PDR®

54

EDITION

2000

PHYSICIANS' DESK REFERENCE®

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Printed on recycled paper

ISBN: 1-56363-330-2

Aricept—Cont.

Postintroduction Reports
Voluntary reports of adverse events temporally associated with ARICEPT® that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block, hemolytic anemia, hyponatremia, pancreatitis, and rash.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.

As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT® overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as gylcopyrrolate. It is not known whether ARICEPT® and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation and lower body surface temperature.

DOSAGE AND ADMINISTRATION

The dosages of ARICEPT® shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day.

The higher dose of 10 mg did not provide a statistically significantly greater clinical benefit than 5 mg. There is a suggestion, however, based upon order of group mean scores and dose trend analyses of data from these clinical trials, that a daily dose of 10 mg of ARICEPT® might provide additional benefit for some patients. Accordingly, whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference.

Evidence from the controlled trials indicates that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5 mg dose. In open label trials using a 6 week titration, the frequency of these same adverse events was similar between the 5 mg and 10 mg dose groups. Therefore, because steady state is not achieved for 15 days and because the incidence of untoward effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4 to 6 weeks.

ARICEPT® should be taken in the evening, just prior to retiring. ARICEPT® can be taken with or without food.

HOW SUPPLIED

ARICEPT® is supplied as film-coated, round tablets containing either 5 mg or 10 mg of donepezil hydrochloride.

The 5 mg tablets are white. The strength, in mg (5), is debossed on one side and ARICEPT is debossed on the other side.

The 10 mg tablets are yellow. The strength, in mg (10), is debossed on one side and ARICEPT is debossed on the other side.

5 mg (White)	Bottles of 30 (NDC# 62856-245-30) Unit Dose Blister Package 100 (10x10) (NDC# 62856-245-41)
10 mg (Yellow)	Bottles of 30 (NDC# 62856-246-30) Unit Dose Blister Package 100 (10x10) (NDC# 62856-246-41)

Storage: Store at controlled room temperature, 15°C to 30°C (59°F to 86°F).

Rx only

ARICEPT® is a registered trademark of
Eisai Co., Ltd., Tokyo, Japan
Manufactured and Marketed by
Eisai Inc., Teaneck, NJ 07666
Distributed/Marketed by
Roerig Division of Pfizer Inc, New York, NY 10017

200005 Revised September, 1998

Shown in Product Identification Guide, page 310

Available to physicians through Eisai Medical Sales Specialists and Representatives, free of charge. Most are available in Spanish.

Understanding Alzheimers Disease Brochure
Managing Alzheimers Disease Brochure
(both are disease specific brochures)
Know your Medicine Brochure – English only
(for patients on Aricept)
26 week patient diary
(also for patients on Aricept)

Elan Pharma

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(888) NEURO-05
(888) 638-7605
To Report Adverse Events Contact:
(877) ELAN GSS
(877) 352–6477

The products below are distributed by Elan Pharma, a business unit of Elan Pharmaceuticals, Inc.

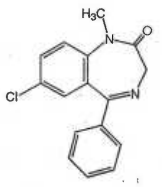
DIASTAT® Rectal Delivery System ℞

[dī 'ă-stat]
(diazepam rectal gel)
Rx only

DESCRIPTION

Diastat* rectal delivery system is a non-sterile diazepam gel provided in a prefilled, unit-dose, rectal delivery system. Diastat contains 5 mg/mL diazepam, propylene glycol, ethyl alcohol (10%), hydroxypropyl methylcellulose, sodium benzoate, benzyl alcohol (1.5%), benzoic acid and water. Diastat is clear to slightly yellow and has a pH between 6.5–7.2.

Diazepam, the active ingredient of Diastat, is a benzodiazepine anticonvulsant with the chemical name 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. The structural formula is as follows:



* Registered trademark of Elan Pharmaceuticals, Inc.

CLINICAL PHARMACOLOGY

Mechanism of Action

Although the precise mechanism by which diazepam exerts its antiseizure effects is unknown, animal and *in vitro* studies suggest that diazepam acts to suppress seizures through an interaction with γ-aminobutyric acid (GABA) receptors of the A-type ($GABA_A$). GABA, the major inhibitory neurotransmitter in the central nervous system, acts at this receptor to open the membrane channel allowing chloride ions to flow into neurons. Entry of chloride ions causes an inhibitory potential that reduces the ability of neurons to depolarize to the threshold potential necessary to produce action potentials. Excessive depolarization of neurons is implicated in the generation and spread of seizures. It is believed that diazepam enhances the actions of GABA by causing GABA to bind more tightly to the $GABA_A$ receptor.

Pharmacokinetics

Pharmacokinetic information of diazepam following rectal administration was obtained from studies conducted in healthy adult subjects. No pharmacokinetic studies were conducted in pediatric patients. Therefore, information from the literature is used to define pharmacokinetic labeling in the pediatric population.

Diastat is well absorbed following rectal administration, reaching peak plasma concentrations in 1.5 hours. The absolute bioavailability of Diastat relative to Valium® injectable is 90%. The volume of distribution of Diastat is calculated to be approximately 1 L/kg. The mean elimination half-life of diazepam and desmethyldiazepam following administration of a 15 mg dose of Diastat was found to be about 46 hours (CV=43%) and 71 hours (CV=37%), respectively. Both diazepam and its major active metabolite desmethyldiazepam bind extensively to plasma proteins (95–98%).

[See Figure 1 at top of next page]

Metabolism and Elimination: It has been reported in the literature that diazepam is extensively metabolized to one major active metabolite (desmethyldiazepam) and two minor active metabolites, 3-hydroxydiazepam (temazepam) and 3-hydroxy-N-diazepam (oxazepam) in plasma. At therapeutic doses, desmethyldiazepam is found in plasma at concentrations equivalent to those of diazepam while oxazepam and temazepam are not usually detectable. The metabolism of diazepam is primarily hepatic and involves demethylation (involving primarily CYP2C19 and CYP3A4) and 3-hydroxylation (involving primarily CYP3A4), followed by glucuronidation. The marked inter-individual variability in the clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19 (which is known to exhibit genetic polymorphism; about 3–5% of Caucasians have little or no activity and are "poor metabolizers") and CYP3A4. No inhibition was demonstrated in the presence of inhibitors selective for CYP2A6, CYP2C9, CYP2D6, CYP2E1, or CYP1A2, indicating that these enzymes are not significantly involved in metabolism of diazepam.

Special Populations

Hepatic Impairment: No pharmacokinetic studies were conducted with Diastat in hepatically impaired subjects. Literature review indicates that following administration of 0.1 to 0.15 mg/kg of diazepam intravenously, the half-life of diazepam was prolonged by two to five-fold in subjects with alcoholic cirrhosis (n=24) compared to age-matched control subjects (n=37) with a corresponding decrease in clearance by half: however, the exact degree of hepatic impairment in these subjects was not characterized in this literature (see PRECAUTIONS section).

Renal Impairment: The pharmacokinetics of diazepam have not been studied in renally impaired subjects (see PRECAUTIONS section).

Pediatrics: No pharmacokinetic studies were conducted with Diastat in the pediatric population. However, literature review indicates that following IV administration (0.33 mg/kg), diazepam has a longer half-life in neonates (birth up to one month; approximately 50–95 hours) and infants (one month up to two years; about 40–50 hours), whereas it has a shorter half-life in children (two to 12 years; approximately 15–21 hours) and adolescents (12 to 16 years; about 18–20 years) (see PRECAUTIONS section).

Elderly: A study of single dose IV administration of diazepam (0.1 mg/kg) indicates that the elimination half-life of diazepam increases linearly with age, ranging from about 15 hours at 18 years (healthy young adults) to about 100 hours at 95 years (healthy elderly) with a corresponding decrease in clearance of free diazepam (see PRECAUTIONS and DOSAGE AND ADMINISTRATION sections).

Effect of Gender, Race, and Cigarette Smoking: No targeted pharmacokinetic studies have been conducted to evaluate the effect of gender, race, and cigarette smoking on the pharmacokinetics of diazepam. However, covariate analysis of a population of treated patients following administration of Diastat indicated that neither gender nor cigarette smoking had any effect on the pharmacokinetics of diazepam.

Clinical Studies

The effectiveness of Diastat has been established in two adequate and well-controlled clinical studies in children and adults exhibiting the seizure pattern described below under INDICATIONS.

A randomized, double-blind study compared sequential doses of Diastat and placebo in 91 patients (47 children, 44 adults) exhibiting the appropriate seizure profile. The first dose was given at the onset of an identified episode. Children were dosed again four hours after the first dose and were observed for a total of 12 hours. Adults were dosed at four and 12 hours after the first dose and were observed for a total of 24 hours. Primary outcomes for this study were seizure frequency during the period of observation and a global assessment that took into account the severity and nature of the seizures as well as their frequency.

The median seizure frequency for the Diastat treated group was zero seizures per hour, compared to a median seizure frequency of 0.3 seizures per hour for the placebo group, a difference that was statistically significant ($p < 0.0001$). All three categories of the global assessment (seizure frequency, seizure severity, and "overall") were also found to be statistically significant in favor of Diastat ($p < 0.0001$). The following histogram displays the results for the "overall" category of the global assessment.

[See Figure 2 on next page]

Patients treated with Diastat experienced prolonged time-to-next-seizure compared to placebo ($p = 0.0002$) as shown in the following graph.

[See Figure 3 on next page]

In addition, 62% of patients treated with Diastat were seizure-free during the observation period compared to 20% of placebo patients.

Analysis of response by gender and age revealed no substantial differences between treatment in either of these subgroups. Analysis of response by race was considered unreliable, due to the small percentage of non-Caucasions.

A second double-blind study compared single doses of Diastat and placebo in 114 patients (53 children, 61 adults). The dose was given at the onset of the identified episode and patients were observed for a total of 12 hours. The primary outcome in this study was seizure frequency. The median seizure frequency for the Diastat-treated group was zero seizures per 12 hours, compared to a median seizure frequency of 2.0 seizures per 12 hours for the placebo group, a difference that was statistically significant ($p < 0.03$). Patients treated with Diastat experienced prolonged time-to-next-seizure compared to placebo ($p = 0.0072$) as shown in the following graph.

[See Figure 4 at top of page 1014]

In addition, 55% of patients treated with Diastat were seizure-free during the observation period compared to 34% of patients receiving placebo. Overall, caregivers judged Diastat to be more effective than placebo ($p=0.018$), based on a 10 centimeter visual analog scale. In addition, investigators also evaluated the effectiveness of Diastat and judged Diastat to be more effective than placebo ($p < 0.001$).

An analysis of response by gender revealed a statistically significant difference between treatments in females but not in males in this study, and the difference between the 2 genders in response to the treatments reached borderline statistical significance. Analysis of response by race was considered unreliable, due to the small percentage of non-Caucasions.

INDICATIONS AND USAGE

Diastat is a gel formulation of diazepam intended for rectal administration in the management of selected, refractory patients with epilepsy, on stable regimens of AEDs, who require intermittent use of diazepam to control bouts of increased seizure activity.

Evidence to support the use of Diastat was adduced in two controlled trials (see CLINICAL PHARMACOLOGY, CLINICAL STUDIES subsection) that enrolled patients with partial onset or generalized convulsive seizures who were identified jointly by their caregivers and physicians as suffering intermittent and periodic episodes of markedly increased seizure activity, sometimes heralded by non-convulsive symptoms, that for the individual patient were characteristic and were deemed by the prescriber to be of a kind for which a benzodiazepine would ordinarily be administered acutely. Although these clusters or bouts of seizures differed among patients, for any individual patient the clusters of seizure activity were not only stereotypic but were judged by those conducting and participating in these studies to be distinguishable from other seizures suffered by that patient. The conclusion that a patient experienced such unique episodes of seizure activity was based on historical information.

CONTRAINDICATIONS

Diastat is contraindicated in patients with a known hypersensitivity to diazepam. Diastat may be used in patients with open angle glaucoma who are receiving appropriate therapy but is contraindicated in acute narrow angle glaucoma.

WARNINGS

General

Diastat should only be administered by caregivers who in the opinion of the prescribing physician 1) are able to distinguish the distinct cluster of seizures (and/or the events presumed to herald their onset) from the patient's ordinary seizure activity, 2) have been instructed and judged to be competent to administer the treatment rectally, 3) understand explicitly which seizure manifestations may or may not be treated with Diastat, and 4) are able to monitor the clinical response and recognize when that response is such that immediate professional medical evaluation is required.

CNS Depression

Because Diastat produces CNS depression, patients receiving this drug who are otherwise capable and qualified to do so should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery, driving a motor vehicle, or riding a bicycle until they have completely returned to their level of baseline functioning.

Although Diastat is indicated for use solely on an intermittent basis, the potential for a synergistic CNS-depressant effect when used simultaneously with alcohol or other CNS depressants must be considered by the prescribing physician, and appropriate recommendations made to the patient and/or caregiver.

Prolonged CNS depression has been observed in neonates treated with diazepam. Therefore, Diastat is not recommended for use in children under six months of age.

Pregnancy Risks

No clinical studies have been conducted with Diastat in pregnant women. Data from several sources raise concerns about the use of diazepam during pregnancy.

Animal Findings: Diazepam has been shown to be teratogenic in mice and hamsters when given orally at single doses of 100 mg/kg or greater (approximately eight times the maximum recommended human dose [MRHD=1 mg/kg/day] or greater on a mg/m^2 basis). Cleft palate and exencephaly are the most common and consistently reported malformations produced in these species by administration of high, maternally-toxic doses of diazepam during organogenesis. Rodent studies have indicated that prenatal exposure to diazepam doses similar to those used clinically can produce long-term changes in cellular immune responses, brain neurochemistry, and behavior.

General Concerns and Considerations About Anticonvulsants: Reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but a smaller number of systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

The reports suggesting an elevated incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors, e.g., genetic factors or the epileptic condition itself, may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent seizures because of the strong possibility of precipitating *status epilepticus* with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even mild seizures do not pose some hazards to the developing embryo or fetus.

General Concerns About Benzodiazepines: An increased risk of congenital malformations associated with the use of benzodiazepine drugs has been suggested in several studies. There may also be non-teratogenic risks associated with the use of benzodiazepines during pregnancy. There have been reports of neonatal flaccidity, respiratory and feeding difficulties, and hypothermia in children born to mothers who have been receiving benzodiazepines late in pregnancy. In addition, children born to mothers receiving benzodiazepines on a regular basis late in pregnancy may be at some risk of experiencing withdrawal symptoms during the postnatal period.

Advice Regarding the Use of Diastat in Women of Childbearing Potential: In general, the use of Diastat in women of childbearing potential, and more specifically during known pregnancy, should be considered only when the clinical situation warrants the risk to the fetus.

The specific considerations addressed above regarding the use of anticonvulsants in epileptic women of childbearing potential should be weighed in treating or counseling these women.

Because of experience with other members of the benzodiazepine class, Diastat is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should also be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physician about the desirability of discontinuing the drug.

Withdrawal Symptoms

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation regular use of benzodiazepines (see DRUG ABUSE AND DEPENDENCE section).

FIGURE 1: Plasma Concentrations of Diazepam and Dimethyldiazepam Following Diastat or IV Diazepam

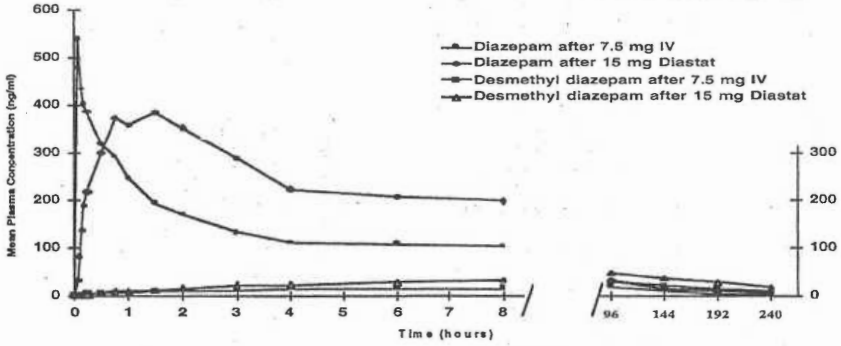


FIGURE 2: Caregiver Overall Global Assessment of the Efficacy of Diastat

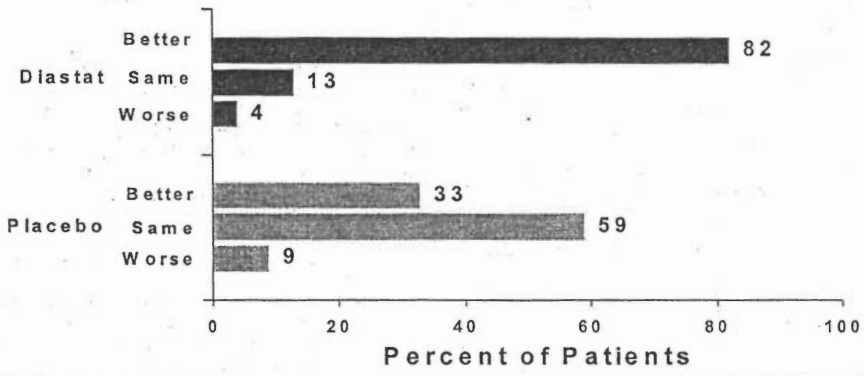
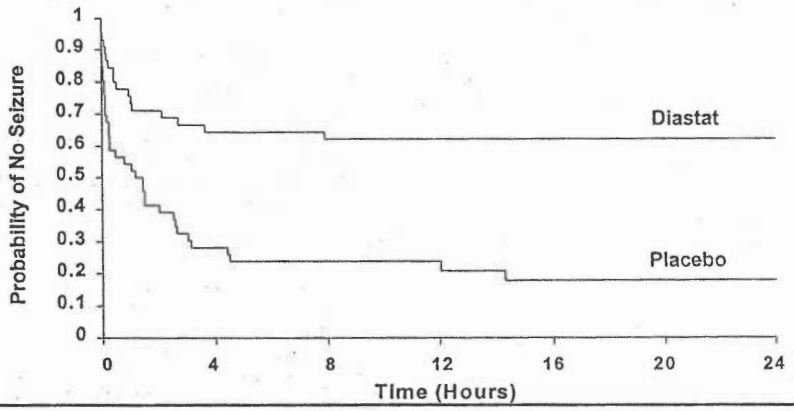


FIGURE 3: Kaplan-Meier Survival Analysis of Time-to-Next-Seizure - First Study



Chronic Use

Diastat is not recommended for chronic, daily use as an anticonvulsant because of the potential for development of tolerance to diazepam. Chronic daily use of diazepam may increase the frequency and/or severity of tonic clonic seizures, requiring an increase in the dosage of standard anticonvulsant medication. In such cases, abrupt withdrawal of chronic diazepam may also be associated with a temporary increase in the frequency and/or severity of seizures.

Use in Patients with Petit Mal Status

Tonic *status epilepticus* has been precipitated in patients treated with IV diazepam for petit mal status or petit mal variant status.

PRECAUTIONS

Caution in Renally Impaired Patients

Metabolites of Diastat are excreted by the kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function.

Caution in Hepatically Impaired Patients

Concomitant liver disease is known to decrease the clearance of diazepam (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment). Therefore, Diastat should be used with caution in patients with liver disease.

Use in Pediatrics

The controlled trials demonstrating the effectiveness of Diastat included children two years of age and older. Clinical studies have not been conducted to establish the efficacy and safety of Diastat in children under two years of age.

Continued on next page

Diastat—Cont.

Use in Patients with Compromised Respiratory Function
Diastat should be used with caution in patients with compromised respiratory function related to a concurrent disease process (e.g., asthma, pneumonia) or neurologic damage.

Use in Elderly
In elderly patients Diastat should be used with caution due to an increase in half-life with a corresponding decrease in the clearance of free diazepam. It is also recommended that the dosage be decreased to reduce the likelihood of ataxia or oversedation.

Information to be Communicated by the Prescriber to the Caregiver
Prescribers are strongly advised to take all reasonable steps to ensure that caregivers fully understand their role and obligations vis a vis the administration of Diastat to individuals in their care. Prescribers should routinely discuss the steps in the Patient/Caregiver Package Insert (see Patient/Caregiver Insert printed at the end of the product labeling and also included in the product carton). The successful and safe use of Diastat depends in large measure on the competence and performance of the caregiver.
Prescribers should advise caregivers that they expect to be informed immediately if a patient develops any new findings which are not typical of the patient's characteristic seizure episode.
Interference With Cognitive and Motor Performance: Because benzodiazepines have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Diastat therapy does not affect them adversely.
Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with Diastat (see WARNINGS section).
Nursing: Because diazepam and its metabolites may be present in human breast milk for prolonged periods of time after acute use of Diastat, patients should be advised not to breast-feed for an appropriate period of time after receiving treatment with Diastat.
Concomitant Medication
Although Diastat is indicated for use solely on an intermittent basis, the potential for a synergistic CNS-depressant effect when used simultaneously with alcohol or other CNS-depressants must be considered by the prescribing physician, and appropriate recommendations made to the patient and/or caregiver.
Drug Interactions
If Diastat is to be combined with other psychotropic agents or other CNS depressants, careful consideration should be given to the pharmacology of the agents to be employed—particularly with known compounds which may potentiate the action of diazepam, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants.
The clearance of diazepam and certain other benzodiazepines can be delayed in association with cimetidine administration. The clinical significance of this is unclear.
Valproate may potentiate the CNS-depressant effects of diazepam.
There have been no clinical studies or reports in literature to evaluate the interaction of rectally administered diazepam with other drugs. As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.
Effect of Other Drugs On Diazepam Metabolism: *In vitro* studies using human liver preparations suggest that CYP2C19 and CYP3A4 are the principal isozymes involved in the initial oxidative metabolism of diazepam. Therefore, potential interactions may occur when diazepam is given concurrently with agents that affect CYP2C19 and CYP3A4 activity. Potential inhibitors of CYP2C19 (e.g., cimetidine, quinidine, and tranylcypromine) and CYP3A4 (e.g., ketoconazole, troleandomycin, and clotrimazole) could decrease the rate of diazepam elimination, while inducers of CYP2C19 (e.g., rifampin) and CYP3A4 (e.g., carbamazepine, phenytoin, dexamethasone and phenobarbital) could increase the rate of elimination of diazepam.
Effect of Diazepam On the Metabolism of Other Drugs: There are no reports as to which isozymes could be inhibited or induced by diazepam. But, based on the fact that diazepam is a substrate for CYP2C19 and CYP3A4, it is possible that diazepam may interfere with the metabolism of drugs which are substrates for CYP2C19, (e.g. omeprazole, propranolol, and imipramine) and CYP3A4 (e.g. cyclosporine, paclitaxel, terfenadine, theophylline, and warfarin) leading to a potential drug-drug interaction.
Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of rectal diazepam has not been evaluated. In studies in which mice and rats were administered diazepam in the diet at a dose of 75 mg/kg/day (approximately six and 12 times, respectively, the maximum recommended human dose [MRHD=1 mg/kg/day] on a mg/m^2 basis) for 80 and 104 weeks, respectively, an increased incidence of liver tumors was observed in males of both species.
The data currently available are inadequate to determine the mutagenic potential of diazepam.
Reproduction studies in rats showed decreases in the number of pregnancies and in the number of surviving offspring following administration of an oral dose of 100 mg/kg/day (approximately 16 times the MRHD on a mg/m^2 basis) prior to and during mating and throughout gestation and lactation. No adverse effects on fertility or offspring viability were noted at a dose of 80 mg/kg/day (approximately 13 times the MRHD on a mg/m^2 basis).
Pregnancy—Category D (see WARNINGS section.)
Labor and Delivery
In humans, measurable amounts of diazepam have been found in maternal and cord blood, indicating placental transfer of the drug. Until additional information is available, Diastat is not recommended for obstetrical use.
Nursing Mothers
Because diazepam and its metabolites may be present in human breast milk for prolonged periods of time after acute use of Diastat, patients should be advised not to breast-feed for an appropriate period of time after receiving treatment with Diastat.

ADVERSE REACTIONS

Diastat adverse event data were collected from double-blind, placebo-controlled studies and open-label studies. The majority of adverse events were mild to moderate in severity and transient in nature.
Two patients who received Diastat died seven to 15 weeks following treatment; neither of these deaths was deemed related to Diastat.
The most frequent adverse event reported to be related to Diastat in the two double-blind, placebo-controlled studies was somnolence (23%). Less frequent adverse events were dizziness, headache, pain, abdominal pain, nervousness, vasodilatation, diarrhea, ataxia, euphoria, incoordination, asthma, rhinitis, and rash, which occurred in approximately 2–5% of patients.
Approximately 1.4% of the 573 patients who received Diastat in clinical trials of epilepsy discontinued treatment because of an adverse event. The adverse event most frequently associated with discontinuation (occurring in three patients) was somnolence. Other adverse events most commonly associated with discontinuation and occurring in two patients were hypoventilation and rash. Adverse events occurring in one patient were asthenia, hyperkinesia, incoordination, vasodilatation and urticaria. These events were judged to be related to Diastat.
In the two domestic double-blind, placebo-controlled, parallel-group studies, the proportion of patients who discontinued treatment because of adverse events was 2% for the group treated with Diastat, versus 2% for the placebo group. In the Diastat group, the adverse events considered the primary reason for discontinuation were different in the two patients who discontinued treatment; one discontinued due to rash and one discontinued due to lethargy. The primary reason for discontinuation in the patients treated with placebo was lack of effect.
Adverse Event Incidence in Controlled Clinical Trials
Table 1 lists treatment-emergent signs and symptoms that occurred in >1% of patients enrolled in parallel-group, placebo-controlled trials and were numerically more common in the Diastat group. Adverse events were usually mild or moderate in intensity.
The prescriber should be aware that these figures, obtained when Diastat was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

FIGURE 4: Kaplan-Meier Survival Analysis of Time-to-Next-Seizure - Second Study

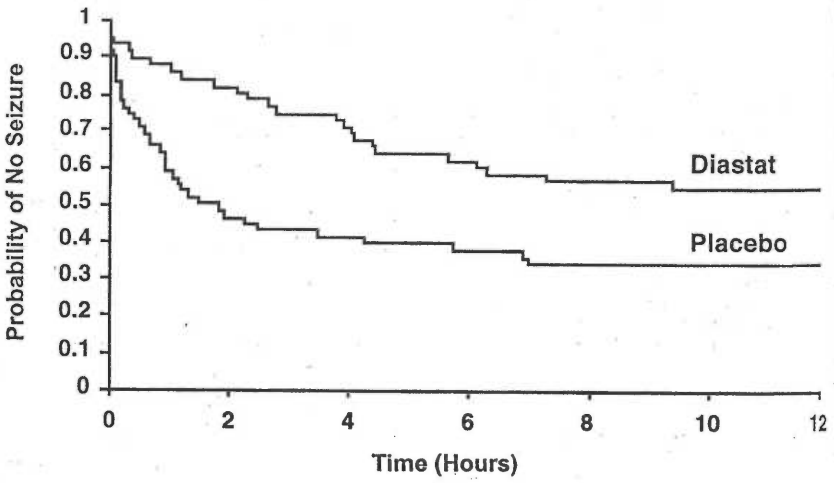


TABLE 1: Treatment-Emergent Signs And Symptoms That Occurred In >1% Of Patients Enrolled In Parallel-Group, Placebo-Controlled Trials And Were Numerically More Common In The Diastat Group

Body System	COSTART Term	Diastat N = 101 %	Placebo N = 104 %
Body As A Whole	Headache	5%	4%
Cardiovascular	Vasodilatation	2%	0%
Digestive	Diarrhea	4%	<1%
Nervous	Ataxia	3%	<1%
	Dizziness	3%	2%
	Euphoria	3%	0%
	Incoordination	3%	0%
	Somnolence	23%	8%
Respiratory	Asthma	2%	0%
Skin and Appendages	Rash	3%	0%

Other events reported by 1% or more of patients treated in controlled trials but equally or more frequent in the placebo group than in the Diastat group were abdominal pain, pain, nervousness, and rhinitis. Other events reported by fewer than 1% of patients were infection, anorexia, vomiting, anemia, lymphadenopathy, grand mal convulsion, hyperkinesia, cough increased, pruritis, sweating, mydriasis, and urinary tract infection.
The pattern of adverse events was similar for different age, race and gender groups.
Other Adverse Events Observed During All Clinical Trials: Diastat has been administered to 573 patients with epilepsy during all clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. All of the events listed below occurred in at least 1% of the 573 individuals exposed to Diastat. All reported events are included except those already listed above, events unlikely to be drug-related, and those too general to be informative. Events are included without regard to determination of a causal relationship to diazepam.
BODY AS A WHOLE: Asthenia
CARDIOVASCULAR: Hypotension, vasodilatation
NERVOUS: Agitation, Confusion convulsion, dysarthria, emotional lability, speech disorder, thinking abnormal, vertigo
RESPIRATORY: Hiccup
The following infrequent adverse events were not seen with Diastat but have been reported previously with diazepam use: depression, slurred speech, syncope, constipation, changes in libido, urinary retention, bradycardia, cardiovascular collapse, nystagmus, urticaria, neutropenia and jaundice.
Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported with diazepam; should these occur, use of Diastat should be discontinued.

DRUG ABUSE AND DEPENDENCE

Diazepam is a Schedule IV controlled substance and can produce drug dependence. It is recommended that patients be treated with Diastat no more frequently than every five days and no more than five times per month.
Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving diazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

Abrupt discontinuation of diazepam following chronic regular use has resulted in withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels for several months.

OVERDOSAGE

Two patients in the clinical studies received more than twice the target dose; no adverse events were reported.

Previous reports of diazepam overdosage have shown that manifestations of diazepam overdosage include somnolence, confusion, coma, and diminished reflexes. Respiration, pulse and blood pressure should be monitored, as in all cases of drug overdosage, although, in general, these effects have been minimal. General supportive measures should be employed, along with intravenous fluids, and an adequate airway maintained. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

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. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and 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.

DOSAGE AND ADMINISTRATION (see Also Patient/Caregiver Package Insert)

This section is intended primarily for the prescriber; however, the prescriber should also be aware of the dosing information and directions for use provided in the patient package insert.

A decision to prescribe Diastat involves more than the diagnosis and the selection of the correct dose for the patient.

First, the prescriber must be convinced from historical reports and/or personal observations that the patient exhibits the characteristic identifiable seizure cluster that can be distinguished from the patient's usual seizure activity by the caregiver who will be responsible for administering Diastat.

Second, because Diastat is only intended for adjunctive use, the prescriber must ensure that the patient is receiving an optimal regimen of standard anti-epileptic drug treatment and is, nevertheless, continuing to experience these characteristic episodes.

Third, because a non-health professional will be obliged to identify episodes suitable for treatment, make the decision to administer treatment upon that identification, administer the drug, monitor the patient, and assess the adequacy of the response to treatment, a major component of the prescribing process involves the necessary instruction of this individual.

Fourth, the prescriber and caregiver must have a common understanding of what is and is not an episode of seizures that is appropriate for treatment, the timing of administration in relation to the onset of the episode, the mechanics of administering the drug, how and what to observe following administration, and what would constitute an outcome requiring immediate and direct medical attention.

Calculating Prescribed Dose

The Diastat dose should be individualized for maximum beneficial effect. The recommended dose of Diastat is 0.2–0.5 mg/kg depending on age. See the dosing table for specific recommendations.

Age (years)	Recommended Dose
2 through 5	0.5 mg/kg
6 through 11	0.3 mg/kg
12 and older	0.2 mg/kg

Because Diastat is provided in fixed, unit-doses of 5, 10, 15 and 20 mg, the prescribed dose is obtained by rounding upward to the next available dose. The following table provides acceptable weight ranges for each dose and age category, such that patients will receive between 90% and 180% of the calculated recommended dose. The safety of this strategy has been established in clinical trials.

2-5 Years 0.5 mg/kg		6-11 Years 0.3 mg/kg		12+ Years 0.2 mg/kg	
Weight (kg)	Dose (mg)	Weight (kg)	Dose (mg)	Weight (kg)	Dose (mg)
6 to 11	5	10 to 18	5	14 to 27	5
12 to 22	10	19 to 37	10	28 to 50	10
23 to 33	15	38 to 55	15	51 to 75	15
34 to 44	20	56 to 74	20	76 to 111	20

The rectal delivery system includes a plastic applicator with a flexible, molded tip available in two lengths, designated for convenience as "Pediatric", "Universal" and "Adult". The 2.5 and 5 mg dosages are available with a 4.4 cm Pediatric tip, the 10 mg dosage is available with a 4.4 cm Universal tip and the 15 and 20 mg dosages are available with a 6.0 cm Adult tip.

It is important to note that if a 15 mg dose is to be administered to a pediatric patient utilizing the plastic applicator with a pediatric tip, prescriptions must be written for 2 different twin packs, one for the 5 mg dosage and one for the 10 mg dosage (see HOW SUPPLIED section).

In elderly and debilitated patients, it is recommended that the dosage be adjusted downward to reduce the likelihood of ataxia or oversedation.

The prescribed dose of Diastat should be adjusted by the physician periodically to reflect changes in the patient's age or weight. It is recommended that dosage be reviewed at six month intervals.

A 2.5 mg dose is available for use as a supplemental dose. This dose may be prescribed at the discretion of the physician for patients who require more precise dose titration than is achieved using one of the four standard doses provided. The 2.5 mg dose may also be used as a partial replacement dose for patients who may expel a portion of the first dose.

Additional Dose

The prescriber may wish to prescribe a second dose of Diastat. A second dose, when required, may be given 4–12 hours after the first dose.

Treatment Frequency

It is recommended that Diastat be used to treat no more than five episodes per month and no more than one episode every five days.

HOW SUPPLIED

Diastat (diazepam rectal gel) rectal delivery system is a non-sterile diazepam gel provided in a prefilled, unit-dose, rectal delivery system. The rectal delivery system includes a plastic applicator with a flexible, molded tip available in two lengths, designated for convenience as "Pediatric", "Universal" or "Adult". Diastat is available in the following five presentations:

Dosage Strength	Rectal Tip Size	NDC Number
2.5 mg Twin Pack	Pediatric (4.4 cm)	NDC 59075-650-20
5 mg Twin Pack	Pediatric	NDC 59075-651-20
10 mg Twin Pack	Universal (4.4 cm)	NDC 59075-652-20
15 mg Twin Pack	Adult (6.0 cm)	NDC 59075-654-20
20 mg Twin Pack	Adult	NDC 59075-655-20

Each Twin Pack contains two Diastat rectal delivery systems, two packets of lubricating jelly, and Patient/Caregiver Package Insert.

Store at controlled room temperature 15–30°C (59–86°F).

CAUTION: Federal law prohibits dispensing without prescription.

CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

Distributed by:
Elan Pharma, a business unit of Elan Pharmaceuticals, Inc.
South San Francisco, California 94080
Manufactured by:
DPT Laboratories, Inc.
San Antonio, Texas 78215

Diastat™ ADMINISTRATION INSTRUCTIONS

(diazepam rectal gel)

IMPORTANT

Read first before using

To the caregiver:

Please do not give DIASTAT® until:

1. you have thoroughly read these instructions,
2. reviewed administration steps with the doctor,
3. understand the directions.

Please do not administer DIASTAT until you feel comfortable with how to use DIASTAT. The doctor will tell you exactly when to use DIASTAT. When you use DIASTAT correctly and safely you will help bring seizures under control. Be sure to discuss every aspect of your role with the doctor. If you are not comfortable, then discuss your role with the doctor again.

To help the person with seizures:

- ✔You must be able to tell the difference between a cluster and ordinary seizures.
- ✔You must be comfortable and satisfied that you are able to give DIASTAT.
- ✔You need to agree with the doctor on the exact conditions when to treat with DIASTAT.
- ✔You must know how and for how long you should check the person after giving DIASTAT.

To know what responses to expect:

- ✔You need to know how soon seizures should stop or decrease in frequency after giving DIASTAT.
- ✔You need to know what you should do if the seizures do not stop or there is a change in the person's breathing, behavior or condition that alarms you.

If you have any questions or feel unsure about using the treatment, CALL THE DOCTOR before using DIASTAT.

Where can I find more information and support?

The two best places to go for information and support are:

ASAP™ (Appropriate Seizure Action Program) sponsored by Elan Pharmaceuticals, Inc. You can reach ASAP by calling 1-888-801-ASAP (2727).

EF (Epilepsy Foundation). You can reach EF by calling 800-EFA-1000 or www.efa.org.

When to treat. *Based on the doctor's directions or prescription.*

Special considerations.

DIASTAT should be used with caution:

- In people with respiratory (breathing) difficulties (e.g., asthma or pneumonia)
- In the elderly
- In women of child bearing potential, pregnancy or nursing mothers

Discuss beforehand with the doctor any additional steps you may need to take if there is leakage of DIASTAT or a bowel movement.

Patient's DIASTAT dosage is: _____ mg

Patient's resting breathing rate _____ Patient's current weight _____

Check expiration date and always remove cap and seal pin before using.

TREATMENT 1

Important things to tell the doctor.

	Seizures Before DIASTAT		
Date	Time	Seizure Type	No. of Seizures

	Seizures After DIASTAT	
Time	Seizure Type	No. of Seizures

Things to do after treatment with DIASTAT.

Stay with the person for 4 hours and make notes of the following:

- Changes in breathing rate _____
- Changes in color _____
- Confirm current weight is still the same as when DIASTAT was prescribed _____
- Possible side effects from treatment _____

TREATMENT 2

Important things to tell the doctor.

	Seizures Before DIASTAT		
Date	Time	Seizure Type	No. of Seizures

	Seizures After DIASTAT	
Time	Seizure Type	No. of Seizures

Things to do after treatment with DIASTAT.

- Changes in resting breathing rate _____
- Changes in color _____
- Confirm current weight is still the same as when DIASTAT was prescribed _____
- Possible side effects from treatment _____

Disposal

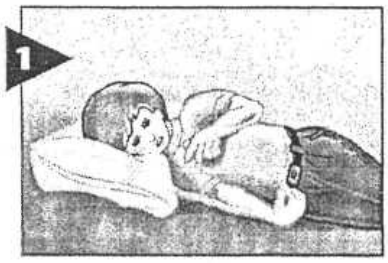
- Discard all used material in the garbage can.
- Do not reuse.
- Discard in a safe place away from children.

DIASTAT is a registered trademark of Elan Pharmaceuticals, Inc.

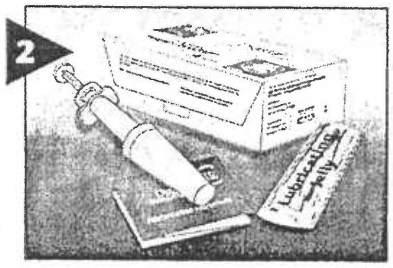
Continued on next page

Diastat—Cont.

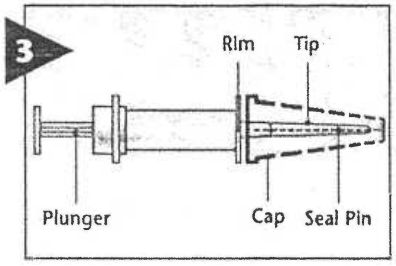
HOW TO ADMINISTER Diastat™ (diazepam rectal gel)



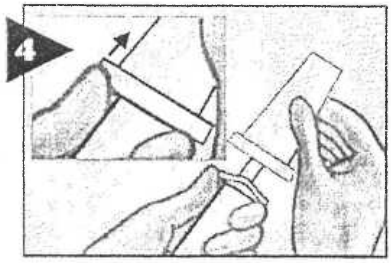
Put person on their side where they can't fall



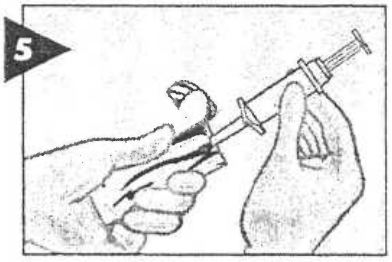
Get medicine



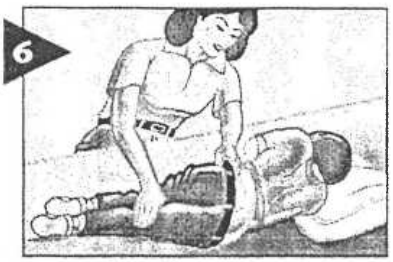
Get syringe



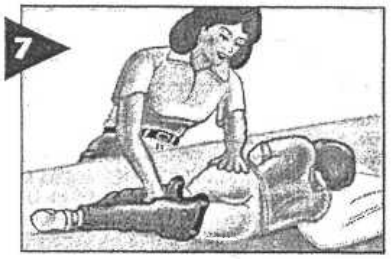
Push up with thumb and pull to remove protective cover from syringe



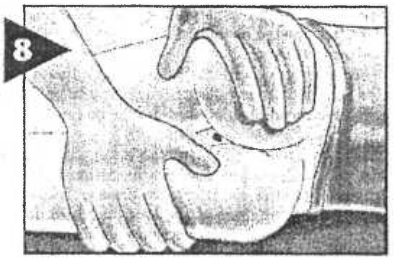
Lubricate rectal tip with lubricating jelly



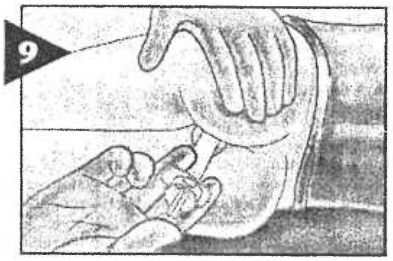
Turn person on side facing you



Bend upper leg forward to expose rectum

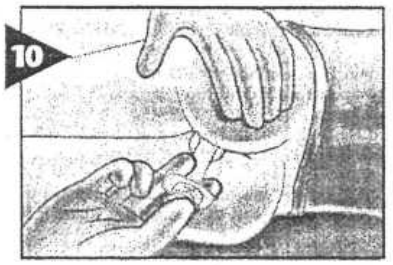


Separate buttocks to expose rectum

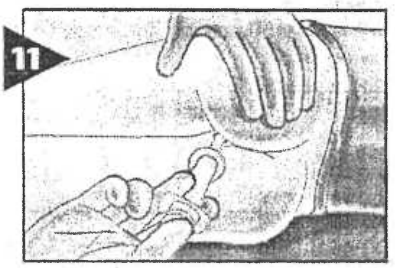


Gently insert syringe tip into rectum
Note: Rim should be snug against rectal opening.

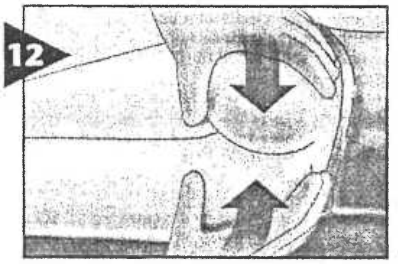
SLOWLY COUNT OUT LOUD TO THREE...1...2...3



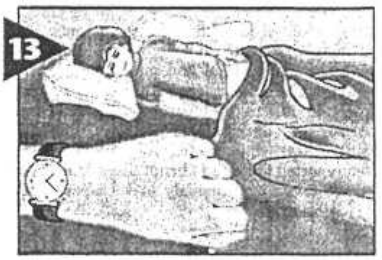
Slowly count to 3 while gently pushing plunger in until it stops



Slowly count to 3 before removing the syringe from rectum



Slowly count to 3 while holding buttocks together to prevent leakage



Keep person on side facing you, note time given and continue to observe

CALL FOR HELP IF ANY OF THE FOLLOWING OCCUR

- Seizure(s) continues 15 minutes after giving DIASTAT or per the doctor's instructions.
- Seizure behavior is different from other episodes.
- You are alarmed by the frequency or severity of the seizure(s).
- You are alarmed by the color or breathing of the person.
- The person is having unusual or serious problems.

Local Emergency Number: **Doctor's Number:**

(please be sure to note if your area has 911)

Information for Emergency Squad: *Time DIASTAT given:* _____ *Dose:*_____

Shown in Product Identification Guide, page 310

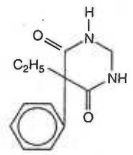
MYSOLINE®

[*mī 'sō-lēn*]
(primidone)
Anticonvulsant

Rx Only

DESCRIPTION

Chemical name: 5-ethyldihydro-5-phenyl-4,6 (1H, 5H) pyrimidinedione.
Structural formula:



Mysoline* (primidone) is a white, crystalline, highly stable substance, M.P. 279–284°C. It is poorly soluble in water (60 mg per 100 mL at 37°C) and in most organic solvents. It possesses no acidic properties, in contrast to its barbiturate analog.
Mysoline 50 mg and 250 mg tablets contain the following inactive ingredients: Microcrystalline Cellulose, NF; Lactose, USP; Methylcellulose, USP; Sodium Starch Glycolate, NF; Talc, USP; Sodium Lauryl Sulfate, NF; Magnesium Stearate, NF; Water, USP, Purified.
Mysoline 250 mg tablets also contain Yellow Iron Oxide, NF.
Mysoline suspension contains these inactive ingredients: Ammonia Solution, Diluted; Citric Acid, USP; D&C Yellow No. 10; FD&C Yellow No. 6; Magnesium Aluminum Silicate; Methylparaben, NF; Propylparaben, NF; Saccharin Sodium, NF; Sodium Alginate; Sodium Citrate; Sodium Hypochlorite Solution, USP; Sorbic Acid, NF; Sorbitan Monolaurate; Water, USP, Purified; Flavors.

* Registered trademark of Elan Pharmaceuticals, Inc.

ACTIONS

Mysoline raises electro- or chemoshock seizure thresholds or alters seizure patterns in experimental animals. The mechanism(s) of primidone's antiepileptic action is not known.
Primidone *per se* has anticonvulsant activity as do its two metabolites, phenobarbital and phenylethylmalonamide (PEMA). In addition to its anticonvulsant activity, PEMA potentiates the anticonvulsant activity of phenobarbital in experimental animals.

INDICATIONS

Mysoline, used alone or concomitantly with other anticonvulsants, is indicated in the control of grand mal, psychomotor, and focal epileptic seizures. It may control grand mal seizures refractory to other anticonvulsant therapy.

CONTRAINDICATIONS

Primidone is contraindicated in: 1) patients with porphyria and 2) patients who are hypersensitive to phenobarbital (see ACTIONS).

WARNINGS

The abrupt withdrawal of antiepileptic medication may precipitate status epilepticus.

Miacalcin Injection—Cont.

It appears that calcitonin-salmon cannot cross the placental barrier and its passage to the cerebrospinal fluid or to breast milk has not been determined.

INDICATIONS AND USAGE

Miacalcin® (calcitonin-salmon) Injection, Synthetic is indicated for the treatment of symptomatic Paget's disease of bone, for the treatment of hypercalcemia, and for the treatment of postmenopausal osteoporosis.

Paget's Disease—At the present time, effectiveness has been demonstrated principally in patients with moderate to severe disease characterized by polyostotic involvement with elevated serum alkaline phosphatase and urinary hydroxyproline excretion.

In these patients, the biochemical abnormalities were substantially improved (more than 30% reduction) in about 2/3 of patients studied, and bone pain was improved in a similar fraction. A small number of documented instances of reversal of neurologic deficits has occurred, including improvement in the basilar compression syndrome, and improvement of spinal cord and spinal nerve lesions. At present, there is too little experience to predict the likelihood of improvement of any given neurologic lesion. Hearing loss, the most common neurologic lesion of Paget's disease, is improved infrequently (4 of 29 patients studied audiometrically).

Patients with increased cardiac output due to extensive Paget's disease have had measured decreases in cardiac output while receiving calcitonin. The number of treated patients in this category is still too small to predict how likely such a result will be.

The large majority of patients with localized, especially monostotic disease do not develop symptoms and most patients with mild symptoms can be managed with analgesics. There is no evidence that the prophylactic use of calcitonin is beneficial in asymptomatic patients, although treatment may be considered in exceptional circumstances in which there is extensive involvement of the skull or spinal cord with the possibility of irreversible neurologic damage. In these instances, treatment would be based on the demonstrated effect of calcitonin on Pagetic bone, rather than on clinical studies in the patient population in question.

Hypercalcemia—Miacalcin® (calcitonin-salmon) Injection, Synthetic is indicated for early treatment of hypercalcemic emergencies, along with other appropriate agents, when a rapid decrease in serum calcium is required, until more specific treatment of the underlying disease can be accomplished. It may also be added to existing therapeutic regimens for hypercalcemia such as intravenous fluids and furosemide, oral phosphate or corticosteroids, or other agents.

Postmenopausal Osteoporosis—Miacalcin® (calcitonin-salmon) Injection, Synthetic is indicated for the treatment of postmenopausal osteoporosis in conjunction with adequate calcium and vitamin D intake to prevent the progressive loss of bone mass. No evidence currently exists to indicate whether or not Miacalcin® (calcitonin-salmon) decreases the risk of vertebral crush fractures or spinal deformity. A recent controlled study, which was discontinued prior to completion because of questions regarding its design and implementation, failed to demonstrate any benefit of salmon calcitonin on fracture rate. No adequate controlled trials have examined the effect of salmon calcitonin injection on vertebral bone mineral density beyond 1 year of treatment. Two placebo-controlled studies with salmon calcitonin have shown an increase in total body calcium at 1 year, followed by a trend to decreasing total body calcium (still above baseline) at 2 years. The minimum effective dose of Miacalcin® (calcitonin-salmon) for prevention of vertebral bone mineral density loss has not been established. It has been suggested that those postmenopausal patients having increased rates of bone turnover may be more likely to respond to anti-resorptive agents such as Miacalcin® (calcitonin-salmon).

CONTRAINDICATIONS

Clinical allergy to synthetic calcitonin-salmon.

WARNINGS

Allergic Reactions

Because calcitonin is protein in nature, the possibility of a systemic allergic reaction exists. **Administration of calcitonin-salmon has been reported in a few cases to cause serious allergic-type reactions (e.g. bronchospasm, swelling of the tongue or throat, and anaphylactic shock), and in one case, death attributed to anaphylaxis.** The usual provisions should be made for the emergency treatment of such a reaction should it occur. Allergic reactions should be differentiated from generalized flushing and hypotension.

For patients with suspected sensitivity to calcitonin, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of Miacalcin® (calcitonin-salmon) Injection, Synthetic. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from the Medical Services Department of Novartis Pharmaceuticals Corporation.

The incidence of osteogenic sarcoma is known to be increased in Paget's disease. Pagetic lesions, with or without therapy, may appear by X-ray to progress markedly, possibly with some loss of definition of periosteal margins. Such lesions should be evaluated carefully to differentiate these from osteogenic sarcoma.

PRECAUTIONS

1. General

The administration of calcitonin possibly could lead to hypocalcemic tetany under special circumstances although no cases have yet been reported. Provisions for parenteral calcium administration should be available during the first several administrations of calcitonin.

2. Laboratory Tests

Periodic examinations of urine sediment of patients on chronic therapy are recommended.

Coarse granular casts and casts containing renal tubular epithelial cells were reported in young adult volunteers at bed rest who were given calcitonin-salmon to study the effect of immobilization on osteoporosis. There was no other evidence of renal abnormality and the urine sediment became normal after calcitonin was stopped. Urine sediment abnormalities have not been reported by other investigators.

3. Instructions for the Patient

Careful instruction in sterile injection technique should be given to the patient, and to other persons who may administer Miacalcin® (calcitonin-salmon) Injection, Synthetic.

4. Carcinogenesis, Mutagenesis, and Impairment of Fertility

An increased incidence of pituitary adenomas has been observed in one-year toxicity studies in Sprague-Dawley rats administered calcitonin-salmon at dosages of 20 and 80 I.U. kg/day and in Fisher 344 rats given 80 I.U./kg/day. The relevance of these findings to humans is unknown. Calcitonin-salmon was not mutagenic in tests using *Salmonella typhimurium, Escherichia coli,* and Chinese Hamster V79 cells.

5. Pregnancy: Teratogenic Effects

Category C

Calcitonin-salmon has been shown to cause a decrease in fetal birth weights in rabbits when given in doses 14-56 times the dose recommended for human use. Since calcitonin does not cross the placental barrier, this finding may be due to metabolic effects on the pregnant animal. There are no adequate and well-controlled studies in pregnant women. Miacalcin® (calcitonin-salmon) Injection, Synthetic should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

6. Nursing Mothers

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on this drug since many drugs are excreted in human milk. Calcitonin has been shown to inhibit lactation in animals.

7. Pediatric Use

Disorders of bone in children referred to as juvenile Paget's disease have been reported rarely. The relationship of these disorders to adult Paget's disease has not been established and experience with the use of calcitonin in these disorders is very limited. There is no adequate data to support the use of Miacalcin® (calcitonin-salmon) Injection, Synthetic in children.

ADVERSE REACTIONS

Gastrointestinal System

Nausea with or without vomiting has been noted in about 10% of patients treated with calcitonin. It is most evident when treatment is first initiated and tends to decrease or disappear with continued administration.

Dermatologic/Hypersensitivity

Local inflammatory reactions at the site of subcutaneous or intramuscular injection have been reported in about 10% of patients. Flushing of face or hands occurred in about 2-5% of patients. Skin rashes, nocturia, pruritus of the ear lobes, feverish sensation, pain in the eyes, poor appetite, abdominal pain, edema of feet, and salty taste have been reported in patients treated with calcitonin-salmon. Administration of calcitonin-salmon has been reported in a few cases to cause serious allergic-type reactions (e.g. bronchospasm, swelling of the tongue or throat, and anaphylactic shock), and in one case, death attributed to anaphylaxis *(see WARNINGS).*

OVERDOSAGE

A dose of 1000 I.U. subcutaneously may produce nausea and vomiting as the only adverse effects. Doses of 32 units per kg per day for 1-2 days demonstrate no other adverse effects.

Data on chronic high dose administration are insufficient to judge toxicity.

DOSAGE AND ADMINISTRATION

Paget's Disease—The recommended starting dose of calcitonin-salmon in Paget's disease is 100 I.U. (0.5 mL) per day administered subcutaneously (preferred for outpatient self-administration) or intramuscularly. Drug effect should be monitored by periodic measurement of serum alkaline phosphatase and 24-hour urinary hydroxyproline (if available) and evaluations of symptoms. A decrease toward normal of the biochemical abnormalities is usually seen, if it is going to occur, within the first few months. Bone pain may also decrease during that time. Improvement of neurologic lesions, when it occurs, requires a longer period of treatment, often more than one year.

In many patients, doses of 50 I.U. (0.25 mL) per day or every other day are sufficient to maintain biochemical and clinical improvement. At the present time, however, there are insufficient data to determine whether this reduced dose will have the same effect as the higher dose on forming more normal bone structure. It appears preferable, therefore, to maintain the higher dose in any patient with serious disability or neurological involvement.

In any patient with a good response initially who loses relapses, either clinically or biochemically, the possibility of antibody formation should be explored. The patient may be tested for antibodies by an appropriate specialized lab or evaluated for the possibility of antibody formation by clinical clinical evaluation.

Patient compliance should also be assessed in the event of relapse.

In patients who relapse, whether because of antibodies or for unexplained reasons, a dosage increase beyond 100 I.U. per day does not usually appear to elicit an improved response.

Hypercalcemia—The recommended starting dose of Miacalcin® (calcitonin-salmon) Injection, Synthetic in hypercalcemia is 4 I.U./kg body weight every 12 hours by subcutaneous or intramuscular injection. If the response to the dose is not satisfactory after one or two days, the dose may be increased to 8 I.U./kg every 12 hours. If the response remains unsatisfactory after two more days, the dose may be further increased to a maximum of 8 I.U./kg every 6 hours.

Postmenopausal Osteoporosis—The minimum effective dose of salmon calcitonin for the prevention of vertebral bone mineral density loss has not been established. Data from a single one-year placebo-controlled study with salmon calcitonin injection suggested that 100 I.U. (subcutaneously or intramuscularly) every other day might be effective in preserving vertebral bone mineral density. Baseline and interval monitoring of biochemical markers of bone resorption/turnover (e.g., fasting AM, second-voided urine hydroxyproline to creatinine ratio) and of bone mineral density may be useful in achieving the minimum effective dose. Patients should also receive supplemental calcium such as calcium carbonate 1.5 g daily and an adequate vitamin D intake (400 units daily). An adequate diet is also essential.

If the volume of Miacalcin® (calcitonin-salmon) Injection, Synthetic to be injected exceeds 2 mL, intramuscular injection is preferable and multiple sites of injection should be used.

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

HOW SUPPLIED

Miacalcin® (calcitonin-salmon) Injection, Synthetic is available as a sterile solution in individual 2 mL vials containing 200 I.U. per mL (NDC 0078-0149-23).

Store in Refrigerator—Between 2°C-8°C (36°F-46°F).

Manufactured by
Novartis Pharma AG
Basle, Switzerland for
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936
REV: MARCH 1999 3016740

MIACALCIN®

℞

[*mī "ă-kal 'sin*]
(calcitonin-salmon)
Nasal Spray

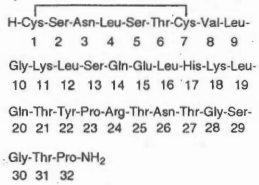
Rx only

The following prescribing information is based on official labeling in effect July 1999.

DESCRIPTION

Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland in mammals and by the ultimobranchial gland of birds and fish.

Miacalcin® (calcitonin-salmon) Nasal Spray is a synthetic polypeptide of 32 amino acids in the same linear sequence that is found in calcitonin of salmon origin. This is shown by the following graphic formula:



It is provided in 2 mL fill glass bottles as a solution for nasal administration. This is sufficient medication for at least 14 doses.

Active Ingredient: calcitonin-salmon, 2200 I.U. per mL (corresponding to 200 I.U. per 0.09 mL actuation).

Inactive Ingredients: sodium chloride, benzalkonium chloride, nitrogen, hydrochloric acid (added as necessary to adjust pH) and purified water.

The activity of Miacalcin® (calcitonin-salmon) Nasal Spray is stated in International Units based on bioassay in comparison with the International Reference Preparation of calcitonin-salmon for Bioassay, distributed by the National Institute of Biologic Standards and Control, Holly Hill, London.

CLINICAL PHARMACOLOGY

Calcitonin acts primarily on bone, but direct renal effects and actions on the gastrointestinal tract are also recog-

nized. Calcitonin-salmon appears to have actions essentially identical to calcitonins of mammalian origin, but its potency per mg is greater and it has a longer duration of action.

The information below, describing the clinical pharmacology of calcitonin, has been derived from studies with *injectable* calcitonin. The mean bioavailability of Miacalcin® (calcitonin-salmon) Nasal Spray is approximately 3% of that of injectable calcitonin in normal subjects and, therefore, the conclusions concerning the *CLINICAL PHARMACOLOGY* of this preparation may be different.

The actions of calcitonin on bone and its role in normal human bone physiology are still not completely elucidated, although calcitonin receptors have been discovered in osteoclasts and osteoblasts.

Single injections of calcitonin cause a marked transient inhibition of the ongoing bone resorptive process. With prolonged use, there is a persistent, smaller decrease in the rate of bone resorption. Histologically, this is associated with a decreased number of osteoclasts and an apparent decrease in their resorptive activity. *In vitro* studies have shown that calcitonin-salmon causes inhibition of osteoclast function with loss of the ruffled osteoclast border responsible for resorption of bone. This activity resumes following removal of calcitonin-salmon from the test system. There is some evidence from the *in vitro* studies that bone formation may be augmented by calcitonin through increased osteoblastic activity.

Animal studies indicate that endogenous calcitonin, primarily through its action on bone, participates with parathyroid hormone in the homeostatic regulation of blood calcium. Thus, high blood calcium levels cause increased secretion of calcitonin which, in turn, inhibits bone resorption. This reduces the transfer of calcium from bone to blood and tends to return blood calcium towards the normal level. The importance of this process in humans has not been determined. In normal adults, who have a relatively low rate of bone resorption, the administration of exogenous calcitonin results in only a slight decrease in serum calcium in the limits of the normal range. In normal children and in patients with Paget's disease in whom bone resorption is more rapid, decreases in serum calcium are more pronounced in response to calcitonin.

Bone biopsy and radial bone mass studies at baseline and after 26 months of daily injectable calcitonin indicate that calcitonin therapy results in formation of normal bone.

Postmenopausal Osteoporosis – Osteoporosis is a disease characterized by low bone mass and architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk as patients approach or fall below a bone mineral density associated with increased frequency of fracture. The most common type of osteoporosis occurs in postmenopausal females. Osteoporosis is a result of a disproportionate rate of bone resorption compared to bone formation which disrupts the structural integrity of bone, rendering it more susceptible to fracture. The most common sites of these fractures are the vertebrae, hip, and distal forearm (Colles' fractures). Vertebral fractures occur with the highest frequency and are associated with back pain, spinal deformity and a loss of height.

Calcitonin, given by the intranasal route, has been shown to increase spinal bone mass in postmenopausal women with established osteoporosis but not in early postmenopausal women.

Calcium Homeostasis – In two clinical studies designed to evaluate the pharmacodynamic response to Miacalcin® (calcitonin-salmon) Nasal Spray, administration of 100-1600 I.U. to healthy volunteers resulted in rapid and sustained small decreases (but still within the normal range) in both total serum calcium and serum ionized calcium. Single doses greater than 400 I.U. did not produce any further biological response to the drug. The development of hypocalcemia has not been reported in studies in healthy volunteers or postmenopausal females.

Kidney – Studies with injectable calcitonin show increases in the excretion of filtered phosphate, calcium, and sodium by decreasing their tubular reabsorption. Comparable studies have not been carried out with Miacalcin® (calcitonin-salmon) Nasal Spray.

Gastrointestinal Tract – Some evidence from studies with injectable preparations suggest that calcitonin may have significant actions on the gastrointestinal tract. Short-term administration of injectable calcitonin results in marked transient decreases in the volume and acidity of gastric juice and in the volume and the trypsin and amylase content of pancreatic juice. Whether these effects continue to be elicited after each injection of calcitonin during chronic therapy has not been investigated. These studies have not been conducted with Miacalcin® (calcitonin-salmon) Nasal Spray.

Pharmacokinetics and Metabolism

The data on bioavailability of Miacalcin® (calcitonin-salmon) Nasal Spray obtained by various investigators using different methods show great variability. Miacalcin® (calcitonin-salmon) Nasal Spray is absorbed rapidly by the nasal mucosa. Peak plasma concentrations of drug appear 11-39 minutes after nasal administration compared to 16-25 minutes following parenteral dosing. In normal volunteers approximately 3% (range 0.3%-30.6%) of a nasally administered dose is bioavailable compared to the same dose administered by intramuscular injection. The half-life of elimination of calcitonin-salmon is calculated to be 43 minutes. There is no accumulation of the drug on repeated nasal administration at 10 hour intervals for up to 15 days. Absorption of nasally administered calcitonin has not been studied in postmenopausal women.

INDICATION AND USAGE

Postmenopausal Osteoporosis – Miacalcin® (calcitonin-salmon) Nasal Spray is indicated for the treatment of postmenopausal osteoporosis in females greater than 5 years postmenopause with low bone mass relative to healthy premenopausal females. Miacalcin® (calcitonin-salmon) Nasal Spray should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated. Use of Miacalcin® (calcitonin-salmon) Nasal Spray is recommended in conjunction with an adequate calcium (at least 1000 mg elemental calcium per day) and vitamin D (400 I.U. per day) intake to retard the progressive loss of bone mass. The evidence of efficacy is based on increases in spinal bone mineral density observed in clinical trials.

Two randomized, placebo controlled trials were conducted in 325 postmenopausal females [227 Miacalcin® (calcitonin-salmon) Nasal Spray treated and 98 placebo treated] with spinal, forearm or femoral bone mineral density (BMD) at least one standard deviation below normal for healthy premenopausal females. These studies conducted over two years demonstrated that 200 I.U. daily of Miacalcin® (calcitonin-salmon) Nasal Spray increases lumbar vertebral BMD relative to baseline and relative to placebo in osteoporotic females who were greater than 5 years postmenopause. Miacalcin® (calcitonin-salmon) Nasal Spray produced statistically significant increases in lumbar vertebral BMD compared to placebo as early as six months after initiation of therapy with persistence of this level for up to 2 years of observation.

No effects of Miacalcin® (calcitonin-salmon) Nasal Spray on cortical bone of the forearm or hip were demonstrated. However, in one study, BMD of the hip showed a statistically significant increase compared with placebo in a region composed of predominantly trabecular bone after one year of treatment changing to a trend at 2 years that was no longer statistically significant.

CONTRAINDICATIONS

Clinical allergy to calcitonin-salmon.

WARNINGS

Allergic Reactions

Because calcitonin is a polypeptide, the possibility of a systemic allergic reaction exists. A few cases of allergic-type reactions have been reported in patients receiving Miacalcin® (calcitonin-salmon) Nasal Spray, including one case of anaphylactic shock, which appears to have been due to the preservative because the patient could tolerate injectable calcitonin-salmon without incident. With injectable calcitonin-salmon there have been a few reports of serious allergic-type reactions (e.g., bronchospasm, swelling of the tongue or throat, anaphylactic shock, and in one case death attributed to anaphylaxis). The usual provisions should be made for the emergency treatment of such a reaction should it occur. Allergic reactions should be differentiated from generalized flushing and hypotension.

For patients with suspected sensitivity to calcitonin, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of Miacalcin® (calcitonin-salmon) Injection, Synthetic. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from the Medical Services Department of Novartis Pharmaceuticals Corporation.

PRECAUTIONS

1. Drug Interactions

Formal studies designed to evaluate drug interactions with calcitonin-salmon have not been done. No drug interaction studies have been performed with Miacalcin® (calcitonin-salmon) Nasal Spray ingredients.

Currently, no drug interactions with calcitonin-salmon have been observed. The effects of prior use of diphosphonates in postmenopausal osteoporosis patients have not been assessed; however, in patients with Paget's Disease prior diphosphonate use appears to reduce the antiresorptive response to Miacalcin® (calcitonin-salmon) Nasal Spray.

2. Periodic Nasal Examinations

Periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum and mucosal blood vessel status are recommended.

The development of mucosal alterations or transient nasal conditions occurred in up to 9% of patients who received Miacalcin® (calcitonin-salmon) Nasal Spray and in up to 12% of patients who received placebo nasal spray in studies in postmenopausal females. The majority of patients (approximately 90%) in whom nasal abnormalities were noted also reported nasally related complaints/symptoms as adverse events. Therefore, a nasal examination should be performed prior to start of treatment with nasal calcitonin and at any time nasal complaints occur. In all postmenopausal patients treated with Miacalcin® (calcitonin-salmon) Nasal Spray, the most commonly reported nasal adverse events included rhinitis (12%), epistaxis (3.5%), and sinusitis (2.3%). Smoking was shown not to have any contributory effect on the occurrence of nasal adverse events. One patient (0.3%) treated with Miacalcin® (calcitonin-salmon) Nasal Spray who was receiving 400 I.U. daily developed a small nasal wound. In clinical trials in another disorder (Paget's Disease), 2.8% of patients developed nasal ulcerations.

If severe ulceration of the nasal mucosa occurs, as indicated by ulcers greater than 1.5 mm in diameter or penetrating below the mucosa, or those associated with heavy bleeding, Miacalcin® (calcitonin-salmon) Nasal Spray should be discontinued. Although smaller ulcers often heal without withdrawal of Miacalcin® (calcitonin-salmon) Nasal Spray, medication should be discontinued temporarily until healing occurs.

3. Information for Patients

Careful instructions on pump assembly, priming of the pump and nasal introduction of Miacalcin® (calcitonin-salmon) Nasal Spray should be given to the patient. Although instructions for patients are supplied with individual bottles, procedures for use should be demonstrated to each patient. Patients should notify their physician if they develop significant nasal irritation.

Patients should be advised of the following:

- Store new, unassembled bottles in the refrigerator between 36°-46°F (2°-8°C).
- Protect the product from freezing.
- Before priming the pump and using a new bottle, allow it to reach room temperature.
- Store bottle in use at room temperature in an upright position, for up to 30 days. Each bottle contains at least 14 doses.
- Store second bottle in refrigerator until ready to use. Protect from freezing.
- Discard all unrefrigerated bottles after 30 days.
- See *DOSAGE AND ADMINISTRATION, Priming (Activation) of Pump* for complete instructions on priming the pump and administering Miacalcin® (calcitonin-salmon) Nasal Spray.

4. Carcinogenicity, Mutagenicity, and Impairment of Fertility

An increased incidence of non-functioning pituitary adenomas has been observed in one-year toxicity studies in Sprague-Dawley and Fischer 344 Rats administered (subcutaneously) calcitonin-salmon at dosages of 80 I.U. per kilogram per day (16-19 times the recommended human parenteral dose and about 130-160 times the human intranasal dose based on body surface area). The findings suggest that calcitonin-salmon reduced the latency period for development of pituitary adenomas that do not produce hormones, probably through the perturbation of physiologic processes involved in the evolution of this commonly occurring endocrine lesion in the rat. Although administration of calcitonin-salmon reduces the latency period of the development of nonfunctional proliferative lesions in rats, it did not induce the hyperplastic/neoplastic process.

Calcitonin-salmon was tested for mutagenicity using *Salmonella typhimurium* (5 strains) and *Escherichia coli* (2 strains), with and without rat liver metabolic activation, and found to be non-mutagenic. The drug was also not mutagenic in a chromosome aberration test in mammalian V79 cells of the Chinese Hamster *in vitro*.

5. Laboratory Tests

Urine sediment abnormalities have not been reported in ambulatory volunteers treated with Miacalcin® (calcitonin-salmon) Nasal Spray. Coarse granular casts containing renal tubular epithelial cells were reported in young adult volunteers at bed rest who were given injectable calcitonin-salmon to study the effect of immobilization on osteoporosis. There was no evidence of renal abnormality and the urine sediment became normal after calcitonin was stopped. Periodic examinations of urine sediment should be considered.

6. Pregnancy

Teratogenic Effects

Category C

Calcitonin-salmon has been shown to cause a decrease in fetal birth weights in rabbits when given by injection in doses 8-33 times the parenteral dose and 70-278 times the intranasal dose recommended for human use based on body surface area.

Since calcitonin does not cross the placental barrier, this finding may be due to metabolic effects on the pregnant animal. There are no adequate and well controlled studies in pregnant women with calcitonin-salmon. Miacalcin® (calcitonin-salmon) Nasal Spray is *not* indicated for use in pregnancy.

7. Nursing Mothers

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on this drug since many drugs are excreted in human milk. Calcitonin has been shown to inhibit lactation in animals.

8. Geriatric Use

Clinical trials using Miacalcin® (calcitonin-salmon) Nasal Spray have included postmenopausal patients up to 77 years of age. No unusual adverse events or increased incidence of common adverse events have been noted in patients over 65 years of age.

9. Pediatric Use

There are no data to support the use of Miacalcin® (calcitonin-salmon) Nasal Spray in children. Disorders of bone in children referred to as idiopathic juvenile osteoporosis have been reported rarely. The relationship of these disorders to postmenopausal osteoporosis has not been established and experience with the use of calcitonin in these disorders is very limited.

ADVERSE REACTIONS

The incidence of adverse reactions reported in studies involving postmenopausal osteoporotic patients chronically

Continued on next page

Miacalcin Nasal Spray—Cont.

exposed to Miacalcin® (calcitonin-salmon) Nasal Spray (N=341) and to placebo nasal spray (N=131) and reported in greater than 3% of Miacalcin® (calcitonin-salmon) Nasal Spray treated patients are presented below in the following table. Most adverse reactions were mild to moderate in severity. Nasal adverse events were most common with 70% mild, 25% moderate, and 5% severe in nature (placebo rates were 71% mild, 27% moderate, and 2% severe).

Adverse Reactions Occurring in at Least 3% of Postmenopausal Patients Treated Chronically

Adverse Reaction	Miacalcin® (calcitonin-salmon) Nasal Spray N=341 % of Patients	Placebo N=131 % of Patients
Rhinitis	12.0	6.9
Symptom of Nose†	10.6	16.0
Back Pain	5.0	2.3
Arthralgia	3.8	5.3
Epistaxis	3.5	4.6
Headache	3.2	4.6

†Symptom of nose includes: nasal crusts, dryness, redness or erythema, nasal sores, irritation, itching, thick feeling, soreness, pallor, infection, stenosis, runny/blocked, small wound, bleeding wound, tenderness, uncomfortable feeling and sore across bridge of of nose.

In addition, the following adverse events were reported in fewer than 3% of patients during chronic therapy with Miacalcin® (calcitonin-salmon) Nasal Spray. Adverse events reported in 1%-3% of patients are identified with an asterisk(*). The remainder occurred in less than 1% of patients. Other than flushing, nausea, possible allergic reactions, and possible local irritative effects in the respiratory tract, a relationship to Miacalcin® (calcitonin-salmon) Nasal Spray has not been established.

Body as a whole – General Disorders: influenza-like symptoms*, fatigue*, periorbital edema, fever

Integumentary: erythematous rash*, skin ulceration, eczema, alopecia, pruritus, increased sweating

Musculoskeletal/Collagen: arthrosis*, myalgia*, arthritis, polymyalgia rheumatica, stiffness

Respiratory/Special Senses: sinusitis*, upper respiratory tract infection*, bronchospasm*, pharyngitis, bronchitis, pneumonia, coughing, dyspnea, taste perversion, parosmia

Cardiovascular: hypertension*, angina pectoris*, tachycardia, palpitation, bundle branch block, myocardial infarction

Gastrointestinal: dyspepsia*, constipation*, abdominal pain*, nausea*, diarrhea*, vomiting, flatulence, increased appetite, gastritis, dry mouth

Liver/Metabolic: cholelithiasis, hepatitis, thirst, weight increase

Endocrine: goiter, hyperthyroidism

Urinary System: cystitis*, pyelonephritis, hematuria, renal calculus

Central and Peripheral Nervous System: dizziness*, paresthesia*, vertigo, migraine, neuralgia, agitation

Hearing/Vestibular: tinnitus, hearing loss, earache

Vision: abnormal lacrimation*, conjunctivitis*, blurred vision, vitreous floater

Vascular: flushing, cerebrovascular accident, thrombophlebitis

Hematologic/Resistance Mechanisms: lymphadenopathy*, infection*, anemia

Psychiatric: depression*, insomnia, anxiety, anorexia

Common adverse reactions associated with the use of injectable calcitonin-salmon occurred less frequently in patients treated with Miacalcin® (calcitonin-salmon) Nasal Spray than in those patients treated with injectable calcitonin. Nausea, with or without vomiting, which occurred in 1.8% of patients treated with the nasal spray (and 1.5% of those receiving placebo nasal spray) occurs in about 10% of patients who take injectable calcitonin-salmon. Flushing, which occurred in less than 1% of patients treated with the Nasal Spray, occurs in 2%-5% of patients treated with injectable calcitonin-salmon. Although the administered dosages of injectable and nasal spray calcitonin-salmon are comparable (50-100 units daily of injectable versus 200 units daily of nasal spray), the nasal dosage form has a mean bioavailability of about 3% (range 0.3%-30.6%) and therefore provides less drug to the systemic circulation, possibly accounting for the decrease in frequency of adverse reactions.

The collective foreign marketing experience with Miacalcin® (calcitonin-salmon) Nasal Spray does not show evidence of any notable difference in the incidence profile of reported adverse reactions when compared with that seen in the clinical trials.

OVERDOSAGE

No instances of overdose with Miacalcin® (calcitonin-salmon) Nasal Spray have been reported and no serious adverse reactions have been associated with high doses. There is no known potential for drug abuse for calcitonin-salmon.

Single doses of Miacalcin® (calcitonin-salmon) Nasal Spray up to 1600 I.U., doses up to 800 I.U. per day for three days and chronic administration of doses up to 600 I.U. per day have been studied without serious adverse effects. A dose of 1000 I.U. of Miacalcin® (calcitonin-salmon) injectable solution given subcutaneously may produce nausea and vomiting. A dose of Miacalcin® (calcitonin-salmon) injectable solution of 32 I.U. per kg per day for one or two days demonstrated no additional adverse effects.

There have been no reports of hypocalcemic tetany. However, the pharmacologic actions of Miacalcin® (calcitonin-salmon) Nasal Spray suggest that this could occur in overdose. Therefore, provisions for parenteral administration of calcium should be available for the treatment of overdose.

DOSAGE AND ADMINISTRATION

The recommended dose of Miacalcin® (calcitonin-salmon) Nasal Spray in postmenopausal osteoporotic females is one spray (200 I.U.) per day administered intranasally, alternating nostrils daily.

Drug effect may be monitored by periodic measurements of lumbar vertebral bone mass to document stabilization of bone loss or increases in bone density. Effects of Miacalcin® (calcitonin-salmon) Nasal Spray on biochemical markers of bone turnover have not been consistently demonstrated in studies in postmenopausal osteoporosis. Therefore, these parameters should not be solely utilized to determine clinical response to Miacalcin® (calcitonin-salmon) Nasal Spray therapy in these patients.

Priming (Activation) of Pump

Before the first dose and administration, Miacalcin® (calcitonin-salmon) Nasal Spray should be at room temperature. To prime the pump, the bottle should be held upright and the two white side arms of the pump depressed toward the bottle until a full spray is produced. The pump is primed once the first full spray is emitted. To administer, the nozzle should be carefully placed into the nostril with the head in the upright position, and the pump firmly depressed toward the bottle. The pump should not be primed before each daily dose.

HOW SUPPLIED

Miacalcin® (calcitonin-salmon) Nasal Spray

Available as a metered dose solution in 2 mL fill glass bottles. It is available in a dosage strength of 200 I.U. per activation (0.09 mL/spray). Screw-on pumps are provided. The pumps, following priming, will deliver 0.09 mL of solution. Miacalcin® (calcitonin-salmon) Nasal Spray contains 2200 I.U./mL calcitonin-salmon and is provided in individual boxes containing two glass bottles and two screw-on pumps (NDC 0078-0311-90).

Store and Dispense

Store unopened bottle(s) in refrigerator between 36°-46°F (2°-8°C). Protect from freezing.

Store bottle in use at room temperature in an upright position, for up to 30 days. Each bottle contains at least 14 doses.

Store second bottle in refrigerator until ready to use. Protect from freezing.

Discard all unrefrigerated bottles after 30 days.

REV: DECEMBER 1998 30367905

Shown in Product Identification Guide, page 326

MIGRANAL® ℞

[mī grā năl]

(dihydroergotamine mesylate, USP)

Nasal Spray

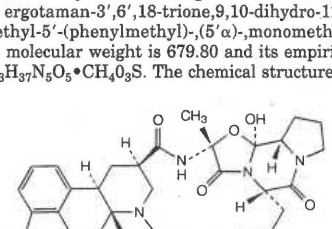
The solution used in Migranal® (dihydroergotamine mesylate, USP) Nasal Spray (4 mg/mL) is intended for intranasal use and must not be injected.

Caution: Federal law prohibits dispensing without prescription.

The following prescribing information is based on official labeling in effect July 1999.

DESCRIPTION

Migranal® is ergotamine hydrogenated in the 9,10 position as the mesylate salt. Migranal® is known chemically as ergotaman-3′,6′,18-trione,9,10-dihydro-12′-hydroxy-2′-methyl-5′-(phenylmethyl)-,(5′α)-,monomethanesulfonate. Its molecular weight is 679.80 and its empirical formula is $C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$. The chemical structure is:



Dihydroergotamine mesylate
$C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$ Mol. wt. 679.80

Migranal® (dihydroergotamine mesylate, USP) Nasal Spray is provided for intranasal administration as a clear, colorless to faintly yellow solution in an amber glass ampul containing:

dihydroergotamine mesylate, USP	4.0 mg
caffeine, anhydrous, USP	10.0 mg
dextrose, anhydrous, USP	50.0 mg
carbon dioxide	qs
water for injection, USP	qs 1.0 mL

CLINICAL PHARMACOLOGY

Mechanism of Action

Dihydroergotamine binds with high affinity to 5-HT, $5\text{-HT}_{1D\beta}$ receptors. It also binds with high affinity to nin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, noradr α_{2A}, α_{2B} and α_1 receptors, and dopamine D_{2} receptors.

The therapeutic activity of dihydroergotamine in m is generally attributed to the agonist effect at 5-HT tors. Two current theories have been proposed to exp efficacy of 5-HT_{1D} receptor agonists in migraine. One suggests that activation of 5-HT_{1D} receptors locat tracranial blood vessels, including those on arteri anastomoses, leads to vasoconstriction, which co with the relief of migraine headache. The alte hypothesis suggests that activation of 5-HT_{1D} re on sensory nerve endings of the trigeminal system in the inhibition of pro-inflammatory neuropeptide In addition, dihydroergotamine possesses oxytocic ties. *(See CONTRAINDICATIONS)*

Pharmacokinetics

Absorption

Dihydroergotamine mesylate is poorly bioavailable ing oral administration. Following intranasal admi tion, however, the mean bioavailability of dihyd amine mesylate is 32% relative to the injectable admi tion. Absorption is variable, probably reflecting intersubject differences of absorption and the tech used for self-administration.

Distribution

Dihydroergotamine mesylate is 93% plasma protein b The apparent steady-state volume of distribution is a imately 800 liters.

Metabolism

Four dihydroergotamine mesylate metabolites hav identified in human plasma following oral adminis The major metabolite, 8′-β-hydroxydihydroergotam hibits affinity equivalent to its parent for adrener 5-HT receptors and demonstrates equivalent potency eral venoconstrictor activity models, *in vivo* and in The other metabolites, i.e., dihydrolysergic acid, dih sergic amide and a metabolite formed by oxidative o of the proline ring are of minor importance. Following administration, total metabolites represent only 20 of plasma AUC. The systemic clearance of dihydro mine mesylate following I.V. and I.M. administra 1.5 L/min. Quantitative pharmacokinetic characte of the four metabolites has not been performed.

Excretion

The major excretory route of dihydroergotamine is bile in the feces. After intranasal administration u nary recovery of parent drug amounts to about 2% administered dose compared to 6% after I.M. admi tion. The total body clearance is 1.5 L/min which mainly hepatic clearance. The renal clearance (0.1 L unaffected by the route of dihydroergotamine admi tion. The decline of plasma dihydroergotamine is bi with a terminal half-life of about 10 hours.

Subpopulations

No studies have been conducted on the effect of re hepatic impairment, gender, race, or ethnicity on dih gotamine pharmacokinetics. Migranal® (dihydro amine mesylate, USP) Nasal Spray is contraindic patients with severely impaired hepatic or renal fu *(See CONTRAINDICATIONS)*

Interactions

The pharmacokinetics of dihydroergotamine did not a to be significantly affected by the concomitant use of vasoconstrictor (e.g., fenoxazoline).

Multiple oral doses of the β-adrenoceptor antagonis pranolol, used for migraine prophylaxis, had no sign influence on the C_{max}, T_{max} or AUC of dihydroergo doses up to 4 mg.

Pharmacokinetic interactions (increased blood levels been reported in patients treated orally with dihydr amine and macrolide antibiotics, principally troleand cin, presumably due to inhibition of cytochrome P4 metabolism of dihydroergotamine by troleandomycin. droergotamine has also been shown to be an inhibi cytochrome P450 3A catalyzed reactions. No pharm kinetic interactions involving other cytochrome P isoenzymes are known.

Clinical Trials

The efficacy of Migranal® (dihydroergotamine me USP) Nasal Spray for the acute treatment of migraine aches was evaluated in four randomized, double blin cebo controlled studies in the U.S. The patient popu for the trials was predominantly female (87%) and C sian (95%) with a mean age of 39 years (range 18 years). Patients treated a single moderate to severe graine headache with a single dose of study medicatio assessed pain severity over the 24 hours following ment. Headache response was determined 0.5, 1, 2, 3 hours after dosing and was defined as a reduction in ache severity to mild or no pain. In studies 1 and 2, a point pain intensity scale was utilized; in studies 3 an five-point scale was used that included both pain re and restoration of function for "severe" or "incapacit pain, a less clear endpoint. Although rescue medicatio allowed in all four studies, patients were instructed use them during the four hour observation period. In ies 3 and 4, a total dose of 2 mg was compared to plac studies 1 and 2, doses of 2 and 3 mg were evaluate showed no advantage of the higher dose for a single ment. In all studies, patients received a regimen con

Toradol—Cont.

Hemic and Lymphatic: postoperative wound hemorrhage (rarely requiring blood transfusion—see Boxed WARNING, WARNINGS and PRECAUTIONS), thrombocytopenia, leukopenia
Hepatic: hepatitis, liver failure, cholestatic jaundice
Nervous System: convulsions, psychosis, aseptic meningitis
Respiratory: asthma, bronchospasm
Urogenital: acute renal failure (see Boxed WARNING, WARNINGS), flank pain with or without hematuria and/or azotemia, nephritis, hyponatremia, hyperkalemia, hemolytic uremic syndrome

OVERDOSAGE

In controlled overdosage, daily doses of 360 mg of TORADOL IV/IM given for 5 days (three times the highest recommended dose), caused abdominal pain and peptic ulcers which healed after discontinuation of dosing. Metabolic acidosis has been reported following intentional overdosage. Dialysis does not significantly clear ketorolac tromethamine from the blood stream.

DOSAGE AND ADMINISTRATION

THE COMBINED DURATION OF USE OF TORADOL IV/IM AND TORADOL ORAL IS NOT TO EXCEED 5 DAYS.
THE USE OF TORADOL ORAL IS ONLY INDICATED AS CONTINUATION THERAPY TO TORADOL IV/IM.

TORADOL IV/IM

TORADOL IV/IM may be used as a single or multiple dose on a regular or prn schedule for the management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Hypovolemia should be corrected prior to the administration of TORADOL (see WARNINGS: *Renal Effects*). Patients should be switched to alternative analgesics as soon as possible, but TORADOL therapy is not to exceed 5 days.
When administering TORADOL IV/IM, the IV bolus must be given over no less than 15 seconds. The IM administration should be given slowly and deeply into the muscle. The analgesic effect begins in 30 minutes with maximum effect in 1 to 2 hours after dosing IV or IM. Duration of analgesic effect is usually 4 to 6 hours.

Single-Dose Treatment: The Following Regimen Should Be Limited To Single Administration Use Only

IM Dosing:

- *Patients <65 years of age: One dose of 60 mg.*
- *Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lbs) of body weight: One dose of 30 mg.*

IV Dosing:

- *Patients <65 years of age: One dose of 30 mg.*
- *Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lbs) of body weight: One dose of 15 mg.*

Multiple-Dose Treatment (IV or IM)

- *Patients <65 years of age:* The recommended dose is 30 mg TORADOL IV/IM every 6 hours. The maximum daily dose should not exceed 120 mg.
- *For Patients ≥65 years of age, renally impaired patients (see WARNINGS) and patients less than 50 kg (110 lbs):* The recommended dose is 15 mg TORADOL IV/IM every 6 hours. The maximum daily dose for these populations should not exceed 60 mg.

For breakthrough pain do not increase the dose or the frequency of TORADOL. Consideration should be given to supplementing these regimens with low doses of opioids prn unless otherwise contraindicated.
Pharmaceutical Information for TORADOL IV/IM: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
TORADOL IV/IM should not be mixed in a small volume (eg, in a syringe) with morphine sulfate, meperidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride; this will result in precipitation of ketorolac from solution.
TORADOL ORAL is indicated ONLY as continuation therapy to TORADOL IV/IM for the management of moderately severe acute pain that requires analgesia at the opioid level (see also PRECAUTIONS: *Information for Patients*).
Transition from TORADOL IV/IM to TORADOL ORAL: The recommended TORADOL ORAL dose is as follows:

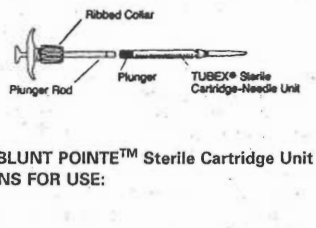
- *Patients <65 years of age:* 2 tablets as a first oral dose for patients who received **60 mg IM single dose, 30 mg IV single dose or 30 mg multiple dose.** TORADOL IV/IM followed by 1 tablet TORADOL ORAL every 4 to 6 hours, not to exceed 40 mg/24 h of TORADOL ORAL
- *Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lbs) of body weight:* 1 tablet as a first oral dose for patients who received **30 mg IM single dose, 15 mg IV single dose or 15 mg multiple dose.** TORADOL IV/IM followed by 1 tablet TORADOL ORAL every 4 to 6 hours, not to exceed 40 mg/24 h of TORADOL ORAL.

Shortening the recommended dosing intervals may result in increased frequency and severity of adverse reactions.
The maximum combined duration of use (parenteral and oral TORADOL) is limited to 5 days.
The TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is suitable for substances to be administered intravenously only. It is intended for use with injection sets specifically manufactured as "needle-less" injection systems. TUBEX® BLUNT POINTE™ is compatible with Abbott's LifeShield® prepierced reseal injection site, Baxter's InterLink® Injection Site, and B. Braun Medical's SafSite® Reflux Valve. Consult manufacturer's recommendations regarding "Directions for Use" of the "needle-less" system. It is also intended for admixture with, and convenient administration of, various medicaments when using Drug Vial Adapters for "needle-less" injection systems.
The TUBEX® Sterile Cartridge-Needle Unit and sterile vial are suitable for substances to be administered intravenously and intramuscularly.

HOW SUPPLIED

TORADOL IV/IM for intramuscular or intravenous use is available in a TUBEX® Cartridge-Needle Unit or a sterial vial:
15 mg: 15 mg/mL, 1 mL TUBEX® Sterile Cartridge-Needle Unit (22 gauge × 1-1/4 inch needle) box of 10 (NDC 0004-6921-06) or 1 mL fill per 2 mL single use vial, box of 10 (NDC 0004-6925-06).
30 mg: 30 mg/mL, 1 mL TUBEX® Sterile Cartridge-Needle Unit (22 gauge × 1-1/4 inch needle) box of 10 (NDC 0004-6923-06) or 1 mL fill per 2 mL single use vial, box of 10 (NDC 0004-6926-06).
For IM Single-Dose Use Only Not Intended for IV Use—60 mg: 30 mg/mL, 2 mL TUBEX® Sterile Cartridge-Needle Unit (22 gauge × 1-1/4 inch needle) box of 1 (NDC 0004-6924-09 or 2 mL fill per 2 mL single use vial, box of 1 (NDC 0004-6927-09).
TORADOL IV for intravenous use is available in a TUBEX® BLUNT POINTE™ Sterile Cartridge Unit:
15 mg: 15 mg/mL, 1 mL TUBEX® BLUNT POINTE™ Sterile Cartridge Unit, box of 10 (NDC 0004-6920-06).
30 mg: 30 mg/mL, 1 mL TUBEX® BLUNT POINTE™ Sterile Cartridge Unit, box of 10 (NDC 0004-6922-06).
Syringes manufactured by Wyeth Laboratories, Inc., Philadelphia, PA 19101 for Roche Laboratories Inc., Nutley, NJ 07110.
Vials manufactured by Hoffmann-La Roche Inc., Nutley, NJ 07110.
Store at 15° to 30°C (59° to 86°F) with protection from light.
TORADOL ORAL 10 mg tablets are available in bottles of 100 tablets (NDC 0004-0273-01).
Store bottles at 15° to 30°C (59° to 86°F).
Manufactured by Syntex Puerto Rico, Inc., Humacao, PR 00791

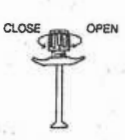
TUBEX® Injector
NOTE: The TUBEX® Injector is reusable: do not discard.
TUBEX® Sterile Cartridge-Needle Unit
DIRECTIONS FOR USE



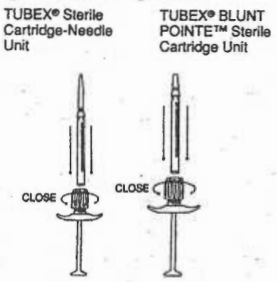
TUBEX® BLUNT POINTE™ Sterile Cartridge Unit
DIRECTIONS FOR USE:

TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is intended for use with injection sets specifically manufactured as "needle-less" injection systems.
TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is compatible with Abbott's LifeShield® prepierced reseal injection site, Baxter's InterLink® Injection Site and B. Braun Medical's SafSite® Reflux Valve. Consult manufacturer's recommendations regarding "Directions for Use" of the "needle-less" injection system.

To load a TUBEX® Sterile Cartridge Unit into the TUBEX® Injector
1. Turn the ribbed collar to the "OPEN" position until it stops.



2. Hold the Injector with the open end



up and fully insert the TUBEX® Sterile Cartridge Unit. Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.

3. Thread the plunger rod into the plunger of the TUBEX® Sterile Cartridge Unit until slight resistance is felt. The Injector is now ready for use in the usual manner.

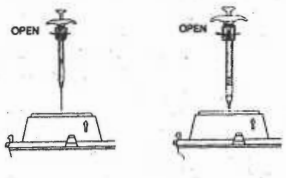
To administer TUBEX® Sterile Cartridge-Needle Units
Method of administration is the same as with conventional syringe. Remove needle cover by grasping it securely, twist and pull. Introduce needle into patient, aspirate by pulling back slightly on the plunger, and inject.

To administer TUBEX® BLUNT POINTE™ Sterile Cartridge Units

"Needle-less" IV set administration is similar to administration with conventional syringes. Remove rubber cover by grasping it securely; twist and pull. For B. Braun Medical's SafSite® Reflux Valves, aseptically swab the luer slip fitting of the BLUNT POINTE™ sterile cartridge tip assembly with a sterile, individually wrapped, saturated 70% Isopropyl Alcohol swab. This action will remove the lubricant coating from the tip to facilitate a tight seal. Introduce TUBEX® BLUNT POINTE™ Sterile Cartridge Unit into the "needle-less" IV set as per manufacturer's "Directions for Use."

To remove the empty TUBEX® Cartridge Unit and dispose into a vertical disposal container
1. Do not recap the needle/point. Disengage the plunger rod.

2. Hold the Injector, needle/point down, over a vertical disposal container and loosen the ribbed collar. TUBEX® Cartridge Unit will drop into the container.



3. Discard the cover.

To remove the empty TUBEX® Cartridge Unit and dispose into a horizontal (mailbox) disposal container
1. Do not recap the needle/point. Disengage the plunger rod.
2. Open the horizontal (mailbox) disposal container. Insert TUBEX® Cartridge Unit, needle/point pointing down, halfway into container. Close the container lid on cartridge. Loosen ribbed collar; TUBEX® Cartridge Unit will drop into the container.
3. Discard the cover.

The TUBEX® Injector is reusable and should not be discarded. Used TUBEX® Cartridge Units should not be employed for successive injections or as multiple-dose containers. They are intended to be used only once and discarded.
NOTE: Any graduated markings on TUBEX® Sterile Cartridge Units are to be used only as a guide in mixing, withdrawing, or administering measured doses.
Wyeth-Ayerst does not recommend and will not accept responsibility for the use of any cartridge-needle units or needle-less units other than TUBEX® Cartridge Units in the TUBEX® Injector.

Revised August 1997
Shown in Product Identification Guide, page 334

VALIUM® ℗

[*val 'ee-um*]
brand of diazepam
INJECTION

The following text is complete prescribing information based on official labeling in effect June 1999.

DESCRIPTION

Each mL contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.
Diazepam is a benzodiazepine derivative developed through original Roche research. Chemically, diazepam is 7-chloro-1,

3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. It is a colorless crystalline compound, insoluble in water and has a molecular weight of 284.74.

ACTIONS

In animals, diazepam appears to act on parts of the limbic system, the thalamus and hypothalamus, and induces calming effects. Diazepam, unlike chlorpromazine and reserpine, has no demonstrable peripheral autonomic blocking action, nor does it produce extrapyramidal side effects; however, animals treated with diazepam do have a transient ataxia at higher doses. Diazepam was found to have transient cardiovascular depressor effects in dogs. Long-term experiments in rats revealed no disturbances of endocrine function. Injections into animals have produced localized irritation of tissue surrounding injection sites and some thickening of veins after intravenous use.

INDICATIONS

Valium is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.
In acute alcohol withdrawal, Valium may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.
As an adjunct prior to endoscopic procedures if apprehension, anxiety or acute stress reactions are present, and to diminish the patient's recall of the procedures. (See WARNINGS.)
Valium is a useful adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology (such as inflammation of the muscles or joints, or secondary to trauma); spasticity caused by upper motor neuron disorders (such as cerebral palsy and paraplegia); athetosis; stiff-man syndrome; and tetanus.
Valium Injection is a useful adjunct in status epilepticus and severe recurrent convulsive seizures.
Valium is a useful premedication (the IM route is preferred) for relief of anxiety and tension in patients who are to undergo surgical procedures. Intravenously, prior to cardioversion for the relief of anxiety and tension and to diminish the patient's recall of the procedure.

CONTRAINDICATIONS

Valium Injection is contraindicated in patients with a known hypersensitivity to this drug; acute narrow angle glaucoma; and open angle glaucoma unless patients are receiving appropriate therapy.

WARNINGS

When used intravenously, the following procedures should be undertaken to reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment: the solution should be injected slowly, taking at least 1 minute for each 5 mg (1 mL) given; do not use small veins, such as those on the dorsum of the hand or wrist; extreme care should be taken to avoid intra-arterial administration or extravasation.
Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly IV, it may be injected slowly through the infusion tubing as close as possible to the vein insertion.
Extreme care must be used in administering Valium Injection, particularly by the IV route, to the elderly, to very ill patients and to those with limited pulmonary reserve because of the possibility that apnea and/or cardiac arrest may occur. Concomitant use of barbiturates, alcohol or other central nervous system depressants increases depression with increased risk of apnea. Resuscitative equipment including that necessary to support respiration should be readily available.
When Valium is used with a narcotic analgesic, the dosage of the narcotic should be reduced by at least one-third and administered in small increments. In some cases the use of a narcotic may not be necessary.
Valium Injection should not be administered to patients in shock, coma or in acute alcoholic intoxication with depression of vital signs. As is true of most CNS-acting drugs, patients receiving Valium should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle.
Tonic status epilepticus has been precipitated in patients treated with IV Valium for petit mal status or petit mal variant status.

Usage in Pregnancy: **An increased risk of congenital malformations associated with the use of minor tranquilizers (diazepam, meprobamate and chlordiazepoxide) during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.**

In humans, measurable amounts of diazepam were found in maternal and cord blood, indicating placental transfer of the drug. Until additional information is available, Valium Injection is not recommended for obstetrical use.
Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE section).

	USUAL ADULT DOSAGE	*DOSAGE RANGE IN PEDIATRIC PATIENTS* **(IV administration should be made slowly)**
Moderate Anxiety Disorders and Symptoms of Anxiety.	2 mg to 5 mg, IM or IV. Repeat in 3 to 4 hours, if necessary.	
Severe Anxiety Disorders and Symptoms of Anxiety.	5 mg to 10 mg, IM or IV. Repeat in 3 to 4 hours, if necessary.	
Acute Alcohol Withdrawal: As an aid in symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.	10 mg, IM or IV initially, then 5 mg to 10 mg in 3 to 4 hours, if necessary.	
Endoscopic Procedures: Adjunctively, if apprehension, anxiety or acute stress reactions are present prior to endoscopic procedures. Dosage of narcotics should be reduced by at least a third and in some cases may be omitted. See *Precautions* for peroral procedures.	Titrate IV dosage to desired sedative response, such as slurring of speech, with slow administration immediately prior to the procedure. Generally 10 mg or less is adequate, but up to 20 mg IV may be given, particularly when concomitant narcotics are omitted. If IV cannot be used, 5 mg to 10 mg IM approximately 30 minutes prior to the procedure.	
Muscle Spasm: Associated with local pathology, cerebral palsy, athetosis, stiff-man syndrome or tetanus.	5 mg to 10 mg, IM or IV initially, then 5 mg to 10 mg in 3 to 4 hours, if necessary. For tetanus, larger doses may be required.	For tetanus in pediatric patients between 30 days and 5 years of age, 1 mg to 2 mg IM or IV, slowly, repeated every 3 to 4 hours as necessary. In pediatric patients 5 years or older, 5 mg to 10 mg repeated every 3 to 4 hours may be required to control tetanus spasms. Respiratory assistance should be available.
Status Epilepticus and Severe Recurrent Convulsive Seizures: In the convulsing patient, the IV route is by far preferred. This injection should be administered slowly. However, if IV administration is impossible, the IM route may be used.	5 mg to 10 mg initially (IV preferred). This injection may be repeated if necessary at 10 to 15 minute intervals up to a maximum dose of 30 mg. If necessary, therapy with Valium may be repeated in 2 to 4 hours; however, residual active metabolites may persist, and readministration should be made with this consideration. Extreme caution must be exercised with individuals with chronic lung disease or unstable cardiovascular status.	Pediatric patients between the ages of 30 days and 5 years, 0.2 mg to 0.5 mg slowly every 2 to 5 minutes up to a maximum of 5 mg (IV preferred). Pediatric patients 5 years or older, 1 mg every 2 to 5 minutes up to a maximum of 10 mg (slow IV administration preferred). Repeat in 2 to 4 hours if necessary. EEG monitoring of the seizure may be helpful.
Preoperative Medication: To relieve anxiety and tension. (If atropine, scopolamine or other premedications are desired, they must be administered in separate syringes.)	10 mg, IM (preferred route), before surgery.	
Cardioversion: To relieve anxiety and tension and to reduce recall of procedure.	5 mg to 15 mg, IV, within 5 to 10 minutes prior to the procedure.	

PRECAUTIONS

Although seizures may be brought under control promptly, a significant proportion of patients experience a return to seizure activity, presumably due to the short-lived effect of Valium after IV administration. The physician should be prepared to readminister the drug. However, Valium is not recommended for maintenance, and once seizures are brought under control, consideration should be given to the administration of agents useful in longer term control of seizures.
If Valium is to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed—particularly with known compounds which may potentiate the action of Valium, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. In highly anxious patients with evidence of accompanying depression, particularly those who may have suicidal tendencies, protective measures may be necessary. The usual precautions in treating patients with impaired hepatic function should be observed. Metabolites of Valium are excreted by the kidney; to avoid their excess accumulation, caution should be exercised in the administration to patients with compromised kidney function.
Since an increase in cough reflex and laryngospasm may occur with peroral endoscopic procedures, the use of a topical anesthetic agent and the availability of necessary countermeasures are recommended.
Until additional information is available, diazepam injection is not recommended for obstetrical use.
Valium Injection has produced hypotension or muscular weakness in some patients particularly when used with narcotics, barbiturates or alcohol.
Lower doses (usually 2 mg to 5 mg) should be used for elderly and debilitated patients.
The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 30 days have not been established. Prolonged central nervous system depression has been observed in neonates, apparently due to inability to biotransform Valium into inactive metabolites.
In pediatric use, in order to obtain maximal clinical effect with the minimum amount of drug and thus to reduce the risk of hazardous side effects, such as apnea or prolonged periods of somnolence, it is recommended that the drug be given slowly over a 3-minute period in a dosage not to exceed 0.25 mg/kg. After an interval of 15 to 30 minutes the initial dosage can be safely repeated. If, however, relief of symptoms is not obtained after a third administration, adjunctive therapy appropriate to the condition being treated is recommended.

ADVERSE REACTIONS

Side effects most commonly reported were drowsiness, fatigue and ataxia; venous thrombosis and phlebitis at the site of injection. Other adverse reactions less frequently reported include: *CNS:* confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo. *GI:* constipation, nausea. *GU:* incontinence, changes in libido, urinary retention. *Cardiovascular:* bradycardia, cardiovascular collapse, hypotension. *EENT:* blurred vision, diplopia, nystagmus. *Skin:* urticaria, skin rash. *Other:* hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after Valium therapy and are of no known significance.
In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm and pain in throat or chest have been reported.

Continued on next page

Valium Injectable—Cont.

Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy.

DRUG ABUSE AND DEPENDENCE

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuance of diazepam. 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. Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving diazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

DOSAGE AND ADMINISTRATION

Dosage should be individualized for maximum beneficial effect. The usual recommended dose in adults ranges from 2 mg to 20 mg IM or IV, depending on the indication and its severity. In some conditions, eg, tetanus, larger doses may be required. (See dosage for specific indications.) In acute conditions the injection may be repeated within 1 hour although an interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 mg to 5 mg) and slow increase in dosage should be used for elderly or debilitated patients and when other sedative drugs are administered (see WARNINGS and ADVERSE REACTIONS).

For dosage in pediatric patients above the age of 30 days, see the specific indications below. When intravenous use is indicated, facilities for respiratory assistance should be readily available.

Intramuscular: Valium Injection should be injected deeply into the muscle.

Intravenous Use: (See WARNINGS and PRECAUTIONS: *Pediatric Use.*) The solution should be injected slowly, taking at least 1 minute for each 5 mg (1 mL) given. Do not use small veins, such as those on the dorsum of the hand or wrist. Extreme care should be taken to avoid intra-arterial administration or extravasation.

Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly IV, it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

[See table at top of previous page]

Once the acute symptomatology has been properly controlled with Valium Injection, the patient may be placed on oral therapy with Valium if further treatment is required.

Management of Overdosage:

Manifestations of Valium overdosage include somnolence, confusion, coma and diminished reflexes. Respiration, pulse and blood pressure should be monitored, as in all cases of drug overdosage, although, in general, these effects have been minimal. General supportive measures should be employed, along with intravenous fluids, and an adequate airway maintained. Hypotension may be combated by the use of Levophed® (levarterenol) or Aramine (metaraminol). Dialysis is of limited value.

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. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and 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.

HOW SUPPLIED

Vials, 10 mL, boxes of 1 (NDC 0004-1932-09). *Tel-E-Ject* ® (disposable syringes), 2 mL, boxes of 10 (NDC 0004-1933-06).

ANIMAL PHARMACOLOGY

Oral LD_{50} of diazepam is 720 mg/kg in mice and 1240 mg/kg in rats. Intraperitoneal administration of 400 mg/kg to a monkey resulted in death on the sixth day.

Reproduction Studies: A series of rat reproduction studies was performed with diazepam in oral doses of 1, 10, 80 and 100 mg/kg given for periods ranging from 60 to 228 days prior to mating. At 100 mg/kg there was a decrease in the number of pregnancies and surviving offspring in these rats. These effects may be attributable to prolonged sedative activity, resulting in lack of interest in mating and lessened maternal nursing and care of the young. Neonatal survival of rats at doses lower than 100 mg/kg was within normal limits. Several neonates, both controls and experimentals, in these rat reproduction studies showed skeletal or other defects. Further studies in rats at doses up to and including 80 mg/kg/day did not reveal significant teratological effects on the offspring. Rabbits were maintained on doses of 1, 2, 5 and 8 mg/kg from day 6 through day 18 of gestation. No adverse effects on reproduction and no teratological changes were noted.

Distributed by Roche Laboratories Inc, Nutley, NJ 07110

Revised: March 1999

VERSED®

[ver-sed ']

midazolam HCl

INJECTION

The following text is complete prescribing information based on official labeling in effect June 1999.

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 (see WARNINGS). For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

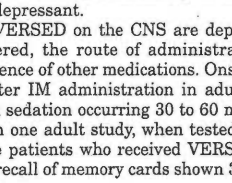
The initial intravenous dose for sedation in adult patients may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other central nervous system (CNS)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

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 (see DOSAGE AND ADMINISTRATION for complete information).

DESCRIPTION

VERSED 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; the pH is adjusted to approximately 3 with hydrochloric acid and, if necessary, sodium hydroxide.

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



CLINICAL PHARMACOLOGY

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

The effects of VERSED 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 VERSED 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 VERSED compared with 5% of the placebo controls.

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

When VERSED 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 µg/kg IV VERSED 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. VERSED did not dependably induce anesthesia at this dose despite concomitant opioid administration in pediatric patients.

VERSED, 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 VERSED administered, coadministration of other medications causing CNS depression and duration of the procedure.

In patients without intracranial lesions, induction of general anesthesia with IV VERSED 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 VERSED and with thiopental during intubation. No similar studies have been reported in pediatric patients.

The usual recommended intramuscular premedicating doses of VERSED do not depress the ventilatory response to carbon dioxide stimulation to a clinically significant extent in adults. Intravenous induction doses of VERSED 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 VERSED 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 VERSED (100 or 200 µg/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 VERSED 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 VERSED (500 µg/kg) with propofol (2.5 mg/kg) revealed a mean 15% decrease in systolic blood pressure in patients who had received IV VERSED 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

Toradol—Cont.

Hemic and Lymphatic: postoperative wound hemorrhage (rarely requiring blood transfusion—see Boxed WARNING, WARNINGS and PRECAUTIONS), thrombocytopenia, leukopenia
Hepatic: hepatitis, liver failure, cholestatic jaundice
Nervous System: convulsions, psychosis, aseptic meningitis
Respiratory: asthma, bronchospasm
Urogenital: acute renal failure (see Boxed WARNING, WARNINGS), flank pain with or without hematuria and/or azotemia, nephritis, hyponatremia, hyperkalemia, hemolytic uremic syndrome

OVERDOSAGE

In controlled overdosage, daily doses of 360 mg of TORADOL$^{IV/IM}$ given for 5 days (three times the highest recommended dose), caused abdominal pain and peptic ulcers which healed after discontinuation of dosing. Metabolic acidosis has been reported following intentional overdosage. Dialysis does not significantly clear ketorolac tromethamine from the blood stream.

DOSAGE AND ADMINISTRATION

THE COMBINED DURATION OF USE OF TORADOL$^{IV/IM}$ AND TORADOL^{ORAL} IS NOT TO EXCEED 5 DAYS.
THE USE OF TORADOL^{ORAL} IS ONLY INDICATED AS CONTINUATION THERAPY TO TORADOL$^{IV/IM}$.

TORADOL$^{IV/IM}$

TORADOL$^{IV/IM}$ may be used as a single or multiple dose on a regular or prn schedule for the management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Hypovolemia should be corrected prior to the administration of TORADOL (see WARNINGS: *Renal Effects*). Patients should be switched to alternative analgesics as soon as possible, but TORADOL therapy is not to exceed 5 days.
When administering TORADOL$^{IV/IM}$, the IV bolus must be given over no less than 15 seconds. The IM administration should be given slowly and deeply into the muscle. The analgesic effect begins in 30 minutes with maximum effect in 1 to 2 hours after dosing IV or IM. Duration of analgesic effect is usually 4 to 6 hours.

Single-Dose Treatment: The Following Regimen Should Be Limited To Single Administration Use Only

IM Dosing:

- *Patients <65 years of age: One dose of 60 mg.*
- *Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lbs) of body weight: One dose of 30 mg.*

IV Dosing:

- *Patients <65 years of age: One dose of 30 mg.*
- *Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lbs) of body weight: One dose of 15 mg.*

Multiple-Dose Treatment (IV or IM)

- *Patients <65 years of age:* The recommended dose is 30 mg TORADOL$^{IV/IM}$ every 6 hours. The maximum daily dose should not exceed 120 mg.
- *For Patients ≥65 years of age, renally impaired patients (see WARNINGS) and patients less than 50 kg (110 lbs):* The recommended dose is 15 mg TORADOL$^{IV/IM}$ every 6 hours. The maximum daily dose for these populations should not exceed 60 mg.

For breakthrough pain do not increase the dose or the frequency of TORADOL. Consideration should be given to supplementing these regimens with low doses of opioids prn unless otherwise contraindicated.
Pharmaceutical Information for TORADOL$^{IV/IM}$: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
TORADOL$^{IV/IM}$ should not be mixed in a small volume (eg, in a syringe) with morphine sulfate, meperidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride; this will result in precipitation of ketorolac from solution.
TORADOL^{ORAL} is indicated ONLY as continuation therapy to TORADOL$^{IV/IM}$ for the management of moderately severe acute pain that requires analgesia at the opioid level (see also PRECAUTIONS: *Information for Patients*).
Transition from TORADOL$^{IV/IM}$ to TORADOL^{ORAL}: The recommended TORADOL^{ORAL} dose is as follows:

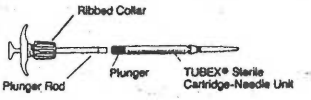
- *Patients <65 years of age:* 2 tablets as a first oral dose for patients who received **60 mg IM single dose, 30 mg IV single dose or 30 mg multiple dose.** TORADOL$^{IV/IM}$ followed by 1 tablet TORADOL^{ORAL} every 4 to 6 hours, not to exceed 40 mg/24 h of TORADOL^{ORAL}
- *Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lbs) of body weight:* 1 tablet as a first oral dose for patients who received **30 mg IM single dose, 15 mg IV single dose or 15 mg multiple dose.** TORADOL$^{IV/IM}$ followed by 1 tablet TORADOL^{ORAL} every 4 to 6 hours, not to exceed 40 mg/24 h of TORADOL^{ORAL}.

Shortening the recommended dosing intervals may result in increased frequency and severity of adverse reactions.
The maximum combined duration of use (parenteral and oral TORADOL) is limited to 5 days.
The TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is suitable for substances to be administered intravenously only. It is intended for use with injection sets specifically manufactured as "needle-less" injection systems. TUBEX® BLUNT POINTE™ is compatible with Abbott's LifeShield® prepierced reseal injection site, Baxter's InterLink® Injection Site, and B. Braun Medical's SafSite® Reflux Valve. Consult manufacturer's recommendations regarding "Directions for Use" of the "needle-less" system. It is also intended for admixture with, and convenient administration of, various medicaments when using Drug Vial Adapters for "needle-less" injection systems.
The TUBEX® Sterile Cartridge-Needle Unit and sterile vial are suitable for substances to be administered intravenously and intramuscularly.

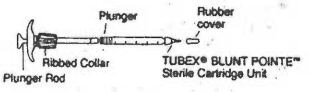
HOW SUPPLIED

TORADOL$^{IV/IM}$ for intramuscular or intravenous use is available in a TUBEX® Cartridge-Needle Unit or a sterial vial:
15 mg: 15 mg/mL, 1 mL TUBEX® Sterile Cartridge-Needle Unit (22 gauge × 1-$^1/_4$ inch needle) box of 10 (NDC 0004-6921-06) or 1 mL fill per 2 mL single use vial, box of 10 (NDC 0004-6925-06).
30 mg: 30 mg/mL, 1 mL TUBEX® Sterile Cartridge-Needle Unit (22 gauge × 1-$^1/_4$ inch needle) box of 10 (NDC 0004-6923-06) or 1 mL fill per 2 mL single use vial, box of 10 (NDC 0004-6926-06).
For IM Single-Dose Use Only Not Intended for IV Use—60 mg: 30 mg/mL, 2 mL TUBEX® Sterile Cartridge-Needle Unit (22 gauge × 1-$^1/_4$ inch needle) box of 1 (NDC 0004-6924-09 or 2 mL fill per 2 mL single use vial, box of 1 (NDC 0004-6927-09).
TORADOL^{IV} for intravenous use is available in a TUBEX® BLUNT POINTE™ Sterile Cartridge Unit:
15 mg: 15 mg/mL, 1 mL TUBEX® BLUNT POINTE™ Sterile Cartridge Unit, box of 10 (NDC 0004-6920-06).
30 mg: 30 mg/mL, 1 mL TUBEX® BLUNT POINTE™ Sterile Cartridge Unit, box of 10 (NDC 0004-6922-06).
Syringes manufactured by Wyeth Laboratories, Inc., Philadelphia, PA 19101 for Roche Laboratories Inc., Nutley, NJ 07110.
Vials manufactured by Hoffmann-La Roche Inc., Nutley, NJ 07110.
Store at 15° to 30°C (59° to 86°F) with protection from light.
TORADOL^{ORAL} 10 mg tablets are available in bottles of 100 tablets (NDC 0004-0273-01).
Store bottles at 15° to 30°C (59° to 86°F).
Manufactured by Syntex Puerto Rico, Inc., Humacao, PR 00791

TUBEX® Injector
NOTE: The TUBEX® Injector is reusable: do not discard.
TUBEX® Sterile Cartridge-Needle Unit
DIRECTIONS FOR USE

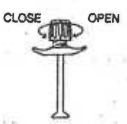


TUBEX® BLUNT POINTE™ Sterile Cartridge Unit
DIRECTIONS FOR USE:

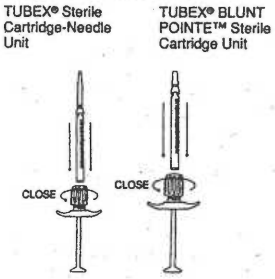


TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is intended for use with injection sets specifically manufactured as "needle-less" injection systems.
TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is compatible with Abbott's LifeShield® prepierced reseal injection site, Baxter's InterLink® Injection Site and B. Braun Medical's SafSite® Reflux Valve. Consult manufacturer's recommendations regarding "Directions for Use" of the "needle-less" injection system.

To load a TUBEX® Sterile Cartridge Unit into the TUBEX® Injector
1. Turn the ribbed collar to the "OPEN" position until it stops.



2. Hold the Injector with the open end



up and fully insert the TUBEX® Sterile Cartridge Unit. Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.

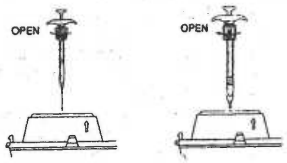
3. Thread the plunger rod into the plunger of the TUBEX® Sterile Cartridge Unit until slight resistance is felt. The Injector is now ready for use in the usual manner.

To administer TUBEX® Sterile Cartridge-Needle Units
Method of administration is the same as with conventional syringe. Remove needle cover by grasping it securely, twist and pull. Introduce needle into patient, aspirate by pulling back slightly on the plunger, and inject.

To administer TUBEX® BLUNT POINTE™ Sterile Cartridge Units
"Needle-less" IV set administration is similar to administration with conventional syringes. Remove rubber cover by grasping it securely; twist and pull. For B. Braun Medical's SafSite® Reflux Valves, aseptically swab the luer slip fitting of the BLUNT POINTE™ sterile cartridge tip assembly with a sterile, individually wrapped, saturated 70% Isopropyl Alcohol swab. This action will remove the lubricant coating from the tip to facilitate a tight seal. Introduce TUBEX® BLUNT POINTE™ Sterile Cartridge Unit into the "needle-less" IV set as per manufacturer's "Directions for Use."

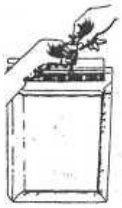
To remove the empty TUBEX® Cartridge Unit and dispose into a vertical disposal container
1. Do not recap the needle/point. Disengage the plunger rod.

2. Hold the Injector, needle/point down, over a vertical disposal container and loosen the ribbed collar. TUBEX® Cartridge Unit will drop into the container.



3. Discard the cover.

To remove the empty TUBEX® Cartridge Unit and dispose into a horizontal (mailbox) disposal container
1. Do not recap the needle/point. Disengage the plunger rod.
2. Open the horizontal (mailbox) disposal container. Insert TUBEX® Cartridge Unit, needle/point pointing down, halfway into container. Close the container lid on cartridge. Loosen ribbed collar; TUBEX® Cartridge Unit will drop into the container.
3. Discard the cover.
The TUBEX® Injector is reusable and should not be discarded.
Used TUBEX® Cartridge Units should not be employed for successive injections or as multiple-dose containers. They are intended to be used only once and discarded.
NOTE: Any graduated markings on TUBEX® Sterile Cartridge Units are to be used only as a guide in mixing, withdrawing, or administering measured doses.



Wyeth-Ayerst does not recommend and will not accept responsibility for the use of any cartridge-needle units or needle-less units other than TUBEX® Cartridge Units in the TUBEX® Injector.

Revised August 1997

Shown in Product Identification Guide, page 334

VALIUM®

[*val 'ee-um*]
brand of diazepam
INJECTION

The following text is complete prescribing information based on official labeling in effect June 1999.

DESCRIPTION

Each mL contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.
Diazepam is a benzodiazepine derivative developed through original Roche research. Chemically, diazepam is 7-chloro-1,

3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. It is a colorless crystalline compound, insoluble in water and has a molecular weight of 284.74.

ACTIONS

In animals, diazepam appears to act on parts of the limbic system, the thalamus and hypothalamus, and induces calming effects. Diazepam, unlike chlorpromazine and reserpine, has no demonstrable peripheral autonomic blocking action, nor does it produce extrapyramidal side effects; however, animals treated with diazepam do have a transient ataxia at higher doses. Diazepam was found to have transient cardiovascular depressor effects in dogs. Long-term experiments in rats revealed no disturbances of endocrine function. Injections into animals have produced localized irritation of tissue surrounding injection sites and some thickening of veins after intravenous use.

INDICATIONS

Valium is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.
In acute alcohol withdrawal, Valium may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.
As an adjunct prior to endoscopic procedures if apprehension, anxiety or acute stress reactions are present, and to diminish the patient's recall of the procedures. (See WARNINGS.)
Valium is a useful adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology (such as inflammation of the muscles or joints, or secondary to trauma); spasticity caused by upper motor neuron disorders (such as cerebral palsy and paraplegia); athetosis; stiff-man syndrome; and tetanus.
Valium Injection is a useful adjunct in status epilepticus and severe recurrent convulsive seizures.
Valium is a useful premedication (the IM route is preferred) for relief of anxiety and tension in patients who are to undergo surgical procedures. Intravenously, prior to cardioversion for the relief of anxiety and tension and to diminish the patient's recall of the procedure.

CONTRAINDICATIONS

Valium Injection is contraindicated in patients with a known hypersensitivity to this drug; acute narrow angle glaucoma; and open angle glaucoma unless patients are receiving appropriate therapy.

WARNINGS

When used intravenously, the following procedures should be undertaken to reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment: the solution should be injected slowly, taking at least 1 minute for each 5 mg (1 mL) given; do not use small veins, such as those on the dorsum of the hand or wrist; extreme care should be taken to avoid intra-arterial administration or extravasation.
Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly IV, it may be injected slowly through the infusion tubing as close as possible to the vein insertion.
Extreme care must be used in administering Valium Injection, particularly by the IV route, to the elderly, to very ill patients and to those with limited pulmonary reserve because of the possibility that apnea and/or cardiac arrest may occur. Concomitant use of barbiturates, alcohol or other central nervous system depressants increases depression with increased risk of apnea. Resuscitative equipment including that necessary to support respiration should be readily available.
When Valium is used with a narcotic analgesic, the dosage of the narcotic should be reduced by at least one-third and administered in small increments. In some cases the use of a narcotic may not be necessary.
Valium Injection should not be administered to patients in shock, coma or in acute alcoholic intoxication with depression of vital signs. As is true of most CNS-acting drugs, patients receiving Valium should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle.
Tonic status epilepticus has been precipitated in patients treated with IV Valium for petit mal status or petit mal variant status.

Usage in Pregnancy: **An increased risk of congenital malformations associated with the use of minor tranquilizers (diazepam, meprobamate and chlordiazepoxide) during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.**

In humans, measurable amounts of diazepam were found in maternal and cord blood, indicating placental transfer of the drug. Until additional information is available, Valium Injection is not recommended for obstetrical use.
Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE section).

	USUAL ADULT DOSAGE	*DOSAGE RANGE IN PEDIATRIC PATIENTS* **(IV administration should be made slowly)**
Moderate Anxiety Disorders and Symptoms of Anxiety.	2 mg to 5 mg, IM or IV. Repeat in 3 to 4 hours, if necessary.	
Severe Anxiety Disorders and Symptoms of Anxiety.	5 mg to 10 mg, IM or IV. Repeat in 3 to 4 hours, if necessary.	
Acute Alcohol Withdrawal: As an aid in symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.	10 mg, IM or IV initially, then 5 mg to 10 mg in 3 to 4 hours, if necessary.	
Endoscopic Procedures: Adjunctively, if apprehension, anxiety or acute stress reactions are present prior to endoscopic procedures. Dosage of narcotics should be reduced by at least a third and in some cases may be omitted. See *Precautions* for peroral procedures.	Titrate IV dosage to desired sedative response, such as slurring of speech, with slow administration immediately prior to the procedure. Generally 10 mg or less is adequate, but up to 20 mg IV may be given, particularly when concomitant narcotics are omitted. If IV cannot be used, 5 mg to 10 mg IM approximately 30 minutes prior to the procedure.	
Muscle Spasm: Associated with local pathology, cerebral palsy, athetosis, stiff-man syndrome or tetanus.	5 mg to 10 mg, IM or IV initially, then 5 mg to 10 mg in 3 to 4 hours, if necessary. For tetanus, larger doses may be required.	For tetanus in pediatric patients between 30 days and 5 years of age, 1 mg to 2 mg IM or IV, slowly, repeated every 3 to 4 hours as necessary. In pediatric patients 5 years or older, 5 mg to 10 mg repeated every 3 to 4 hours may be required to control tetanus spasms. Respiratory assistance should be available.
Status Epilepticus and Severe Recurrent Convulsive Seizures: In the convulsing patient, the IV route is by far preferred. This injection should be administered slowly. However, if IV administration is impossible, the IM route may be used.	5 mg to 10 mg initially (IV preferred). This injection may be repeated if necessary at 10 to 15 minute intervals up to a maximum dose of 30 mg. If necessary, therapy with Valium may be repeated in 2 to 4 hours; however, residual active metabolites may persist, and readministration should be made with this consideration. Extreme caution must be exercised with individuals with chronic lung disease or unstable cardiovascular status.	Pediatric patients between the ages of 30 days and 5 years, 0.2 mg to 0.5 mg slowly every 2 to 5 minutes up to a maximum of 5 mg (IV preferred). Pediatric patients 5 years or older, 1 mg every 2 to 5 minutes up to a maximum of 10 mg (slow IV administration preferred). Repeat in 2 to 4 hours if necessary. EEG monitoring of the seizure may be helpful.
Preoperative Medication: To relieve anxiety and tension. (If atropine, scopolamine or other premedications are desired, they must be administered in separate syringes.)	10 mg, IM (preferred route), before surgery.	
Cardioversion: To relieve anxiety and tension and to reduce recall of procedure.	5 mg to 15 mg, IV, within 5 to 10 minutes prior to the procedure.	

PRECAUTIONS

Although seizures may be brought under control promptly, a significant proportion of patients experience a return to seizure activity, presumably due to the short-lived effect of Valium after IV administration. The physician should be prepared to readminister the drug. However, Valium is not recommended for maintenance, and once seizures are brought under control, consideration should be given to the administration of agents useful in longer term control of seizures.
If Valium is to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed—particularly with known compounds which may potentiate the action of Valium, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. In highly anxious patients with evidence of accompanying depression, particularly those who may have suicidal tendencies, protective measures may be necessary. The usual precautions in treating patients with impaired hepatic function should be observed. Metabolites of Valium are excreted by the kidney; to avoid their excess accumulation, caution should be exercised in the administration to patients with compromised kidney function.
Since an increase in cough reflex and laryngospasm may occur with peroral endoscopic procedures, the use of a topical anesthetic agent and the availability of necessary countermeasures are recommended.
Until additional information is available, diazepam injection is not recommended for obstetrical use.
Valium Injection has produced hypotension or muscular weakness in some patients particularly when used with narcotics, barbiturates or alcohol.
Lower doses (usually 2 mg to 5 mg) should be used for elderly and debilitated patients.
The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 30 days have not been established. Prolonged central nervous system depression has been observed in neonates, apparently due to inability to biotransform Valium into inactive metabolites.
In pediatric use, in order to obtain maximal clinical effect with the minimum amount of drug and thus to reduce the risk of hazardous side effects, such as apnea or prolonged periods of somnolence, it is recommended that the drug be given slowly over a 3-minute period in a dosage not to exceed 0.25 mg/kg. After an interval of 15 to 30 minutes the initial dosage can be safely repeated. If, however, relief of symptoms is not obtained after a third administration, adjunctive therapy appropriate to the condition being treated is recommended.

ADVERSE REACTIONS

Side effects most commonly reported were drowsiness, fatigue and ataxia; venous thrombosis and phlebitis at the site of injection. Other adverse reactions less frequently reported include: *CNS:* confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo. *GI:* constipation, nausea. *GU:* incontinence, changes in libido, urinary retention. *Cardiovascular:* bradycardia, cardiovascular collapse, hypotension. *EENT:* blurred vision, diplopia, nystagmus. *Skin:* urticaria, skin rash. *Other:* hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after Valium therapy and are of no known significance.
In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm and pain in throat or chest have been reported.

Continued on next page

Valium Injectable—Cont.

Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy.

DRUG ABUSE AND DEPENDENCE

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuance of diazepam. 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. Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving diazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

DOSAGE AND ADMINISTRATION

Dosage should be individualized for maximum beneficial effect. The usual recommended dose in adults ranges from 2 mg to 20 mg IM or IV, depending on the indication and its severity. In some conditions, eg, tetanus, larger doses may be required. (See dosage for specific indications.) In acute conditions the injection may be repeated within 1 hour although an interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 mg to 5 mg) and slow increase in dosage should be used for elderly or debilitated patients and when other sedative drugs are administered (see WARNINGS and ADVERSE REACTIONS).

For dosage in pediatric patients above the age of 30 days, see the specific indications below. When intravenous use is indicated, facilities for respiratory assistance should be readily available.

Intramuscular: Valium Injection should be injected deeply into the muscle.

Intravenous Use: (See WARNINGS and PRECAUTIONS: *Pediatric Use.*) The solution should be injected slowly, taking at least 1 minute for each 5 mg (1 mL) given. Do not use small veins, such as those on the dorsum of the hand or wrist. Extreme care should be taken to avoid intra-arterial administration or extravasation.

Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly IV, it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

[See table at top of previous page]

Once the acute symptomatology has been properly controlled with Valium Injection, the patient may be placed on oral therapy with Valium if further treatment is required.

Management of Overdosage:

Manifestations of Valium overdosage include somnolence, confusion, coma and diminished reflexes. Respiration, pulse and blood pressure should be monitored, as in all cases of drug overdosage, although, in general, these effects have been minimal. General supportive measures should be employed, along with intravenous fluids, and an adequate airway maintained. Hypotension may be combated by the use of Levophed® (levarterenol) or Aramine (metaraminol). Dialysis is of limited value.

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. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and 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.

HOW SUPPLIED

Vials, 10 mL, boxes of 1 (NDC 0004-1932-09). *Tel-E-Ject* ® (disposable syringes), 2 mL, boxes of 10 (NDC 0004-1933-06).

ANIMAL PHARMACOLOGY

Oral LD_{50} of diazepam is 720 mg/kg in mice and 1240 mg/kg in rats. Intraperitoneal administration of 400 mg/kg to a monkey resulted in death on the sixth day.

Reproduction Studies: A series of rat reproduction studies was performed with diazepam in oral doses of 1, 10, 80 and 100 mg/kg given for periods ranging from 60 to 228 days prior to mating. At 100 mg/kg there was a decrease in the number of pregnancies and surviving offspring in these rats. These effects may be attributable to prolonged sedative activity, resulting in lack of interest in mating and lessened maternal nursing and care of the young. Neonatal survival of rats at doses lower than 100 mg/kg was within normal limits. Several neonates, both controls and experimentals, in these rat reproduction studies showed skeletal or other defects. Further studies in rats at doses up to and including 80 mg/kg/day did not reveal significant teratological effects on the offspring. Rabbits were maintained on doses of 1, 2, 5 and 8 mg/kg from day 6 through day 18 of gestation. No adverse effects on reproduction and no teratological changes were noted.

Distributed by Roche Laboratories Inc, Nutley, NJ 07110

Revised: March 1999

VERSED®

[ver-sed ']

midazolam HCl

INJECTION

The following text is complete prescribing information based on official labeling in effect June 1999.

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 (see WARNINGS). For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

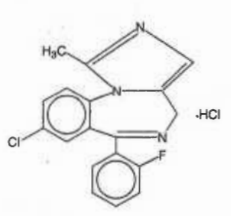
The initial intravenous dose for sedation in adult patients may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other central nervous system (CNS)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

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 (see DOSAGE AND ADMINISTRATION for complete information).

DESCRIPTION

VERSED 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; the pH is adjusted to approximately 3 with hydrochloric acid and, if necessary, sodium hydroxide.

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



CLINICAL PHARMACOLOGY

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

The effects of VERSED 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 VERSED 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 VERSED compared with 5% of the placebo controls.

Sedation in adult and pediatric patients is achieved within 3 to 5 minutes after intravenous (IV) injection; the time of onset is affected by total dose administered and the concurrent administration of narcotic premedication. Seventy-one percent of the adult patients in endoscopy studies had no recall of introduction of the endoscope; 82% of the patients had no recall of withdrawal of the endoscope. In one study of pediatric patients undergoing lumbar puncture or bone marrow aspiration, 88% of patients had impaired recall vs 9% of the placebo controls. In another pediatric oncology study, 91% of VERSED treated patients were amnestic compared with 35% of patients who had received fentanyl alone. When VERSED 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 µg/kg IV VERSED 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. VERSED did not dependably induce anesthesia at this dose despite concomitant opioid administration in pediatric patients.

VERSED, 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 VERSED administered, coadministration of other medications causing CNS depression and duration of the procedure.

In patients without intracranial lesions, induction of general anesthesia with IV VERSED 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 VERSED and with thiopental during intubation. No similar studies have been reported in pediatric patients.

The usual recommended intramuscular premedicating doses of VERSED do not depress the ventilatory response to carbon dioxide stimulation to a clinically significant extent in adults. Intravenous induction doses of VERSED 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 VERSED 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 VERSED (100 or 200 µg/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 VERSED 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 VERSED (500 µg/kg) with propofol (2.5 mg/kg) revealed a mean 15% decrease in systolic blood pressure in patients who had received IV VERSED 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