CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 13-263/S-072/S-075
16-087/S-079/S-081

APPROVAL LETTER

NDA 13-263/S-072/075
NDA 16-087/S-079/081

Roche Products Inc.
Attention: Lynn DeVenezia-Tobias
Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. DeVenezia-Tobias:

Please refer to your new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Valium (diazepam) Tablets (NDA 13-263) and Valium (diazepam) Injection (NDA 16-087).

We additionally refer to the following supplemental applications:

NDA	Supplement	Dated
13-263	S-072	March 2, 1988
13-263	S-075	January 18, 1994
16-087	S-079	October 2, 1987 and amended on March 2, 1988
16-087	S-081	January 18, 1994

These "Changes Being Effected" supplemental new drug applications provide for the following revisions to product labeling:

13-263/S-072 & 16-087/S-079

1. The replacement of the subsection entitled **Physical and Psychological Dependence** with a **Drug Abuse and Dependence** subsection under the **WARNINGS** section.
2. The addition of a section under the **WARNINGS** section referring the prescriber to the **Drug Abuse and Dependence** section.
3. The addition of a subsection entitled **Information for Patients** under the **PRECAUTIONS** section.
4. The addition of the dye contents to the Valium tablet prescriber labeling under the **DESCRIPTION** section in accordance with a Federal Register Notice dated June 8, 1987.
5. The deletion of the Valium injection 10 ml vials packaged in configurations of 10 vials to the Valium injection prescriber labeling under the **HOW SUPPLIED** section.

We note that these revisions were requested by the Agency in letters dated July 6, 1987 and January 5, 1988.

13-263/S-075 & 16-087/S-081

Revisions to the **MANAGEMENT of OVERDOSAGE** section regarding the use of flumazenil for the complete or partial reversal of the sedative effects due to suspected benzodiazepine overdose as requested in an Agency letter dated January 28, 1993.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted January 18, 1994/Label Codes 13-06-78950-0693 [NDA 13-263] and 13-06-78965-0282 [NDA 16-087]). Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
2/7/02 08:01:22 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 16-087/S-079/S-081

FINAL PRINTED LABELING

APPROVED

FEB - 7 2002

Date Code 0693

ROCHE®

A.H.F.S. Category 28:16.08

C IV

INJECTABLE VALIUM®

brand of

diazepam

For relief of acute anxiety when rapid action is required

In acute alcohol withdrawal

As a useful adjunct in

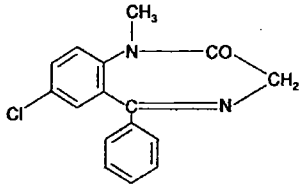
• endoscopic procedures • skeletal muscle spasm associated with local pathology, cerebral palsy, athetosis, stiff-man syndrome, tetanus • status epilepticus and severe recurrent convulsive seizures

As premedication in patients undergoing

• surgical procedures • cardioversion

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. Its structural formula is as follows:



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 severe 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.

Injectable Valium is a useful adjunct in status epilepticus and severe recurrent convulsive seizures.

Valium is a useful premedication (the IV 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: Injectable Valium 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, it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Extreme care must be used in administering Injectable Valium, 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.

Copyright © 1987, 1993 by Roche Products Inc. All rights reserved.

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.

Injectable Valium 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 Injectable is not recommended for obstetrical use.

Use in Children: Efficacy and safety of parenteral Valium has not been established in the neonate (30 days or less of age).

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.

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

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 advisable.

Until additional information is available, Injectable diazepam is not recommended for obstetrical use.

Injectable Valium 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.

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. *G.I.:* constipation, nausea. *G.U.:* 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.

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

INJECTABLE VALIUM®
(diazepam)

[redacted]

89620693

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 older children and adults ranges from 2 mg to 20 mg [redacted] or [redacted] 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 infants above the age of 30 days and children, see the specific indications below. When intravenous use is indicated, facilities for respiratory assistance should be readily available.

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

Intravenous Use: (See WARNINGS, particularly for use in children.) 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.

	USUAL ADULT DOSAGE	*DOSAGE RANGE IN CHILDREN* (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 infants over 30 days of age, 1 mg to 2 mg IM or IV, slowly, repeated every 3 to 4 hours as necessary. In children 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.	Infants over 30 days of age and children under 5 years, 0.2 mg to 0.5 mg slowly every 2 to 5 minutes up to a maximum of 5 mg (IV preferred). Children 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.

(Continued)

(Cont.)

	USUAL ADULT DOSAGE
	Extreme caution must be exercised with individuals with chronic lung disease or unstable cardiovascular status.
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.

Once the acute symptomatology has been properly controlled with injectable Valium, 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 overdosage 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 a substitute for, proper management of benzodiazepine overdosage. Patients should be closely observed and monitored for recurrent sedation, 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. For complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, should be consulted prior to use.

HOW SUPPLIED: *Ampuls*, 2 mL, boxes of 10; *Vials*, 10 mL, boxes of 1. *Tel-E-Ject®* (disposable syringes), 2 mL, boxes of 10.

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 during gestation. 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.

ROCHE®

Manufactured by
HOFFMANN-LA ROCHE INC.
Nutley, New Jersey 07110-1199

Distributed by
ROCHE PRODUCTS INC.
Manati, Puerto Rico 00674

13-06-78962-0693
13-20-78962-0693

Revised: June 1993
Printed in U.S.A.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 13-263/S-072/S-075

FINAL PRINTED LABELING

APPROVED

FEB - 7 2003

FEB - 7 2003

ROCHE®

A.H.F.S. Category 28:16.08

C IV

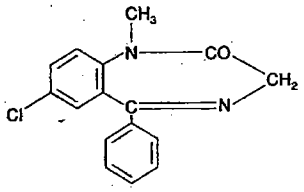
VALIUM®

brand of

diazepam

TABLETS

DESCRIPTION: Valium (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. Its structural formula is as follows:



Valium 5-mg tablets contain FD&C Yellow No. 6 and D&C Yellow No. 10 dyes. Valium 10-mg tablets contain FD&C Blue No. 1 dye. Valium 2-mg tablets contain no dye.

PHARMACOLOGY: In animals, Valium appears to act on parts of the limbic system, the thalamus and hypothalamus, and induces calming effects. Valium, unlike chlorpromazine and reserpine, has no demonstrable peripheral autonomic blocking action, nor does it produce extrapyramidal side effects; however, animals treated with Valium do have a transient ataxia at higher doses. Valium was found to have transient cardiovascular depressor effects in dogs. Long-term experiments in rats revealed no disturbances of endocrine function.

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. At 100 mg/kg there was a decrease in the number of pregnancies and surviving offspring in these rats. Neonatal survival of rats at doses lower than 100 mg/kg was within normal limits. Several neonates 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 teratological effects on the offspring.

In humans, measurable blood levels of Valium were obtained in maternal and cord blood, indicating placental transfer of the drug.

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.

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; and stiff-man syndrome.

Oral Valium may be used adjunctively in convulsive disorders, although it has not proved useful as the sole therapy.

Copyright © 1987, 1993 by Roche Products Inc. All rights reserved.

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS: Valium is contraindicated in patients with a known hypersensitivity to this drug and, because of lack of sufficient clinical experience, in children under 6 months of age. It may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in acute narrow angle glaucoma.

WARNINGS: Valium is not of value in the treatment of psychotic patients and should not be employed in lieu of appropriate treatment. As is true of most preparations containing 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.

As with other agents which have anticonvulsant activity, when Valium is used as an adjunct in treating convulsive disorders, the possibility of an increase in the frequency and/or severity of grand mal seizures may require an increase in the dosage of standard anticonvulsant medication. Abrupt withdrawal of Valium in such cases may also be associated with a temporary increase in the frequency and/or severity of seizures.

Since Valium has a central nervous system depressant effect, patients should be advised against the simultaneous ingestion of alcohol and other CNS-depressant drugs during Valium therapy.

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.**

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 following overdosage. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be combated by the use of Levophed® (levarterenol) or Aramine (metaraminol). Dialysis is of limited value. As with the management of intentional overdosage with any drug, it should be borne in mind that multiple agents may have been ingested.

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.

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

PRECAUTIONS: If Valium is to be combined with other

VALIUM®
(diazepam)

89500693

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. The usual precautions are indicated for severely depressed patients or those in whom there is any evidence of latent depression; particularly the recognition that suicidal tendencies may be present and protective measures may be necessary. The usual precautions in treating patients with impaired renal or hepatic function should be observed.

In elderly and debilitated patients, it is recommended that the dosage be limited to the smallest effective amount to preclude the development of ataxia or oversedation (2 mg to 2½ mg once or twice daily, initially, to be increased gradually as needed and tolerated).

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Information for Patients: To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

ADVERSE REACTIONS: Side effects most commonly reported were drowsiness, fatigue and ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo and blurred vision. 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.

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

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

veillance 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. While the usual daily dosages given below will meet the needs of most patients, there will be some who may require higher doses. In such cases dosage should be increased cautiously to avoid adverse effects.

ADULTS:	*USUAL DAILY DOSE*
Management of Anxiety Disorders and Relief of Symptoms of Anxiety.	Depending upon severity of symptoms—2 mg to 10 mg, 2 to 4 times daily
Symptomatic Relief in Acute Alcohol Withdrawal.	10 mg, 3 or 4 times during the first 24 hours, reducing to 5 mg, 3 or 4 times daily as needed
Adjunctively for Relief of Skeletal Muscle Spasm.	2 mg to 10 mg, 3 or 4 times daily
Adjunctively in Convulsive Disorders.	2 mg to 10 mg, 2 to 4 times daily
Geriatric Patients, or in the presence of debilitating disease.	2 mg to 2½ mg, 1 or 2 times daily initially; increase gradually as needed and tolerated
CHILDREN:	
Because of varied responses to CNS-acting drugs, initiate therapy with lowest dose and increase as required. Not for use in children under 6 months.	1 mg to 2½ mg, 3 or 4 times daily initially; increase gradually as needed and tolerated

HOW SUPPLIED: For oral administration, round, scored tablets with a cut out "V" design—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100 and 500. Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10.

Imprint on tablets:
2 mg—2 VALIUM® (front)
ROCHE (scored side)
5 mg—5 VALIUM® (front)
ROCHE (scored side)
10 mg—10 VALIUM® (front)
ROCHE (scored side)

ROCHE **Roche Products**

Roche Products Inc.
Manati, Puerto Rico 00674

13-06-78950-0693
13-20-78950-0693

Revised June 1993
Printed in U.S.A.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 13-263/S-072/S-075
16-087/S-079/S-081

ADMINISTRATIVE DOCUMENTS

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date: January 24, 2002
DRUG/NDA: Valium (diazepam) Tablets (NDA 13-263)
and Valium (diazepam) Injection (NDA 16-087)
Sponsor: Roche Pharmaceuticals
Indications: Generalized Anxiety Disorder/Acute Alcohol Withdrawal/Relief of Skeletal Muscle Spasm associated with local pathology, Cerebral Palsy, Athetosis, Stiff-man Syndrome, Tetanus /Adjunctive Therapy in Convulsive Disorders/Adjunct in Endoscopic Procedures/Premedication in Patients Undergoing Surgical Procedures or Cardioversion

Supplements:

NDA	Supplement	Dated	Action
Valium (diazepam) Tablets (NDA 13-263)			
13-263	SLR-067/ SCS-068	10-31-83	AP Letter dated 1-13-84
13-263	SLR-072	3-2-88	Open
13-263	SLR-075	1-18-94	Open
Valium (diazepam) Injection (NDA 16-087)			
16-087	SLR-051	3-17-82, and amended on 7-22-82	AP Letter Dated 8-5-82
16-087	SLR-079	10-2-87, and amended on 3-2-88	AE Letter Dated 1-5-88 Open
16-087	SLR-081	1-18-94	Open

Notes of interest:

1. The labeling for both Valium (diazepam) Tablets (NDA 13-263) and Valium (diazepam) Injection (NDA 16-087) are separate and not combined formulation labeling. Although, as may be expected, many sections are identical. Therefore, this labeling review encompasses both product formulations. Additionally, all labeling revisions, which are open, for both the Valium Tablets and Injection are identical since these were all safety related revisions.
2. Although the open labeling supplements for both the tablet and injection parallel one another in terms of content, there is a labeling supplement submitted to the injection application, [redacted] The corresponding supplement

[redacted] was administratively closed in an acknowledge and retain action on 7-13-84. The 7-13-84 Agency letter was a stay letter since these supplements provided for content and format labeling revisions. This labeling review will not encompass a review of the proposed content and format labeling revisions submitted to [redacted] Although, it will recommend regulatory action in regard to this open supplement (see **Conclusions**).

3. I was unable to find many of the older, open labeling supplement submissions since these have transcended numerous reviewing medical officers and Project Managers throughout the years. I had, therefore, requested and received from Roche copies of these open labeling supplements.

REVIEW

13-263/SLR-072 Label Code No: 13-20-78980-0288
16-087/SLR-079 Label Code No: 13-06-78965-0282
Date: 10-2-87, and amended on 3-2-88
CBE: Yes
Reviewed by Medical Officer and Chemist: No reviews on file

These supplements provide for the following revisions:

1. The replacement of the subsection entitled **Physical and Psychological Dependence** with a **Drug Abuse and Dependence** subsection under the **WARNINGS** section.
2. The addition of a section under the **WARNINGS** section referring the prescriber to the to the **Drug Abuse and Dependence** section.
3. The addition of a subsection entitled **Information for Patients** under the **PRECAUTIONS** section.
4. The addition of the dye contents to the Valium tablet prescriber labeling under the **DESCRIPTION** section in accordance with a Federal Register Notice dated June 8, 1987.
5. The deletion of the Valium injection 10 ml vials packaged in configurations of 10 vials to the Valium injection prescriber labeling under the **HOW SUPPLIED** section.

Notes of Interest:

1. The 10-2-87 submission was only coded as a supplement to the injection NDA. However, the 3-2-88 submission was coded to both the tablet and the injection applications, i.e., as an original supplement to the tablet and as an amendment to the injection application.
2. The labeling revisions were requested by the Agency in a letter dated 7-6-87. The Agency subsequently issued an AE action on the injection application, solely, in a letter dated 1-5-88. Roche agreed to the changes requested in the 1-5-88 letter, verbatim, and submitted these changes as CBE. Although the 1-5-88 Agency letter was coded as an AE action, the letter states that the draft labeling submitted on 10-2-87 is approved and requests 12 copies of FPL.

13-263/SLR-075 Label Code No: 13-06-78950-0693
16-087/SLR-081 Label Code No: 13-06-78962-0693
Date: 1-18-94
CBE: Yes
Reviewed by Medical Officer: No review on file

- These supplements provide for revisions to the **MANAGEMENT of OVERDOSAGE** section regarding the use of flumazenil for the complete or partial reversal of the sedative effects due to suspected benzodiazepine overdose.

Notes of Interest:
These revisions were requested in an Agency letter dated 1-28-93.

[redacted]

[redacted]

n

[redacted]

[redacted]

CONCLUSIONS

1. In regard to the open supplement, [redacted] recommend that this be administratively closed similar to the action taken for the tablet application [redacted] The 7-13-84 action letter which close [redacted] should have also incorporated [redacted] I believe that this was an administrative oversight, and that open supplement 16-087 should be closed by the 7-13-84 action letter as well.

2. I was informed by Roche that they are no longer marketing the Valium Injection. This was confirmed when I reviewed their last annual report dated August 17, 2001.

3. The four open labeling supplements submitted under CBE, 13-263/SLR-072/SLR-075 & 16-087/SLR-079/SLR-081, were in response to Agency letters requesting revisions to the labeling. These revisions were submitted verbatim as requested in these letters. If the medical officer and team leader concur, I recommend that an approval letter issue for these CBE supplements. Even though Valium injection is no longer marketed, I recommend that an approval letter issue for these supplemental applications since the labeling will be used as a base for generic products.

4. In regard to the four open labeling supplements submitted as Prior Approval supplements, [redacted] these supplements provide for extensive changes to the labeling. The sponsor intends to submit a withdrawal letter for [redacted] Once this is received, a formal acknowledgement of withdrawal letter should issue.

[redacted]

[redacted] Prior to taking an action on these supplements, they will need to be reviewed by the medical officer, chemistry reviewer, pharmacology reviewer, and the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) to ensure that all of the changes are appropriate. I will obtain desk copies of these submissions and consult the supplements.

Paul David, R.Ph., Regulatory Project Manager

Robbin Nighswander, R.Ph., Supervisory Regulatory Health Officer

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul David
1/30/02 11:39:03 AM
CSO

Robbin Nighswander
1/30/02 01:44:39 PM
CSO