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:

<table>
<thead>
<tr>
<th>NDA</th>
<th>Supplement</th>
<th>Dated</th>
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<tr>
<td>13-263</td>
<td>S-072</td>
<td>March 2, 1988</td>
</tr>
<tr>
<td>13-263</td>
<td>S-075</td>
<td>January 18, 1994</td>
</tr>
<tr>
<td>16-087</td>
<td>S-079</td>
<td>October 2, 1987 and amended on March 2, 1988</td>
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<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)

Resuscitative equipment including that necessary to support respiration should be readily available.

When Valem 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 Valem should not be administered to patients in shock, coma, or acute alcoholic intoxication with depression of vital signs. In the case of drugs whose effects are not to be reversed by any known procedure, the use of Valem is not recommended. Tonic status epilepticus has been precipitated in patients treated with I Valam for petit mal status or petit mal status.

Usage in Pregnancy: As increased risk of congenital malformations is associated with the use of minor tranquilizers (diazepam, meprobamate, 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 fetal injury and the potential for maternal harm when such a drug is used for indications as mentioned previously may be greater than that of the potential risk from the use of the drug during pregnancy. Therefore, the possibility of these effects should be weighed against the importance of the drug to the patient. The administration of any drug other than Valem to a woman in pregnancy requires that the patient be informed of the possible hazards to the fetus.

Use in Children: Efficacy and safety of parenteral Valam has not been established in the neonate (50 weeks of life or less). When the use of Valam is indicated during the neonatal or early infancy period, the possibility of withdrawal symptoms occurring is great and the need for treatment must be carefully assessed. Since the use of Valam in children has not been adequately studied, its use is not recommended in this age group.

In infants, measurable amounts of diazepam were found in maternal and cord blood, indicating placental transfer of the drug. Until more information is available, Valam injectable is not recommended for obstetric use.

Refer to the enclosed insert for complete prescribing information. (See Drug Abuse and Dependence Section.)

Safety and Dependence: These drugs may produce physical dependence and the possibility of rebound depression, particularly in patients with a history of alcohol or other drug abuse. The abrupt withdrawal of these drugs, especially in patients who have been receiving high doses for an extended period of time, can lead to severe symptoms of withdrawal, including liver damage. Therefore, it is recommended that the direction be carefully followed and that the patient be told that the drug must be tapered slowly and that withdrawal symptoms may occur. The patient should be informed that these symptoms may include headache, dizziness, anxiety, irritability, dysphoria, insomnia, nervousness, restlessness, agitation, irritability, and tremor. The withdrawal symptoms may begin within 1 to 7 days after abrupt discontinuation of the drug and may persist for several weeks. Patients should be told to consult their physician if withdrawal symptoms occur and to follow the directions given by the physician for their management.

Precautions: These drugs may produce physical dependence and the possibility of withdrawal symptoms may occur with abrupt discontinuation of the drug. The abrupt withdrawal of these drugs, especially in patients who have been receiving high doses for an extended period of time, can lead to severe symptoms of withdrawal, including liver damage. Therefore, it is recommended that the direction be carefully followed and that the patient be told that the drug must be tapered slowly and that withdrawal symptoms may occur. The patient should be informed that these symptoms may include headache, dizziness, anxiety, irritability, dysphoria, insomnia, nervousness, restlessness, agitation, irritability, and tremor. The withdrawal symptoms may begin within 1 to 7 days after abrupt discontinuation of the drug and may persist for several weeks. Patients should be told to consult their physician if withdrawal symptoms occur and to follow the directions given by the physician for their management.

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Instructed those patients who had received excessive doses for an extended period of time. Generally, wider withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuation of benzodiazepines taken concomitantly at therapeutic levels for several months. Consequently, after extended therapeutic discontinue should generally be avoided and a gradual dosage tapering schedule followed. Addiction-prone individuals (such as drug addicts or alcoholics) should receive careful surveillance when receiving discontinuance or other pharmacologic agents because of the predisposition of such patients is habituation and dependence.

DOSE AND ADMINISTRATION: Dosage should be individualized for maximum effectiveness. The usual recommended dose in older children and adults ranges from 2 mg to 20 mg daily depending on the indication and its severity. In some conditions, eg, anxiety, larger doses may be required. (See dosage for specific indications.) In acute conditions the injection may be repeated within 1 hour through an interval of 3 to 4 hours or until 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.)

Dosage in infants above the age of 3 days and children, see the specific indications below. When inoffensive use is indicated, facilities for respiratory assistance should be readily available.

Intramuscular: Inj ectable Valium should be injected deeply into the muscle. Injection sites: (See WARNINGS, particularly for use in children.) The solution should be injected slowly. A test dose of 1 mg is given. Do not use small veins, such as those on the dorsum of the hand or wrist. Extreme care should be taken to avoid intravascular administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion bottle. It is not feasible to administer Valium directly IV. It may be injected slowly through the infusion tubing as close as possible in the vein insertion.

USUAL ADULT DOSAGE

(Various administration should be made slowly)

2 mg to 5 mg, IM or IV. Repeat at 3 to 4 hours, if necessary.

5 mg to 10 mg, IM or IV. Repeat at 3 to 4 hours, if necessary.

10 mg, IM or IV IV initially; then 5 mg to 10 mg in 3 to 4 hours, if necessary.

Dosage in children should be adjusted according to age, treatment, and acute delirious and hallucinatory procedures.

Neuroleptic Procedures: Addictively, if apprehensive. In an acute anxiety or acute nonpharmacologic procedures. Dosage of benzodiazepines should be increased by at least a 10 mg increase in the first 24 to 48 hours and in some cases may be increased more rapidly. (See Dosage for special situations.)

DOSAGE RANGES IN CHILDREN

(Various administration should be made slowly)

5 mg to 10 mg, IM or IV in 3 to 4 hours, if necessary. For tinnitus, larger doses may be required.

Triturate IV dosage to desired sedative response, up to a maximum of 5 mg IV, approximately 30 minutes prior to the procedure.

Status Epilepticus and Ineffective Salivary: In the overwhelming patient, the IV route is preferable. This injection should be administered slowly. However, if IV administration is impossible, the IM route may be used.

USUAL ADULT DOSAGE

(Continued)

DOSEAGE

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

Preparatory Medication: To relieve anxiety and tension. (If atropine, scopalamine or other premedications are desired, they must be administered in separate synges.)

Contraindications: To relieve anxiety and tension and to reduce recall of procedures. Once the acute amnesia has been properly controlled with Inj ectable Valium, the patient may be placed on oral therapy with Valium if further treatment is required.

Management of Overdosage: Manifestations of Valium overdose include somnolence, coma, and dilated pupils. Respiratory, 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 toxoids, and an adequate airway maintained. Hyperosmolality may be combated by the use of Normosol R (Laventisol) or Armona (sol committee) or Armona (intravenous), DIAZ is limited value.

Valium is a specific benzodiazepine-rapid-effect anticonvulsant, is indicated for the control of anxiety and while the effects of the initial doses of benzodiazepines and may be used in situations where control of convulsions is rapid and significant. Prior to the administration of Valium, necessary measures should be taken to ensure that the patient is not fatigued or dehydrated. Valium is intended as an anticonvulsant agent and as such is used in the management of benzodiazepine withdrawal symptoms. Valium is not intended for use in the management of status epilepticus or status epilepticus, and it is not recommended for use in status epilepticus. The minimum therapeutic response for any of the benzodiazepines used in status epilepticus or status epilepticus should be noted prior to the IV administration.

DOSAGE FOR PARALYSIS:

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

NOW SUPPLIED: Ampoule, 2 ml, boxes of 10; Vial, 50 ml, boxes of 2.

ANIMAL PHARMACOLOGY: Oral LD50 of diazepam is 729 mg/kg in mice and 1240 mg/kg in rats. Intraperitoneal administration of 400 mg/kg to a monkey resulted in death in less than 24 hours.

Reproduction Studies: A series of rat reproduction studies was performed with diazepam in oral doses of 10, 60, and 100 mg/kg for periods ranging from 60 to 208 days prior to mating. At 100 mg/kg there was a decrease in the number of progeny surviving and offspring to rats in these studies that may be attributable to prolonged sedative activity resulting in lack of interest in mating and in return 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 experimental, in these rat reproduction studies showed slight to moderate other defects. Further studies in rats up to 208 days of pregnancy and 60 days post partum did not reveal significant toxicological effects on the offspring. Rats were maintained on doses of 1, 5, and 10 mg/kg from day 4 through day 20 of gestation. No adverse effects on reproduction and no teratogenic changes were noted.

Manufactured by
Hoffman-La Roche Inc.
Nutley, New Jersey 07110-1199

Distributed by
Roche Products Inc.
Manati, Puerto Rico 00674

ROCHE

15-05-79062-0083
15-05-79062-0083

Revised: June 1993
Printed in U.S.A.
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 psychiatric 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, the use during this period should 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 Overdose: 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 Levothroid* (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, has been used successfully in reversing the effects of benzodiazepines and may be useful 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 reedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. The physician should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cycloplegic antispasmodic use. Omit 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...
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 1 to 2 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 muscular activity, 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, insomnia and nervousness) 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. Abstinence-prone individuals (such as alcoholics) should probably be tapered more slowly.

Tolerance to the sedative, anxiolytic, and anticonvulsant effects of diazepam develops over a period of days to weeks and is generally not serious. However, abrupt discontinuation may precipitate an abstinence syndrome characterized by anxiety, irritability, insomnia, and rigidity. The discontinuation of diazepam should be gradual to avoid withdrawal symptoms.

No definite teratogenic effects have been demonstrated. (See Precautions.)

DOSE AND ADMINISTRATION: Dosage should be individualized for maximum beneficial effect. While the usual daily dosages indicated 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.

Symptomatic Relief in Acute Alcohol Withdrawal.

Adjunctively for Relief of Skeletal Muscle Spasm.

Valium® (diazepam)

2 mg to 10 mg, 2 to 4 times daily

Geriatric Patients, or in the presence of debilitating disease.

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.

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)

5 mg—5 VALIUM® (front)

10 mg—10 VALIUM® (front)

Roche Products

Roche Products Inc.
Marati, Puerto Rico 00714

13-06-78950-0893

Revised June 1990

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:

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<td>16-087</td>
<td>SLR-081</td>
<td>1-18-94</td>
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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 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
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
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