivation, drooling. *Central Nervous System:* dysphoria, disinhibition, excitation, aggression, mood swings, hallucinations, adverse behavior, agitation, dizziness, confusion, ataxia, vertigo, dysarthria. *Special Senses:* diplopia, strabismus, loss of balance, blurred vision.

DRUG ABUSE AND DEPENDENCE: VERSED Syrup is a benzodiazepine and is a Schedule IV controlled substance that can produce drug dependence of the diazepam type. Benzodiazepines can cause physical dependence. Physical dependence results in withdrawal symptoms (ie, convulsions, hallucinations, tremors, abdominal and muscle cramps, vomiting and sweating), similar in characteristics to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of midazolam following chronic administration. Abdominal distention, nausea, vomiting and tachycardia are prominent symptoms of withdrawal in infants. Therefore, VERSED Syrup may be subject to misuse, abuse and addiction. The handling of VERSED Syrup should be managed to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law.

OVERDOSAGE: The manifestations of VERSED overdosage reported are similar to those observed with other benzodiazepines, including sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, and deleterious effects on vital signs. No evidence of specific organ toxicity from VERSED overdosage has been reported. *Treatment of Overdosage:* Treatment of VERSED 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. 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. Gastrointestinal decontamination with lavage and/or activated charcoal once the patient's airway is secure is also recommended. Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of VERSED and may be used in situations when an overdose with a benzodiazepine is known or suspected. There are anecdotal reports of adverse hemodynamic responses associated with VERSED following administration of flumazenil to pediatric patients. Prior to the administration of flumazenil, necessary measures should be instituted to secure the airway, assure adequate ventilation, and establish adequate intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. 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.

ISSUED: OCTOBER 1998

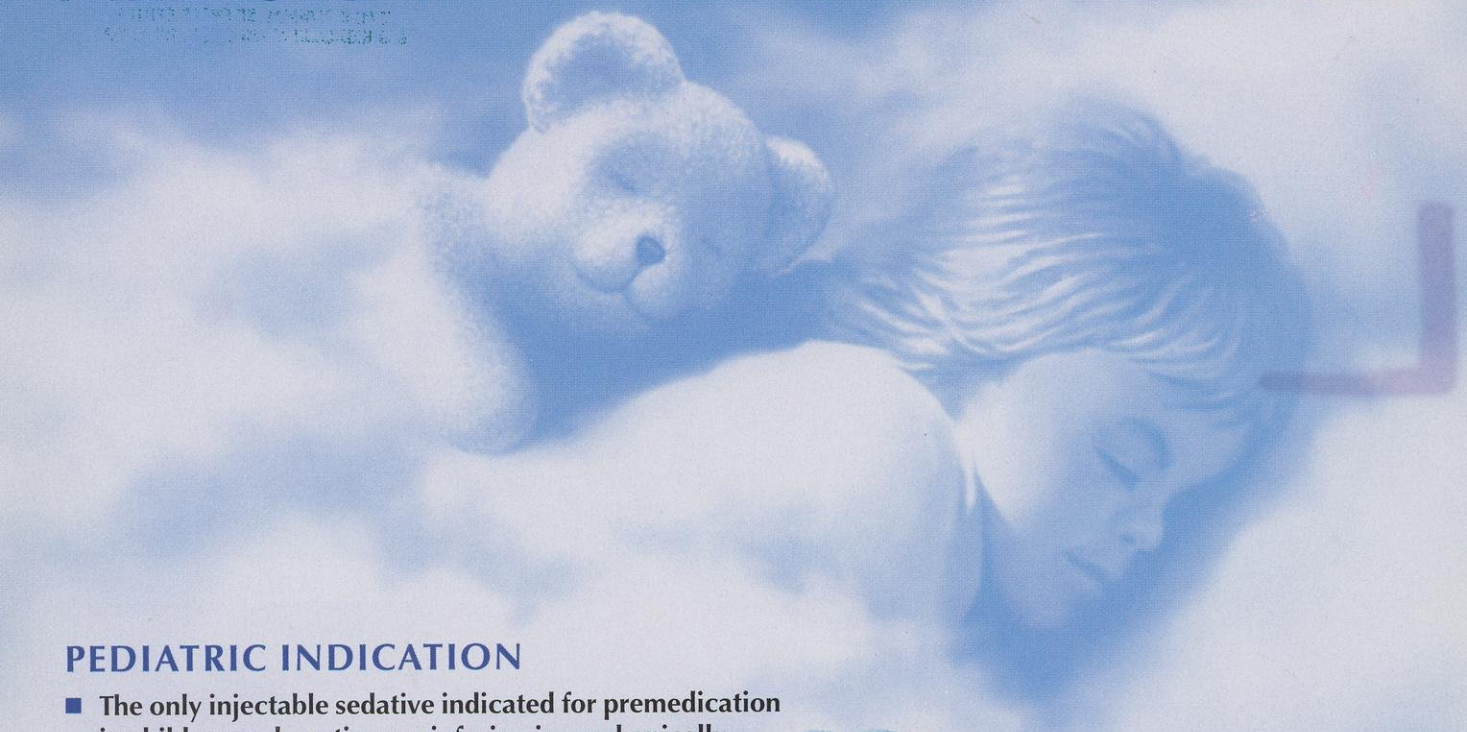
Roche Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

VS02

In most pediatric patients

ALL IS CALM. ALL IS FORGOTTEN.



PEDIATRIC INDICATION

- **The only injectable sedative indicated for premedication in children and continuous infusion in mechanically ventilated children and neonates**
- **For IM or IV premedication in children 6 months and older...may ease separation from parents[1]**
- **Most children do not remember painful procedures[2]**
- **Smooth, steady control of sedation in critical care settings with continuous infusion[3-5]**
- **Administered safely in over 24 million pediatric patients[6]**

VERSED®
midazolam HCl (IV)
INJECTION
VERSED is available in 1 mg/mL and 5 mg/mL strengths.

Calms the Child, Reduces the Recall

IMPORTANT SAFETY AND DOSING CONSIDERATIONS FOR PEDIATRIC SEDATION WITH VERSED

Because serious and life-threatening cardiorespiratory adverse events have been reported with VERSED (midazolam HCl), standard precautions for IV administration should include continuous monitoring (ie, pulse oximetry), detection and correction of these reactions, and immediate availability of oxygen and age- and size-appropriate resuscitative equipment. Ensure the availability of personnel skilled in early detection of hypoventilation, maintenance of a patent airway and ventilatory support. For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

VERSED should be titrated slowly, never given as a bolus. Respiratory depression and/or arrest may result from excess doses or rapid or single bolus. VERSED is 3 to 4 times as potent per mg as diazepam.

Drug elimination may be delayed in patients receiving erythromycin and/or other P450 3A4 enzyme inhibitors 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, and in preterm and term infants, particularly those receiving opioids and/or when VERSED is rapidly administered.

When VERSED is given in conjunction with opioids or other sedatives, the potential for respiratory depression/airway obstruction is increased, and the minimum effective VERSED dose is generally reduced.

Roche **Pharmaceuticals**

Please see adjacent page for boxed warning and summary of product information.

References: 1. Klein RL, Kingston HGG, Childs D. Refinements in the use of intramuscular midazolam premedication in pediatric day surgery patients. *Anesth Analg.* 1989;68:S148. Abstract. **2.** Friedman AG, et al. Midazolam premedication for pediatric bone marrow aspiration and lumbar puncture. *Med Pediatr Oncol.* 1991;19:499-504. **3.** Rosen DA, Rosen KR. Midazolam for sedation in the paediatric intensive care unit. *Intensive Care Med.* 1991;17:S15-S19. **4.** Hartwig S, Roth B, Theisohn M. Clinical experience with continuous intravenous sedation using midazolam and fentanyl in the paediatric intensive care unit. *Eur J Pediatr.* 1991;150:784-788. **5.** 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. **6.** Data on file (Abs. 069-032), Hoffmann-La Roche Inc., Nutley, New Jersey.

VERSED®
(midazolam HCl) ℂ
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

WARNING

Adults and Pediatrics: Intravenous VERSED 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 VERSED 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. 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 VERSED for sedation/anxiolysis/amnesia is age, procedure, and route dependent.

Neonates: VERSED 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.

CONTRAINDICATIONS: Injectable VERSED 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 VERSED; patients with glaucoma have not been studied.

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

WARNINGS: VERSED 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 VERSED 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 VERSED depresses respiration and because opioid agonists and other sedatives can add to this depression, VERSED 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, VERSED 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.

Serious cardiorespiratory adverse events have occurred after administration of VERSED. 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 VERSED; 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 VERSED 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 VERSED. 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. 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 VERSED is recommended, and the possibility of profound and/or prolonged effect should be considered.

Injectable VERSED 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 VERSED 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 VERSED. 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 VERSED following nonintravenous and nonintramuscular routes of administration have not been established. VERSED should only be administered intramuscularly or intravenously.

The decision as to when patients who have received injectable VERSED, 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 VERSED 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.

Usage in Preterm Infants and Neonates: Rapid injection should be avoided in the neonatal population. VERSED 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 VERSED.

VERSED® (midazolam HCl)

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 VERSED) containing this preservative must take into account the total amount of benzyl alcohol administered. The recommended dosage range of VERSED 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 of 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 VERSED should be decreased for elderly and for debilitated patients. These patients will also probably take longer to recover completely after VERSED administration for the induction of anesthesia.VERSED 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 VERSED 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 VERSED 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 VERSED and concomitant medications, and have the personnel and size-appropriate equipment and facilities available for monitoring and intervention. Practitioners administering VERSED must have the skills necessary to manage reasonably foreseeable adverse effects, particularly skills in airway management. For information regarding withdrawal see DRUG ABUSE AND DEPENDENCE section.

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

1. Inform your physician about any alcohol consumption and medicine you are now taking, especially blood pressure medication and antibiotics, including drugs you buy without a prescription. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol during benzodiazepine treatment.
2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.
4. Patients should be informed of the pharmacological effects of VERSED, such as sedation and amnesia, which in some patients may be profound. The decision as to when patients who have received injectable VERSED, 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 VERSED 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 VERSED should be adjusted according to the type and amount of concomitant medications administered and the desired clinical response.

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.

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 VERSED for premedication in adults.

The intravenous administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED 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, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration in adults. VERSED 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. VERSED 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, succinylcholine, d-tubocurarine and other nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed in adults or pediatric patients. In neonates, however, severe hypotension has been reported with concomitant administration of fentanyl. This effect has been observed in neonates on an infusion of midazolam who received a rapid injection of fentanyl and in patients on an infusion of fentanyl who have received a rapid injection of midazolam.

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

Carcinogenesis, Mutagenesis 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.

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 VERSED 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, VERSED is not recommended for obstetrical use.

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

Pediatric Use: The safety and efficacy of VERSED for sedation/anxiolysis/amnesia following single dose intramuscular administration, intravenously by intermittent injections and continuous infusion have been established in pediatric and neonatal patients. UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE INCREMENTS OF VERSED ON A MG/KG BASIS. As a group, pediatric patients generally require higher dosages of VERSED (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 VERSED 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.

VERSED 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.

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 VERSED in adults and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and