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>
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<tr>
<th>NDA</th>
<th>Supplement</th>
<th>Dated</th>
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<tbody>
<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>
</tr>
<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
INJECTABLE VALIUM®

For relief of acute anxiety when rapid action is required
In acute alcohol withdrawal
As a sedative adjunct to
- endoscopic procedures
- skeletal muscle spasm associated with local pathology
- central pain, spasticity, stiff-neck syndrome, tetanus
- status epilepticus and severe recurrent convulsive seizure
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 benzyl alcohol as solvents.
Diazepam is a benzoiazepine derivative developed through original Roche research. It is 3-ethyl-4-[methyl[4-ethyl-5-(1-methyl-4-
benzoyl-2-indole)phenyl]amino]-2-oxo-1,4-dihydropyridine-2-one. It is a colorless crystalline compound, insoluble in water and has a molecular weight of 284.4. Its structural formula is as follows:

![Chemical Structure of Diazepam]

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 many other drugs, 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 reduced cardiovascular depressor affects in dogs. Long term experiments in rats revealed no disturbances of endocrine function. Injections into animals have produced localized areas of tissue surrounding injection sites and some thickening of veins after intravenous use.

CONTRAINDICATIONS: Valium is contraindicated in patients with a known hypersensitivity to this drug; drug, acute narrow angle glaucoma, or 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, inflammation and pain at the injection site. The needle should be inserted slowly, taking at least 5 minutes for each 5 mg (1 ml) dose; do not use small veins, such as antecubital veins; inject over 2-3 minutes. Anesthetic care should be taken to avoid intra-arterial administration or extravasation.

Do not mix or dilute Valium with other solutions or drugs in syringes or infusion bags. If it is not possible 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 I.M. 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.

INJECTABLE VALIUM® (diazepam)
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.

When used as part of a total anesthetic regimen with nitrous oxide and oxygen, use of an oxygen concentrator and controlled ventilation must be included in the anesthetic regimen. Hypothermia is contraindicated during administration. Concomitant use of Valium and a narcotic analgesic may increase respiratory depression resulting from central nervous system depression. When used with a narcotic analgesic, the dosage of the narcotic may 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® (diazepam) should not be admistered to patients in shock, coma or in acute alcohol intoxication with depression of vital signs. In cases of true CNS-depressing 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: As 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 of a harmful effect potential may be present at the time of institution of therapy should be considered. Patients should be advised of the risk of potential hazards to the fetus in cases where therapy must be continued. As with all drugs, Valium should be administered during pregnancy only if the clinical need justifies the potential risk to the fetus.

INJECTABLE VALIUM® (diazepam) is not recommended for obstetrical use.

Use in Children: Efficacy and safety of parenteral Valium has not been established in children less than 16 years of age.

Prolonged central nervous system depression has been observed in neonates, apparently due to inability to bilirubinform 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 15 minute period in a dose not to exceed 0.1 mg/kg when the infant is over 2 months of age. After the first 15 minutes the initial dosing can be safely repeated. If, however, signs of depression 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 experiences a return to seizure activity, possibly due to the short-lived effect of Valium after IV administration. The physician should be prepared to reschedule the drug. However, Valium is not recommended for maintenance use, 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 antidepressant 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, monoamine oxidase inhibitors and other antipsychotics. 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.

In those cases in which significant relief of tremors, rigidity, and other symptoms of tremorigenic diseases is desired, Valium may be useful in the symptomatic relief of these manifestations, including Huntington's chorea, parkinsonism, and dystonias. Restriction of dosage is indicated; the availability of a smaller dosage form makes it possible to more readily titrate and avoid any unnecessary toxicity.

As an aid in the treatment of patients who are undergoing surgical procedures, intravenously, prior to the administration of anesthetics, to reduce anxiety and tension in patients who are undergoing surgical procedures, intravenously, prior to the administration of anesthetics, to reduce anxiety and tension in patients who are undergoing surgical procedures.

CONTRAINDICATIONS: Injectable Valium is contraindicated in patients with a known hypersensitivity to this drug, drug, acute narrow angle glaucoma, or 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, inflammation and pain at the injection site. The needle should be inserted slowly, taking at least 5 minutes for each 5 mg (1 ml) dose; do not use small veins, such as antecubital veins; inject over 2-3 minutes. Anesthetic care should be taken to avoid intra-arterial administration or extravasation.

Do not mix or dilute Valium with other solutions or drugs in syringes or infusion bags. If it is not possible 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 I.M. 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.

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Injectable VALUM®
(diazepam)

89620693

Injectable VALUM® (diazepam) should be used only in patients who have had a previous satisfactory response to oral diazepam. It is not intended for routine use in the treatment of anxiety or insomnia. The injection dosage is designed to produce effects similar to those of oral administration, but the duration of action may be shorter than that of the oral preparation.

Dosage and Administration: The usual adult dose is 20 mg or 0.4 mg/kg intramuscularly, intravenously, or subcutaneously. The dose may be repeated every 4 hours as needed. The maximum daily dose is 40 mg or 0.8 mg/kg.Dosage in children: The usual dose is 0.5 to 2 mg/kg intramuscularly, intravenously, or subcutaneously, repeated every 4 hours as needed. The maximum daily dose is 4 mg/kg.

Usual Adult Dose

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

Usual Child Dose

2 mg/kg to 5 mg/kg, IM or IV. Repeat in 3 to 4 hours if necessary.
10 mg/kg to 20 mg/kg, IM or IV.

DOSAGE IN CHILDS

(IV administration should be made slowly)

Mild Anxiety Disorders: 2 mg to 5 mg, IM or IV. Repeat in 3 to 4 hours if necessary.
Severe Anxiety Disorders: 5 mg to 10 mg, IM or IV.

Acute Alcohol Withdrawal: 10 mg IM or IV initially, then 5 mg to 10 mg every 4 hours, up to a total of 100 mg per 24 hours.

Tetrathionate IV dosage to desired sedative response, repeat in 4 to 6 hours as necessary. Duration 10 ng or less, 100 mcg/kg IV or IM. For children, 20 mg IV may be used. For children with concomitant paroxysms and alcohol withdrawal 30 mg to 60 mg IV.

Muscle Spasm: 5 mg to 10 mg, IM or IV. May be repeated every 4 hours if necessary. For tetrathionate, larger doses may be required.

Status Epilepticus: 5 mg to 10 mg IV initially (IV preferred). The injection may be repeated if necessary at 10 to 15 minutes intervals up to a maximum of 30 mg. If necessary, therapy with Valium may be repeated in 2 to 4 hours; however, repeated active metabolites may persist, and readministration should be made with this consideration.

For tetrathionate in infants over 30 days 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 administered. For children 5 years and older, 1 mg every 2 to 5 minutes up to a maximum of 10 mg (by IV administration), repeated in 2 to 4 hours if necessary. Benzodiazepine administration is not recommended in patients with renal failure.
CENTER FOR DRUG EVALUATION AND RESEARCH

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

FINAL PRINTED LABELING
VALUM® (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 chlordiazepoxide) during the first trimester of pregnancy has been suggested in several studies. Use of these drugs is rarely a matter of urgency, therefore the decision to continue therapy 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 Overdose: Manifestations of Valium overdose include somnolence, confusion, coma and diminished reflexes. Respiratory, puls and blood pressure should be monitored, as in all cases of drug overdose, although, in general, these effects have been minimal following overdose. 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® (epinephrine) 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 management of benzodiazepine overdose in cases where the 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 reexcitation, 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 cyclic antidepressant overdose. 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 for 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 at night 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, insomniac, pills in the lining, nausea, changes in libido, nightmares, changes in salivation, skin rash, strabismus speech, tremor, urinary retention, vertigo and blurred vision. Paradoxical reactions such as acute hypotension, states, anxiety, hallucinations, increased muscle spasms, 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, tremor 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. High-dose individuals (such as

ADULTS:

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 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

VALUM (diazepam)

Adjunctively in Convulsive Disorders. 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 "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 VALUM® (front) ROCHE (scored side) 5 mg—5 VALUM® (front) ROCHE (scored side) 10 mg—10 VALUM® (front) ROCHE (scored side)
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>10-31-83</td>
<td>AP Letter dated 1-13-84</td>
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<td>13-263</td>
<td>SLR-072</td>
<td>3-2-88</td>
<td>Open</td>
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<td>13-263</td>
<td>SLR-075</td>
<td>1-18-94</td>
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Valium (diazepam) Injection (NDA 16-087)

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<td>SLR-051</td>
<td>3-17-82, and amended on 7-22-82</td>
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<td>16-087</td>
<td>SLR-081</td>
<td>1-18-94</td>
<td>Open</td>
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</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 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
CSO