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:

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<tr>
<td>13-263</td>
<td>S-072</td>
<td>March 2, 1988</td>
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<td>13-263</td>
<td>S-075</td>
<td>January 18, 1994</td>
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<tr>
<td>16-087</td>
<td>S-079</td>
<td>October 2, 1987 and amended on March 2, 1988</td>
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<tr>
<td>16-087</td>
<td>S-081</td>
<td>January 18, 1994</td>
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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
Injectable VALIUM® (diazepam)

Use in Pregnancy: As increased risk of congenital malformations associated with the use of minor tranquilizers (diazepam, meprobamates, and chlorpromazine) 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 of a potential risk must be weighed against the necessity of the drug in a particular case. 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 risk to the fetus. If the drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the possible risk of RSUDE and, if possible, should be referred to a specialist for counseling before and during pregnancy. If the patient is known to be pregnant, the use of this drug should be discontinued as soon as possible. If the infant shows any signs of depression, the mother should be referred to a specialist for further evaluation. If the patient is known to be pregnant, the use of this drug should be discontinued as soon as possible. If the infant shows any signs of depression, the mother should be referred to a specialist for further evaluation.

Use in Children: Efficacy and safety of parvalbumin have not been established in neonates (20 weeks of age). Therefore, use in neonates is not recommended for use in neonates. Use in children younger than 12 years of age is not recommended. Use in 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 liver function.

Since an increase in cough reflex and laryngospasm may occur with penicillin, the use of this drug is not recommended for use with penicillin. 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 hepatic encephalopathy. The clinical significance of this is unknown. ADVERSE REACTIONS: Side effects most commonly reported were drowsiness, fatigue, and ataxia; venous thrombosis and phlebitis at the site of injection. Other adverse reactions may occur more frequently with diazepam than with other benzodiazepines. Diazepam should not be used in patients with impaired hepatic function. The incidence of these adverse reactions is unknown. 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 hepatic encephalopathy. The clinical significance of this is unknown.

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Injectable VALIUM® (diazepam)

10 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.

For tetanus in infants under 5 years of age and children under 5 years, 0.2 mg to 0.5 mg every 2 to 5 minutes, up to a maximum of 5 mg (IV preferred). Over 5 years, 1 mg every 2 to 3 minutes up to a maximum of 10 mg (IV administration preferred). Repeat in 2 to 4 hours if necessary. ECG monitoring of the patient may be helpful.

Injectable VALIUM® (diazepam)

USUAL ADULT DOSAGE

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

Preparatory Medication: 10 mg IM (preferred route), before surgery.

5 mg to 15 mg, IV within 5 to 10 minutes prior to the procedure.

Once the acute symptomatic phase 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: The manifestations of Valium overdose include somnolence, confusion, coma and dilated pupils. Respiration, pulse and blood pressure should be monitored, as in all cases of drug overdose, although, in general, these effects have been minimal. Several supportive measures should be employed, along with tetanus toxoid, and an adequate airway maintained. Hyperventilation may be counteracted by the use of L-carnitine* (levocarnitine) or Artenol (atenolol). Dialysis is of limited value.

A specific antagonist-anticonvulsant-intervention, is in an advanced stage of clinical trials, and the definitive effects of the agent have not been firmly established. It may be used in conjunction with diazepam in cases where its longer and more convenient action is required.

Prior to the administration of benzodiazepines, necessary measures should be taken to ensure that adequate monitoring of the patient is available. Intravenous fluid access should be available, and the patient should be closely monitored. When associated, hyperventilation, seizures and other manifestations of increased intracranial pressure should be treated aggressively. The complete experimental animal study, which included the animals and their biochemical effects, with appropriate time controls, and the patients, should be realized prior to use.

JOW SYMPLIF: Amput, 2 mg, base of 25 mg, 10 mg, base of 1, 1 mg-Ef- (dissolvable tablets), 2 mg, base of 2 mg.

ANIMAL PHARMACOLOGY: Oral LD50 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 in 4 days.

Reproduction Studies: A series of rat reproduction studies was performed with diazepam in oral doses of 1, 10, 50 and 100 mg/kg for periods ranging from 69 to 288 days prior to mating. At 100 mg/kg there was a decrease in both preimplantation and post-implantation death in all doses, with some signs of lethality and some signs of developmental effects. These effects may be attributable to prolonged sedative activity resulting in loss of interest in mating and impaired maternal nursing and care of the young. Neonatal survival of rats at doses lower than 100 mg/kg was within normal limits. Several necroscopy, both controls and experimental, in these rat reproduction studies showed slight to moderate other effects. Further studies in rats at doses of 2.5 and 8 mg/kg did not reveal significant teratological effects on the offspring. Reproductive studies in rabbits were maintained on doses of 1, 2.5 and 8 mg/kg from day 6 through day 9 of gestation. No adverse effects on reproduction or any 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

15-09-7862-0692
12-09-7862-0692

ROCHE

Revised: June 1992
Printed in U.S.A.
CENTER FOR DRUG EVALUATION AND RESEARCH

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

FINAL PRINTED LABELING
VALIUM® (diazepam)

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 chloridiazepoxide) during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, they should be used only if the benefits outweigh the possible hazards. Valium should be used during pregnancy only if clearly needed. 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 it is becoming the custom to become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

Management of Overdose: Manifestations of Valium overdose include somnolence, confusion, coma and diminished reflexes. Respiratory, pulse and blood pressure should be monitored, as in all cases of drug overdose, 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 Levaloline® (levarterenol) or Aramine® (metaraminol).

In humans, measurable blood levels of Valium were observed in the infants born to mothers taking the drug near the end of pregnancy.

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); ataxia; and stiff-man syndrome.

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

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PRECAUTIONS: If Valium is to be combined with other
Valium* (diazepam)

Psychotropic agents or antiepileptic drugs, care should be given to the pharmacology of the patient or by other drugs, 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 p.o. 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 the administration of tolbutamide in elderly patients. 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 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, muscle stiffness, changes in libido, nausea, alterations in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo, and blurred vision. Paradoxical reactions such as acute hyperactivity states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and agitation have been reported; should occur, the 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 discontinuation 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, tremor and insomnia) have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. Addiction-prone individuals (such as alcoholics and drug addicts) should be given special consideration 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:

Management of Anxiety Disorders and Relief of Symptoms of Anxiety.

Usual Daily Dose: Depending upon severity of symptoms—2 mg to 10 mg.

Symptomatic Relief in Acute Alcohol Withdrawal.

10 mg, 3 or 4 times daily during the first 24 hours, reducing to 5 mg, 3 or 4 times daily as needed

Adjuvantly for Relief of Skeletal Muscle Spasm.

2 mg to 10 mg, 3 or 4 times daily
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:

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<td>SLR-067/</td>
<td>10-31-83</td>
<td>AP Letter dated 1-13-84</td>
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<td>13-263</td>
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<td>SLR-075</td>
<td>1-18-94</td>
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Valium (diazepam) Injection (NDA 16-087)

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<td>3-17-82, and amended on 7-22-82</td>
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<td>16-087</td>
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<td>10-2-87, and amended on 3-2-88</td>
<td>AE Letter Dated 1-5-88</td>
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<tr>
<td>16-087</td>
<td>SLR-081</td>
<td>1-18-94</td>
<td>Open</td>
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</tbody>
</table>

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, The corresponding supplement
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 __________. 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 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.
CONCLUSIONS

1. In regard to the open supplement, recommend that this be administratively closed similar to the action taken for the tablet application. The 7-13-84 action letter which close should have also incorporated 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, these supplements provide for extensive changes to the labeling. The sponsor intends to submit a withdrawal letter for Once this is received, a formal acknowledgement of withdrawal letter should issue.
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