Summary Basis of Approval
Cover Form

Appl #: 074314

Firm: ROXANE LABS
Reviewing Div: 600
Trade Name:
Generic Name:
ALPRAZOLAM

Approval Letter: Y	Statistician Review: N
SBA Form: N	Bio/Dissolution Review: Y
Final Printed Labeling: Y	Microbiologist Review: N
Medical Officer Review: N	NAS/NRC Review: N
Chemist Review: Y	Pharmacologist Review: N
Federal Register Notice: N	Completion Date: 01-APR-94

APPROVAL

LETTER

ANDA 74-312 (Concentrate, 1 mg/mL)
74-314 (0.5 mg/5 mL)

Roxane Laboratories, Inc.
Attention: Sue A. Touse
P. O. Box 16532
Columbus, Ohio 43216

OCT 31 1993

Dear Madam:

This is in reference to your abbreviated new drug applications dated January 6 (ANDA 74-312) and January 11 (ANDA 74-314) 1993, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Alprazolam Oral Solution.

Reference is also made to your amendments dated January 6 and 11, August 19, September 23 and 29, October 15, 18 and 27, 1993.

We have completed the review of these abbreviated applications and have concluded that the drugs are safe and effective for use as recommended in the submitted labeling. Accordingly, the applications are approved. The Division of Bioequivalence has determined that your Alprazolam Oral Solution, 1mg/mL (Concentrate) and 0.5 mg/5 mL, can be expected to have the same therapeutic effect as that of the reference listed drug product which the Agency relied upon to establish safety and effectiveness (Xanax® Tablets of Upjohn Company).

Under 21 CFR 314.70, certain changes in the conditions described in these abbreviated applications require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for these abbreviated applications are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of these drugs.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

10/31/93

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #74-312, 74-314
ANDA #74-312, 74-314/Division File
HFC-130/JAllen
HFD-600/Reading File
HFD-82

Endorsements:

HFD-630/N.Nashed/10-18-93 10/19/93

HFD-638/M.Gonitzke/10-19-93 10/19/93

HFD-630/P.Schwartz, Ph.D./10-19-93 10/20/93

HFD-630/J.Dawson/CSO/10-19-93 10/20/93
X:\Majors\ Dawson\74-312.AP2
F/T by MM 10-19-93
Approval

9/23/9

10/27/93

LABELING

ALPRAZOLAM
ORAL SOLUTION

063 4040870

ROXANE LABORATORIES, INC.

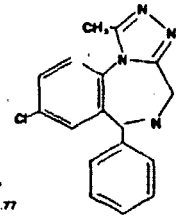
ALPRAZOLAM ORAL SOLUTION
0.5 mg per 5 mL

DESCRIPTION

Alprazolam Oral Solution contains alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds.

The chemical name of alprazolam is 8-Chloro-1-methyl-6-phenyl-4*H*-s-triazolo[4,3-a][1,4]benzodiazepine.

The structural formula is represented below:



$C_{17}H_{13}ClN_4$

M.W. 308.77

Alprazolam is a white to off-white crystalline powder, which is soluble in alcohol but which has no appreciable solubility in water at physiological pH.

Each 5 mL for oral administration contains 0.5 mg of alprazolam.

Inactive Ingredients: propylene glycol, sorbitol, methylparaben, propylparaben, citric acid, sodium citrate, sodium saccharin, flavor and water.

CLINICAL PHARMACOLOGY

CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereo specific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Following oral administration, alprazolam is readily absorbed. Peak concentrations in the plasma occur in one to two hours following administration. Plasma levels are proportionate to the dose given; over the dose range of 0.5 to 3 mg, peak levels of 8.0 to 37 ng/mL were observed. Using a specific assay methodology, the mean plasma elimination half-life of alprazolam has been found to be about 11.2 hours (range: 6.3 to 26.9 hours) in healthy adults.

The predominant metabolites are α-hydroxy-alprazolam and a benzophenone derived from alprazolam. The biological activity of α-hydroxy-alprazolam is approximately one-half that of alprazolam. The benzophenone metabolite is essentially inactive. Plasma levels of these metabolites are extremely low, thus precluding precise pharmacokinetic description. However, their half-lives appear to be of the same order of magnitude as that of alprazolam. Alprazolam and its metabolites are excreted primarily in the urine.

The ability of alprazolam to induce human hepatic enzyme systems has not yet been determined. However, it is not a property of benzodiazepines in general. Further, alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

In vitro, alprazolam is bound (80 percent) to human serum protein.

Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have been reported in a variety of disease states including cirrhosis, impaired hepatic function and impaired renal function. Changes have also been demonstrated in geriatric patients. A mean half-life of alprazolam of 16.3 hours has been observed in healthy elderly subjects (range: 9.0 to 40.4 hours, n = 16) compared to 11.2 hours (range: 6.3 to 15.8 hours, n = 16) in healthy adult subjects. The co-administration of oral contraceptives to healthy women increased the half-life of alprazolam as compared to that in healthy control women (mean: 18.4 hours, n = 11 versus 9.6 hours, n = 9). There was a prolongation in the mean half-life of alprazolam from 12.4 hours (range: 7.2 to 19.4 hours, n = 9) to 16.8 hours (range: 10.8 to 34.3 hours, n = 9) by the co-administration of cimetidine to the same healthy adults. In patients with alcoholic liver disease the half-life of alprazolam ranged between 5.8 and 65.3 hours (mean: 19.7

INDICATIONS AND USAGE

Alprazolam oral solution is indicated for the management of anxiety disorder (a condition corresponding most closely to the APA Diagnostic and Statistical Manual [DSM-III-R] diagnosis of generalized anxiety disorder) or the short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Generalized anxiety disorder is characterized by unrealistic or excessive anxiety and worry (apprehensive expectation) about two or more life circumstances, for a period of six months or longer, during which the person has been bothered more days than not by these concerns. At least 6 of the following 18 symptoms are often present in these patients: *Motor Tension* (trembling, twitching, or feeling shaky; muscle tension, aches, or soreness; restlessness, easy fatigability); *Autonomic Hyperactivity* (shortness of breath or smothering sensations; palpitations or accelerated heart rate; sweating, or cold clammy hands; dry mouth; dizziness or lightheadedness; nausea, diarrhea, or other abdominal distress; flushes or chills; frequent urination; trouble swallowing or "lump in throat"); *Vigilance and Scanning* (feeling keyed up or on edge; exaggerated startle response; difficulty concentrating or "mind going blank" because of anxiety; trouble falling or staying asleep; irritability). These symptoms must not be secondary to another psychiatric disorder or caused by some organic factor.

Anxiety associated with depression is responsive to alprazolam.

Demonstrations of the effectiveness of alprazolam by systematic clinical study are limited to four months duration for anxiety disorder. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Alprazolam oral solution is contraindicated in patients with known sensitivity to this drug or other benzodiazepines. Alprazolam may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in patients with acute narrow angle glaucoma.

WARNINGS

Dependence and withdrawal reactions, including seizures:

Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to alprazolam. These include a spectrum of withdrawal symptoms; the most important is seizure (See DRUG ABUSE AND DEPENDENCE). Even after relatively short-term use at the doses recommended for the treatment of transient anxiety and anxiety disorder (ie, 0.75 to 4 mg per day), there is some risk of dependence. Postmarketing surveillance does suggest that the risk of dependence and its severity appear to be greater in patients treated with relatively high doses (above 4 mg per day) and for long periods (more than 6 to 12 weeks).

Status epilepticus and its treatment:

The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of alprazolam. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well. Ordinarily, the treatment of status epilepticus of any etiology involves use of intravenous benzodiazepines plus phenytoin or barbiturates, maintenance of a patent airway and adequate hydration. For additional details regarding therapy, consultation with an appropriate specialist may be considered.

Risk of dose reduction:

Withdrawal reactions may occur when dosage reduction occurs for any reason. This includes purposeful tapering, but also inadvertent reduction of dose (e.g., the patient forgets, the patient is admitted to a hospital, etc.). Therefore, the dosage of alprazolam should be reduced or discontinued gradually (See DOSAGE AND ADMINISTRATION).

Alprazolam oral solution is not of value in the treatment of psychotic patients and should not be employed in lieu of appropriate treatment for psychosis. Because of its CNS depressant effects, patients receiving alprazolam should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with alprazolam.

Benzodiazepines can potentially cause fetal harm when administered to pregnant woman. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Because of experience with other members of the benzodiazepine class, alprazolam is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, their use during the first trimester 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.

PRECAUTIONS

General: If alprazolam 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 compounds which might potentiate the action of benzodiazepines (See Drug Interactions).

As with other psychotropic medications, the usual precautions with respect to administration of the drug and size of the prescription are indicated for severely depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in elderly or debilitated patients. (See DOSAGE AND ADMINISTRATION). The usual precautions in treating patients with impaired renal, hepatic or pulmonary function should be observed. There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with alprazolam. A decreased systemic alprazolam elimination rate (e.g., increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving alprazolam (See CLINICAL PHARMACOLOGY).

Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression.

Alprazolam has a weak uricosuric effect. Although other medications with weak uricosuric effect have been reported to cause acute renal failure, there have been no reported instances of acute renal failure attributable to therapy with alprazolam.

Information for Patients:

For all users of alprazolam:

To assure safe and effective use of benzodiazepines, all patients prescribed alprazolam should be provided with the following guidance.

1. Inform your physician about any alcohol consumption and medicines you are taking now, including medication you may buy without a prescription. Alcohol should generally not be used during treatment with benzodiazepines.
2. Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.

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2. Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.
3. Inform your physician if you are nursing.
4. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.
5. Do not increase the dose even if you think the medication "does not work anymore" without consulting your physician. Benzodiazepines, even when used as recommended, may produce emotional and/or physical dependence.
6. Do not stop taking this medication abruptly or decrease the dose without consulting your physician, since withdrawal symptoms can occur.

Laboratory Tests:

Laboratory tests are not ordinarily required in otherwise healthy patients.

Drug Interactions:

The benzodiazepines, including alprazolam, produce additive CNS depressant effects when co-administered with other psychotropic medications, anticonvulsants, antihistamines, ethanol and other drugs which themselves produce CNS depression.

The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20%, respectively, by the concomitant administration of alprazolam in doses up to 4 mg/day. The clinical significance of these changes is unknown.

Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. For example, the clearance of alprazolam and certain other benzodiazepines can be delayed by the co-administration of cimetidine. The clearance of alprazolam can also be delayed by the co-administration of oral contraceptives (See CLINICAL PHARMACOLOGY). The clinical significance of these interactions is unclear.

Drug/Laboratory Test Interactions:

Although interactions between benzodiazepines and commonly employed clinical laboratory tests have occasionally been reported, there is no consistent pattern for a specific drug or specific test.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose).

Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg, which is 500 times the maximum recommended daily human dose of 10 mg/day. Alprazolam also was not mutagenic *in vitro* in the DNA Damage/Alkaline Elution Assay or the Ames Assay.

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

Pregnancy: Teratogenic Effects:

Pregnancy Category D: (See WARNINGS Section)

Nonteratogenic Effects:

It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines.

Labor and Delivery:

Alprazolam has no established use in labor or delivery.

Nursing Mothers:

Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use alprazolam.

Pediatric Use:

Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS

Side effects to alprazolam, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of alprazolam, e.g., drowsiness or lightheadedness.

The data cited in the table below are estimates of untoward clinical event incidence among patients who participated under the following clinical conditions: relatively short duration (i.e., four weeks) placebo-controlled clinical studies with dosages up to 4 mg/day of alprazolam (for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety).

These data cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics, and other factors often differ from those in clinical trials. These figures cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials are conducted under a different set of conditions.

Comparison of the cited figures, however, can provide the prescriber with some basis for estimating the relative contributions of drug and non-drug factors to the untoward event incidence in the population studied. Even this use must be approached cautiously, as a drug may relieve a symptom in one patient but induce it in others. (For example, an anxiolytic drug may relieve dry mouth [a symptom of anxiety] in some subjects but induce it [an untoward event] in others.)

Additionally, the cited figures can provide the prescriber with an indication as to the frequency with which physician intervention (e.g., increased surveillance, decreased dosage or discontinuation of drug therapy) may be necessary because of the untoward clinical event.

ANXIETY DISORDERS

	Treatment-Emergent Symptom Incidence*		Incidence of Intervention Because of Symptom
	Alprazolam	Placebo	Alprazolam
Num# ons/Patients	566	505	566
% of Patients Reporting:			
Central Nervous System:			
Drowsiness	41.0	21.8	18.1
Light-headedness	20.8	18.3	1.2
Depression	13.8	16.1	2.4
Headache	12.8	16.8	1.1
Confusion	9.9	10.0	0.9
Insomnia	8.8	16.4	1.3
Nervousness	4.1	10.3	1.1
Syncope	3.1	4.0	*
Dizziness	1.8	6.8	2.8
Akathisia	1.4	1.2	*
Tiredness/Sleepiness	*	*	1.8
Gastrointestinal:			
Dry Mouth	14.7	13.3	0.7
Constipation	10.4	11.4	0.9
Diarrhea	10.1	10.3	1.2
Nausea/Vomiting	9.6	12.8	1.7
Increased Salivation	4.2	3.4	*
Cardiovascular:			
Tachycardia/ Palpitations	7.7	15.6	0.4
Hypotension	4.7	2.2	*
Sensory:			
Blurred Vision	6.2	6.2	0.4
Musculoskeletal:			
Rigidity	4.2	3.3	*
Tremor	4.0	0.8	0.4
Cutaneous:			
Dermatitis/Allergy	3.8	3.1	0.6
Other:			
Nasal Congestion	7.3	9.3	*
Weight Gain	2.7	2.7	*
Weight Loss	2.3	3.0	*

*None reported
*Events reported by 1% or more of alprazolam patients are included.

In addition to the relatively common (i.e., greater than 1%) untoward events enumerated above, the following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of alprazolam (See WARNINGS).

To discontinue treatment in patients taking alprazolam, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of alprazolam be decreased by no more than 0.5 mg every three days (See DOSAGE AND ADMINISTRATION). Some patients may require an even slower dosage reduction.

As with all benzodiazepines, paradoxical reactions such as stimulation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects such as agitation, rage, irritability, and aggressive or hostile behavior have been reported rarely. In many of the spontaneous case reports of adverse behavioral effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Should any of the above events occur, alprazolam should be discontinued. Isolated published reports involving small numbers of patients have suggested that patients with pre-existing borderline personality disorder, a prior history of violent or aggressive behavior, or alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility, and intrusive thoughts have been reported during discontinuation of alprazolam in patients with posttraumatic stress disorder.

Laboratory analyses were performed on patients participating in the clinical program for alprazolam. The following incidences of abnormalities as shown below were observed in patients receiving alprazolam and in patients in the corresponding placebo group. Few of these abnormalities were considered to be of pathological significance.

	Alprazolam		Placebo	
	Low	High	Low	High
Hematology				
Hematocrit	*	*	*	*
Hemoglobin	*	*	*	*
Total WBC Count	1.4	2.3	1.0	2.0
Neutrophil Count	2.2	9.0	4.2	1.7
Lymphocyte Count	5.5	7.4	5.4	9.5
Monocyte Count	5.3	2.8	6.4	*
Eosinophil Count	3.2	9.5	9.3	7.2
Basophil Count	*	*	*	*
Urinalysis				
Albumin	-	*	-	*
Sugar	-	*	-	*
RBC/HPF	-	3.4	-	8.0
WBC/HPF	-	95.7	-	25.9
Blood Chemistry				
Creatinine	2.2	1.9	1.8	1.0
Bilirubin	*	1.6	*	*
SGOT	*	3.2	1.0	1.7
Alkaline Phosphatase	*	1.7	*	1.8

*Less than 1%

When treatment with alprazolam is instituted, periodic blood counts, urinalysis and liver chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during therapy with alprazolam and are of no known significance.

Post Introduction Reports: Various adverse drug reactions have been reported in association with the use of alprazolam since market introduction. The majority of these reactions were reported through the medical event voluntary reporting system. Because of the spontaneous nature of the reporting of medical events and the lack of controls, a causal relationship to the use of alprazolam cannot be readily determined. Reported events include: liver enzyme elevations, gynecomastia and galactorrhea.

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence:

Withdrawal symptoms similar in character to those noted with sedative/hypnotics and alcohol have occurred following discontinuance of benzodiazepines, including alprazolam. The symptoms can range from mild dysphoria and insomnia to a major syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors and convulsions. Distinguishing between withdrawal emergent signs and symptoms and the recurrence of illness is often difficult in patients undergoing dose reduction. The long term strategy for treatment of these phenomena will vary with their cause and the therapeutic goal. When necessary, immediate management of withdrawal symptoms requires re-institution of treatment at doses of alprazolam sufficient to suppress symptoms. There have been reports of failure of other benzodiazepines to fully suppress these withdrawal symptoms. These failures have been attributed to incomplete cross-tolerance but may also reflect the use of an inadequate dosing regimen of the substituted benzodiazepine or the effects of concomitant medications.

While it is difficult to distinguish withdrawal and recurrence for certain patients, the time course and the nature of the symptoms may be helpful. A withdrawal syndrome typically includes the occurrence of new symptoms, tends to appear toward the end of taper or shortly after discontinuation, and will decrease with time.

While the severity and incidence of withdrawal phenomena appear to be related to dose and duration of treatment, withdrawal symptoms, including seizures, have been reported after only brief therapy with alprazolam at doses within the recommended range for the treatment of anxiety (eg, 0.75 to 4 mg/day). Signs and symptoms of withdrawal are often more prominent after rapid decrease of dosage or abrupt discontinuance. The risk of withdrawal seizures may be increased at doses above 4 mg/day (See WARNINGS).

Patients, especially individuals with a history of seizures or epilepsy, should not be abruptly discontinued from any CNS depressant agent, including alprazolam. It is recommended that all patients on alprazolam who require a dosage reduction be gradually tapered under close supervision (See WARNINGS and DOSAGE AND ADMINISTRATION).

Psychological dependence is a risk with all benzodiazepines, including alprazolam. The risk of psychological dependence may also be increased at higher doses and with longer term use, and this risk is further increased in patients with a history of alcohol or drug abuse. Some patients have experienced considerable difficulty in tapering and discontinuing from alprazolam, especially those receiving higher doses for extended periods. Addiction-prone individuals should be under careful surveillance when receiving alprazolam. As with all anxiolytics, repeat prescriptions should be limited to those who are under medical supervision.

Controlled Substance Class:

Alprazolam is a controlled substance under the Controlled Substance Act by the Drug Enforcement Administration and alprazolam oral solution has been assigned to Schedule IV.

OVERDOSAGE

Manifestations of alprazolam overdosage include somnolence, confusion, impaired coordination, diminished reflexes and coma. Death has been reported in association with overdoses of alprazolam by itself, as it has with other benzodiazepines. In addition, fatalities have been reported in patients who have overdosed with a combination of a single benzodiazepine, including alprazolam, and alcohol; alcohol levels seen in some of these patients have been lower than those usually associated with alcohol-induced fatality.

The acute oral LD_{50} in rats is 331 to 2171 mg/kg. Other experiments in animals have indicated that cardiopulmonary collapse can occur following massive intravenous doses of alprazolam (over 195 mg/kg; 975 times the maximum recommended daily human dose of 10 mg/day). Animals could be resuscitated with positive mechanical ventilation and the intravenous infusion of norepinephrine bitartrate.

Animal experiments have suggested that forced diuresis or hemodialysis are probably of little value in treating overdosage.

General Treatment of Overdosage:

Overdosage reports with alprazolam are limited. As in all cases of drug overdosage, respiration, pulse rate, and blood pressure should be monitored. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. If hypotension occurs, it may be combated by the use of vasopressors. Dialysis is of limited value. As with the management of intentional overdosing 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 re-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. The complete flumazenil package insert including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS should be consulted prior to use.

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 require higher doses. In such cases, dosage should be increased cautiously to avoid adverse effects.

Anxiety disorders and transient symptoms of anxiety:

Treatment for patients with anxiety should be initiated with a dose of 0.25 to 0.5 mg (2.5 to 5 mL) given three times daily. The dose may be increased to achieve a maximum therapeutic effect, at intervals of 3 to 4 days, to a maximum daily dose of 4 mg (40 mL), given in divided doses. The lowest possible effective dose should be employed and the need for continued treatment reassessed frequently. The risk of dependence may increase with dose and duration of treatment.

In elderly patients, in patients with advanced liver disease or in patients with debilitating disease, the usual starting dose is 0.25 mg (2.5 mL), given two or three times daily. This may be gradually increased as needed and tolerated. The elderly may be especially sensitive to the effects of benzodiazepines.

If side effects occur at the recommended starting dose, the dose may be lowered.

In all patients, dosage should be reduced gradually when

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 require higher doses. In such cases, dosage should be increased cautiously to avoid adverse effects.

Anxiety disorders and transient symptoms of anxiety:

Treatment for patients with anxiety should be initiated with a dose of 0.25 to 0.5 mg (2.5 to 5 mL) given three times daily. The dose may be increased to achieve a maximum therapeutic effect, at intervals of 3 to 4 days, to a maximum daily dose of 4 mg (40 mL), given in divided doses. The lowest possible effective dose should be employed and the need for continued treatment reassessed frequently. The risk of dependence may increase with dose and duration of treatment.

In elderly patients, in patients with advanced liver disease or in patients with debilitating disease, the usual starting dose is 0.25 mg (2.5 mL), given two or three times daily. This may be gradually increased as needed and tolerated. The elderly may be especially sensitive to the effects of benzodiazepines.

If side effects occur at the recommended starting dose, the dose may be lowered.

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific [illegible] discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 (5 mL) mg every three days. Some patients may require an even slower dosage reduction.

HOW SUPPLIED

Alprazolam Oral Solution for oral administration is available as:
0.5 mg per 5 mL Oral Solution
A clear, colorless, fruit-mint flavored solution.
NDC 0054-8067-16: Unit dose Patient Cup™ filled to deliver 2.5 mL (0.25 mg Alprazolam), ten 2.5 mL Patient Cups™ per shelf pack, four shelf [illegible] per shipper.
NDC 0054-8068-16: Unit dose Patient Cup™ filled to deliver 5 mL (0.5 mg Alprazolam), ten 5 mL Patient Cups™ per shelf pack, four shelf packs per shipper.
NDC 0054-8090-16: Unit dose Patient Cup™ filled to deliver 10 mL (1 mg Alprazolam), ten 10 mL Patient Cups™ per shelf pack, four shelf packs per shipper.
NDC 0054-3067-63: Bottles of 500 mL.

Store at Controlled Room Temperature
15°-30°C (59°-86°F).

Protect from Light.

Dispense in a tight, light-resistant container.

Caution: Federal law prohibits dispensing
without prescription.

ANIMAL PHARMACOLOGY

Animal Studies

When rats were treated with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended human dose) orally for 2 years, a tendency for a dose related increase in the number of cataracts was observed in females and a tendency for a dose related increase in corneal vascularization was observed in males. These lesions did not appear until after 11 months of treatment.

CLINICAL STUDIES

Alprazolam tablets were compared to placebo in double blind clinical studies (doses up to 4 mg/day) in patients with a diagnosis of anxiety or anxiety with associated depressive symptomatology. Alprazolam was significantly better than placebo at each of the evaluation periods of these four week studies as judged by the following psychometric instruments: Physician's Global Impressions, Hamilton Anxiety Rating Scale, Target Symptoms, Patient's Global Impressions and Self-Rating Symptom Scale.

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Revised June 1993

Roxane Laboratories, Inc.
Columbus, Ohio 43216

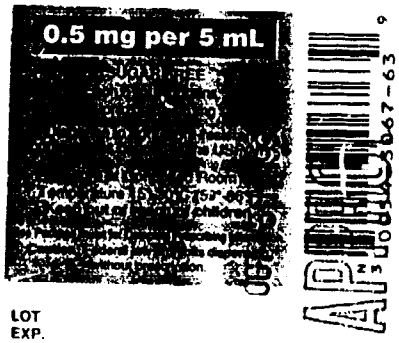
NDC 0054-
3067-63

500 mL

IV

ALPRAZOLAM

Oral Solution



LOT
EXP.

4113602

Roxane Laboratories, Inc.

063

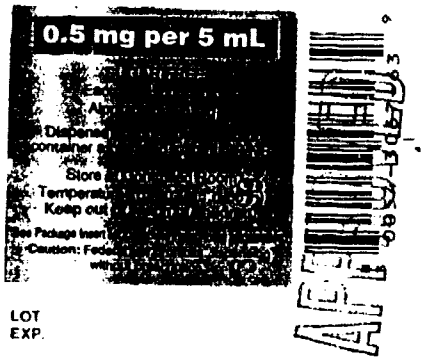
NDC 0054-
3067-63

500 mL

IV

ALPRAZOLAM

Oral Solution



LOT
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Roxane Laboratories, Inc.

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© RLI, 1993

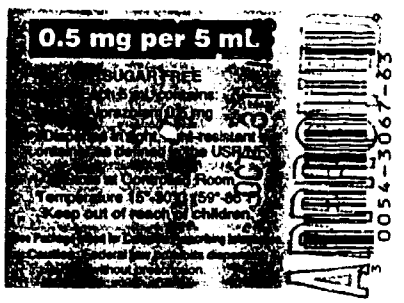
NDC 0054-
3067-63

500 mL

IV

ALPRAZOLAM

Oral Solution



LOT
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Roxane Laboratories, Inc.

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© RLI, 1993

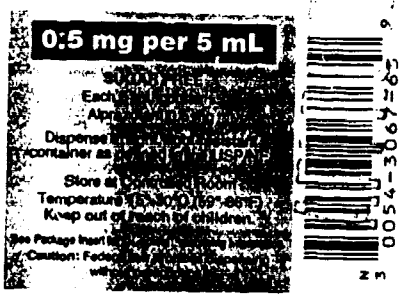
NDC 0054-
3067-63

500 mL

IV

ALPRAZOLAM

Oral Solution



LOT
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Roxane Laboratories, Inc.

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© RLI, 1993

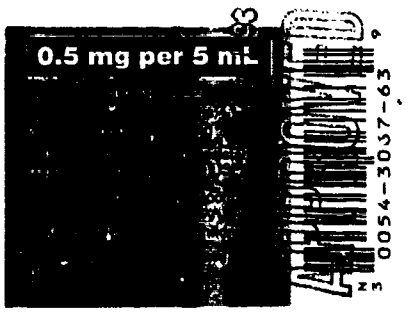
NDC 0054-
3067-63

500 mL

IV

ALPRAZOLAM

Oral Solution



LOT
EXP.

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Roxane Laboratories, Inc.

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© RLI, 1993

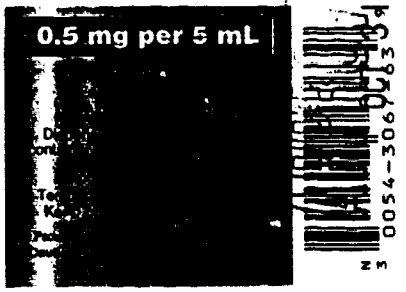
NDC 0054-
3067-63

500 mL

IV

ALPRAZOLAM

Oral Solution



LOT
EXP.

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Roxane Laboratories, Inc.

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© RLI, 1993

PEEL
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PEEL
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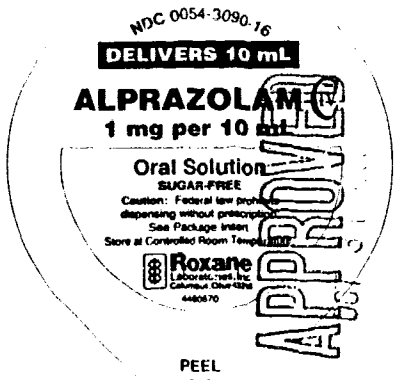

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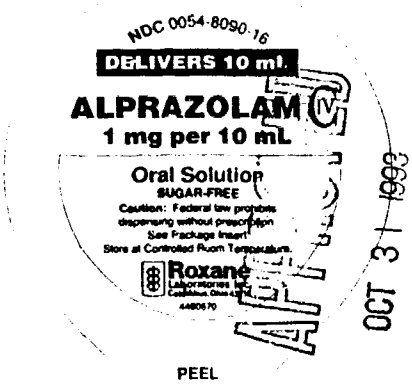

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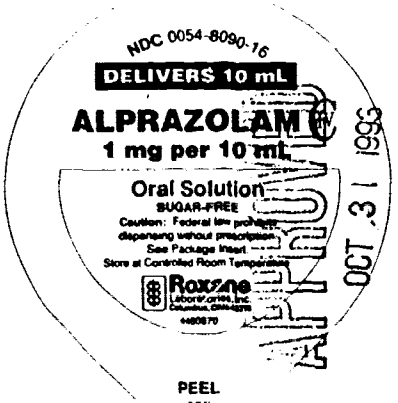

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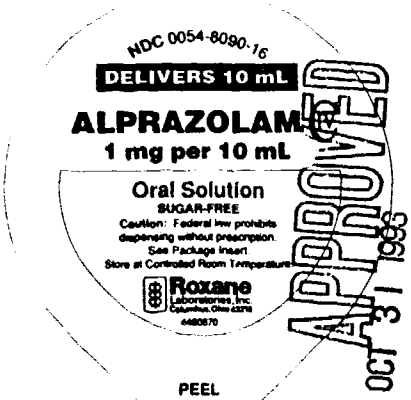

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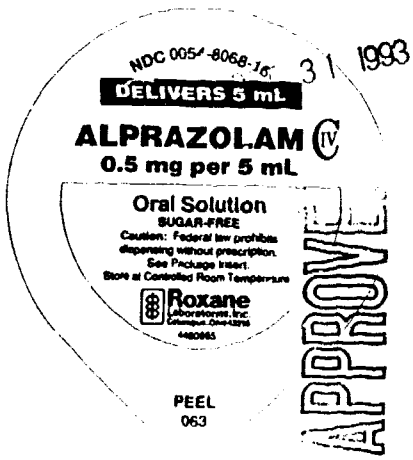
NDC 0054-8068-16
DELIVERS 5 mL
ALPRAZOLAM
0.5 mg per 5 mL
Oral Solution
SUGAR-FREE
Caution: Federal law prohibits dispensing without prescription.
See Package Insert.
Store at Controlled Room Temperature
Roxane
Laboratories, Inc.
PEEL
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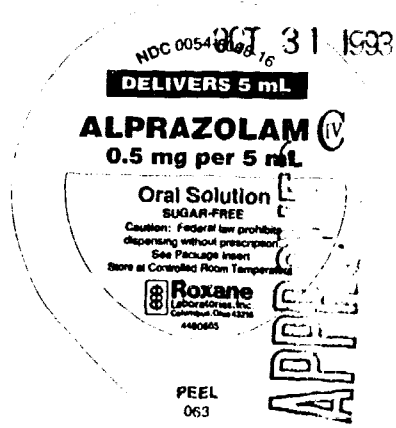
APPROVED
OCT 31 1993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Oral Solution
SUGAR-FREE
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Store at Controlled Room Temperature
Roxane
Laboratories, Inc.
PEEL
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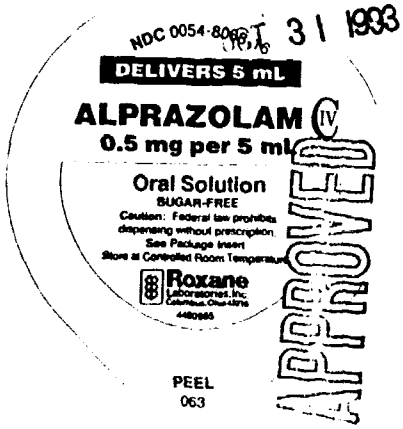
OCT 31 1993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Laboratories, Inc.
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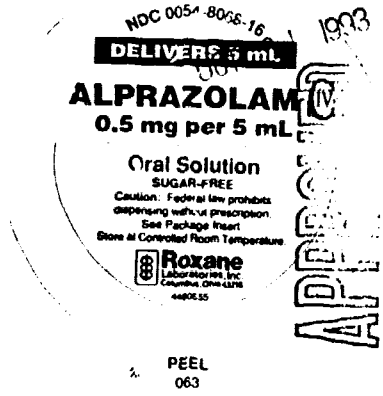
OCT 31 1993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Roxane
Laboratories, Inc.
PEEL
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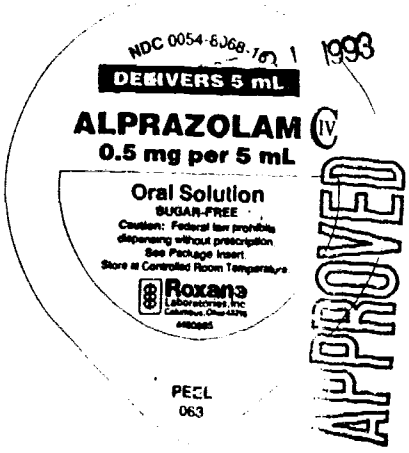
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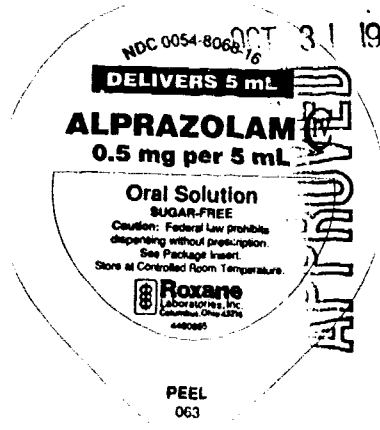
1993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DELIVERS 5 mL
ALPRAZOLAM
0.5 mg per 5 mL
Oral Solution
SUGAR-FREE
Caution: Federal law prohibits dispensing without prescription.
See Package Insert.
Store at Controlled Room Temperature.
Roxane
Laboratories, Inc.
PEEL
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OCT 31 1993

Marg.
7431
AI-009

NDC 0054-8067-16

DELIVERS 2.5 mL

ALPRAZOLAM (CIV)

0.25 mg per 2.5 mL

Oral Solution

SUGAR-FREE

Caution: Federal law prohibits dispensing without prescription.

See Package Insert.

Store at Controlled Room Temperature.

Roxane Laboratories, Inc.
Columbus, Ohio 43216

4460680

PEEL
063

OCT 31 1993

NDC 0054-8067-16

DELIVERS 2.5 mL

ALPRAZOLAM (CIV)

0.25 mg per 2.5 mL

Oral Solution

SUGAR-FREE

Caution: Federal law prohibits dispensing without prescription.

See Package Insert.

Store at Controlled Room Temperature.

Roxane Laboratories, Inc.
Columbus, Ohio 43216

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PEEL
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OCT 31 1993

APPROVED

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Columbus, Ohio 43216

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Columbus, Ohio 43216

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OCT 31 1993

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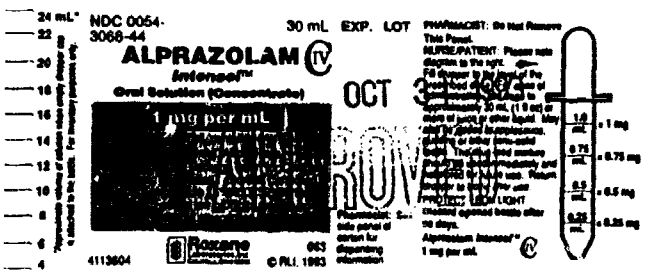
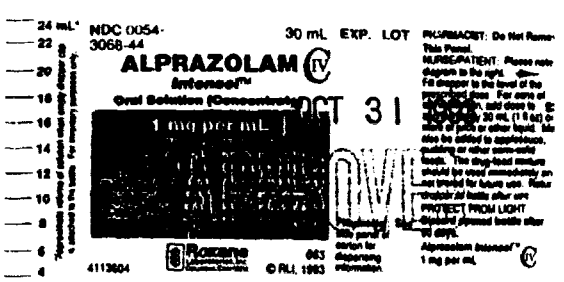

NDC 0054-
3068-44
30 mL
EXP. LOT
ALPRAZOLAM
Intensol™
Oral Solution (Concentrate)
1 mg per mL
OCT
4113604
© RLI 1993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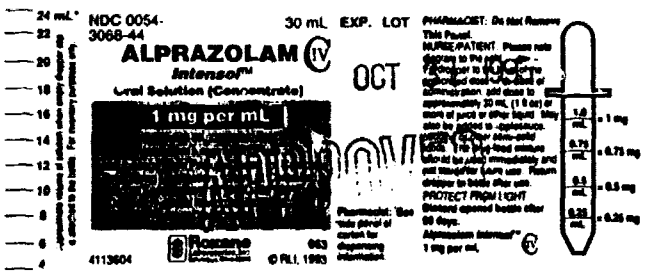
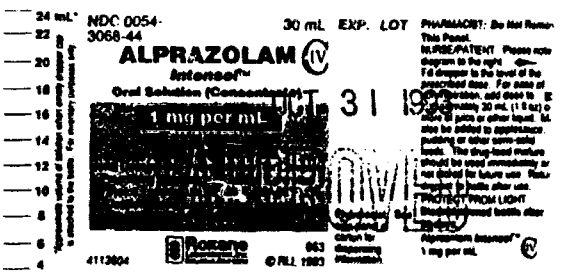
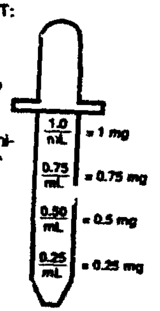
3068-44
30 mL
EXP. LOT
ALPRAZOLAM
Intensol™
1 mg per mL
OCT 31
4113604
© RLI 1993


NDC 0054-
3068-44
30 mL
EXP. LOT
ALPRAZOLAM
Intensol™
Oral Solution (Concentrate)
1 mg per mL
OCT
4113604
© RLI 1993


NDC 0054-
3068-44
30 mL
EXP. LOT
ALPRAZOLAM
Intensol™
1 mg per mL
OCT 31
4113604
© RLI 1993

NURSE/PATIENT:
Please note diagram to the right. ←
Fill the dropper to the level of the prescribed dose.
For ease of administration, add dose to approximately 30 mL (1 fl oz) or more of juice or other liquid. May also be added to applesauce, pudding or other semi-solid foods.
The drug-food mixture should be used immediately and not stored for future use.
Return dropper to bottle after use.



ALPRAZOLAM (IV)
Intensol™
1 mg per mL

Roxane
Laboratories, Inc.
Columbus, Ohio 43216

0054-3068-44

093

NDC 0054-3068-44

30 mL BOTTLE and DROPPER

ALPRAZOLAM (IV)

Intensol™

Oral Solution (Concentrate)

1 mg per mL

Each mL contains:
Alprazolam 1 mg
Alcohol-free [illegible]
[illegible] Dosage: See Package Insert [illegible] information.
[illegible] Container [illegible] Temperature 15° [illegible]
[illegible] law prohibits [illegible] prescription.

APPROVED

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Laboratories, Inc.
Columbus, Ohio 43216

Pharmacist: Do not repackage the contents of the bottle. To dispense as a child-resistant package, replace bottle closure only with the calibrated dropper provided.

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ROXANE LABORATORIES, INC.

6040860

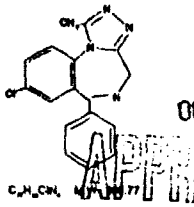
ALPRAZOLAM *INTENSOL*™ ℞
Oral Solution (Concentrate)
1 mg per mL

DESCRIPTION

Alprazolam Intensol™ contains alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds.

The chemical name of alprazolam is 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine.

The structural formula is represented below:



$C_{17}H_{13}ClN_4$ M.W. 308.77

Alprazolam is a white to off-white crystalline powder, which is soluble in methanol or ethanol but which has no appreciable solubility in water at physiological pH.

Each mL, for oral administration, contains 1 mg of alprazolam.

Inactive Ingredients: propylene glycol, succinic acid, and water.

CLINICAL PHARMACOLOGY

CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at diverse specific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Following oral administration, alprazolam is rapidly absorbed. Peak concentrations in the plasma occur in one to two hours following administration. Plasma levels are proportionate to the dose given; over the dose range of 0.5 to 3 mg, peak levels of 5.0 to 37 ng/ml were observed. Using a specific assay methodology, the mean plasma elimination half-life of alprazolam has been found to be about 11.2 hours (range: 5.3 to 26.8 hours) in healthy adults.

The predominant metabolites are α-hydroxyalprazolam and a benzophenone derived from alprazolam. The biological assay of α-hydroxyalprazolam is approximately one-half that of alprazolam. The benzophenone metabolite is considered inactive. Plasma levels of these metabolites are extremely low, thus precluding precise pharmacokinetic description. However, their half-lives appear to be of the same order of magnitude as that of alprazolam. Alprazolam and its metabolites are excreted primarily in the urine.

The ability of alprazolam to induce human hepatic enzyme systems has not yet been determined. However, this is not a property of benzodiazepines in general. Further, alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

In vitro, alprazolam is bound (80 percent) to human serum proteins.

Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function and impaired renal function. Changes have also been demonstrated in geriatric patients. A mean half-life of alprazolam of 16.3 hours has been observed in healthy elderly subjects (range: 9.0 to 26.9 hours, n = 16) compared to 11.0 hours (range: 6.3 to 15.8 hours, n = 16) in healthy adult subjects. The co-administration of oral contraceptives to healthy women increased the half-life of alprazolam as compared to that in healthy control women (mean: 12.4 hours, n = 11 versus 9.7 hours, n = 9). There was a prolongation in the mean half-life of alprazolam from 12.4 hours (range: 7.2 to 19.4 hours, n = 9) to 16.8 hours (range: 10.0 to 34.8 hours, n = 9) by the co-administration of cimetidine to the same healthy adults. In patients with alcoholic liver disease the half-life of alprazolam ranged between 12.2 and 66.3 hours (mean: 19.7 hours, n = 17) as compared to between 9.3 and 36.9 hours (mean = 11.4 hours, n = 17) in healthy subjects. In another group of subjects the half-life of alprazolam ranged between 9.9 and 40.4 hours (mean = 21.8 hours, n = 18) as compared to between 7.3 and 15.8 hours (mean = 10.9 hours, n = 18) in healthy subjects.

Because of its similarity to other benzodiazepines, it is assumed that alprazolam undergoes transplacental passage and that it is excreted in human milk.

INDICATIONS AND USAGE

Alprazolam Intensol™ is indicated for the management of anxiety disorder (a condition corresponding most closely to the APA Diagnostic and Statistical Manual [DSM-III-R] diagnosis of generalized anxiety disorder) or the short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Generalized anxiety disorder is characterized by unrealistic or excessive anxiety and worry (apprehensive expectation) about two or more life circumstances, for a period of six months or longer, during which the person has been bothered more days than not by these concerns. At least 6 of the following 18 symptoms are often present in these patients: Motor Tension (trembling, twitching, or feeling shaky; muscle tension, aches, or soreness; restlessness; easy fatigability); Autonomic Hyperactivity (shortness of breath or smothering sensations; palpitations or accelerated heart rate; sweating, or cold clammy hands; dry mouth; dizziness or lightheadedness; nausea, diarrhea, or other abdominal distress; flushes or chills; frequent urination; trouble swallowing or "lump in throat"); Vigilance and Scanning (feeling keyed up or on-edge; exaggerated startle response; difficulty concentrating or "mind going blank" because of anxiety; trouble falling or staying asleep; irritability). These symptoms must not be secondary to another psychiatric disorder or caused by some organic factor.

Anxiety associated with depression is responsive to alprazolam.

Demonstrations of the effectiveness of alprazolam by systematic clinical study are limited to four months duration for anxiety disorder. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Alprazolam Intensol™ is contraindicated in patients with known sensitivity to this drug or other benzodiazepines. Alprazolam may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in patients with acute narrow angle glaucoma.

OCT 31 1996

WARNINGS

Dependence and withdrawal reactions, including seizure:

Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to alprazolam. These include a spectrum of withdrawal symptoms; the most important is seizure (See DRUG ABUSE AND DEPENDENCE). Even after relatively short-term use at the doses recommended for the treatment of persistent anxiety and anxiety disorder (ie, 0.75 to 4 mg per day), there is some risk of dependence. Postmarketing surveillance data suggest that the risk of dependence and its severity appear to be greater in patients treated with relatively high doses (above 4 mg per day) and for long periods (more than 6 to 12 weeks).

Status epilepticus and its treatment:

The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of alprazolam. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well. Ordinarily, the treatment of status epilepticus of any etiology involves use of intravenous benzodiazepines plus phenytoin or barbiturates, maintenance of a patent airway and adequate hydration. For additional details regarding therapy, consultation with an appropriate specialist may be considered.

Risk of dose reduction.

Withdrawal reactions may occur when dosage reduction occurs for any reason. This includes purposeful tapering, but also inadvertent reduction of dose (eg, the patient forgets, the patient is admitted to a hospital, etc.). Therefore, the dosage of alprazolam should be reduced or discontinued gradually (See DOSAGE AND ADMINISTRATION).

Alprazolam Intensol™ is not of value in the treatment of psychotic patients and should not be employed in lieu of appropriate treatment for psychosis. Because of its CNS depressant effects, patients receiving alprazolam should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with alprazolam.

Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Because of experience with other members of the benzodiazepine class, alprazolam is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, their use during the first trimester 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.

PRECAUTIONS

General:

If alprazolam 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 compounds which might potentiate the action of benzodiazepines (See Drug Interactions).

As with other psychotropic medications, the usual precautions with respect to administration of the drug and also of the preparation are indicated for severely depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in elderly or debilitated patients. (See DOSAGE AND ADMINISTRATION). The usual precautions in treating patients with impaired renal, hepatic or pulmonary function should be observed. There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with alprazolam. A depressed systemic alprazolam elimination rate (e.g., increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients, receiving alprazolam (See CLINICAL PHARMACOLOGY).

Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression.

Alprazolam has a weak uricosuric effect. Although other medications with weak uricosuric effect have been reported to cause acute renal failure, there have been no reported instances of acute renal failure attributable to therapy with alprazolam.

Information for Patients:

For all users of alprazolam:

To assure safe and effective use of benzodiazepines, all patients prescribed alprazolam should be provided with the following guidance:

1. Inform your physician about any alcohol consumption and medicines you are taking now, including medication you may buy without a prescription. Alcohol should generally not be used during treatment with benzodiazepines.
2. Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.
3. Inform your physician if you are nursing.
4. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.
5. Do not increase the dose even if you think the medication "does not work anymore" without consulting your physician. Benzodiazepines, even when used as recommended, may produce emotional and/or physical dependence.
6. Do not stop taking this medication abruptly or decrease the dose without consulting your physician, since withdrawal symptoms can occur.

Laboratory Tests:

Laboratory tests are not ordinarily required in otherwise healthy patients.

Drug Interactions:

The benzodiazepines, including alprazolam, produce additive CNS depressant effects when co-administered with other psychotropic medications, anticonvulsants, antihistamines, ethanol and other drugs which themselves produce CNS depression.

The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 50%, respectively, by the concomitant administration of alprazolam in doses up to 4 mg/day. The clinical significance of these changes is unknown.

Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. For example, the clearance of alprazolam and certain other benzodiazepines can be decreased by the co-administration of cimetidine. The clearance of alprazolam can also be delayed by the co-administration of oral contraceptives (See CLINICAL PHARMACOLOGY). The clinical significance of these interactions is unclear.

Drug/Laboratory Test Interactions:

Although interactions between benzodiazepines and commonly employed clinical laboratory tests have occasionally been reported, there is no consistent pattern for a specific drug or specific test.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (180 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (60 times the maximum recommended daily human dose).

Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg, which is 600 times the maximum recommended daily human dose of 10 mg/day. Also, alprazolam was not mutagenic *in vitro* in the DNA Damage/Alkaline Elution Assay or the Ames Assay.

Alprazolam produced no impairment of fertility in rats at doses, up to 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

Pregnancy: Teratogenic Effects:

Pregnancy Category D: (See WARNINGS Section)

Nonteratogenic Effects:

It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines.

Labor and Delivery:

Alprazolam has no established use in labor or delivery.

Nursing Mothers:

Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use alprazolam.

Pediatric Use:

Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS

Side effects to alprazolam, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of alprazolam, e.g., drowsiness or lightheadedness.

The data cited in the table below are based on those of untoward clinical event incidence among patients who participated under the following clinical conditions: relatively short duration (i.e., four weeks) placebo-controlled clinical studies with dosages up to 4 mg/day of alprazolam (for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety).

These data cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors often differ from those in clinical trials. These figures cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials are conducted under a different set of conditions.

Comparison of the cited figures, however, can provide the prescriber with some basis for estimating the relative contributions of drug and non-drug factors to the untoward event incidence in the population studied. Even this use must be approached cautiously, as a drug may relieve a symptom in one patient but induce it in others. (For example, an anxiolytic drug may relieve dry mouth [a symptom of anxiety] in some subjects but induce it [an untoward event] in others.)

Additionally, for anxiety disorders, the cited figures can provide the prescriber with an indication as to the frequency with which physician intervention (e.g., increased surveillance, decreased dosage or discontinuation of drug therapy) may be necessary

because of the untoward clinical event.

ANXIETY DISORDERS

	Treatment-Emergent Symptom Incidence†		Incidence of Intervention Because of Symptom
	Alprazolam	Placebo	Alprazolam
Number of Patients	565	505	565
% of Patients Reporting:			
Central Nervous System			
Drowsiness	41.0	21.6	15.1
Light-headedness	20.8	19.3	1.2
Depression	13.9	18.1	2.4
Headache	12.9	19.6	1.1
Confusion	9.9	10.0	0.9
Insomnia	8.9	18.4	1.3
Nervousness	4.1	10.3	1.1
Syncope	3.1	4.0	*
Dizziness	1.8	0.8	2.5
Akathisia	1.6	1.2	*
Tiredness/Sleepiness	*	*	1.8
Gastrointestinal			
Dry Mouth	14.7	13.3	0.7
Constipation	10.4	11.4	0.9
Diarrhea	10.1	10.3	1.2
Nausea/Vomiting	9.6	12.8	1.7
Increased Salivation	4.2	2.4	*
Cardiovascular			
Tachycardia/Palpitations	7.7	15.6	0.4
Hypotension	4.7	2.2	*
Sensory			
Blurred Vision	6.2	6.2	0.4
Musculoskeletal			
Rigidity	4.2	5.3	*
Tremor	4.0	8.8	0.4
Cutaneous			
Dermatitis/Allergy	3.8	3.1	0.6
Other			
Nasal Congestion	7.3	9.3	*
Weight Gain	2.7	2.7	*
Weight Loss	2.3	3.0	*

*None reported

†Events reported by 1% or more of alprazolam patients are included.

In addition to the relatively common (i.e., greater than 1%) untoward events enumerated in the table above, the following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of alprazolam (See WARNINGS).

To discontinue treatment in patients taking alprazolam, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of alprazolam be decreased by no more than 0.5 mg every three days (See DOSAGE AND ADMINISTRATION). Some patients may require an even slower dosage reduction.

As with all benzodiazepines, paradoxical reactions such as stimulation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects such as agitation, rage, irritability, and aggressive or hostile behavior have been reported rarely. In many of the spontaneous case reports of adverse behavioral effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Should any of the above events occur, alprazolam should be discontinued. Isolated published reports involving small numbers of patients have suggested that patients who have borderline personality disorder, a prior history of violent or aggressive behavior, or alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility, and intrusive thoughts have been reported during discontinuation of alprazolam in patients with posttraumatic stress disorder.

Laboratory analyses were performed on patients participating in the clinical program for alprazolam. The following incidences of abnormalities shown below were observed in patients receiving alprazolam and in patients in the corresponding placebo group. Few of these abnormalities were considered to be of physiological significance.

	Alprazolam		Placebo	
	Low	High	Low	High
Hematology				
Hematocrit	*	*	*	
Hemoglobin	*	*	*	*
Total WBC Count	1.4	2.3	1.0	2.0
Neutrophil Count	2.3	3.0	4.2	1.7
Lymphocyte Count	5.5	7.4	5.4	9.5
Monocyte Count	5.3	2.8	6.4	*
Eosinophil Count	3.2	9.5	3.3	7.2
Basophil Count	*	*	*	*
Urinalysis				
Albumin	*	*	*	*
Sugar	*	*	*	*
RBC/HPF	*	3.4	*	5.0
WBC/HPF	*	25.7	*	25.9
Blood Chemistry				
Creatinine	2.2	1.9	3.5	1.0
Bilirubin	*	1.6	*	*
SGOT	*	3.2	1.0	1.8
Alkaline Phosphatase	*	1.7	*	1.8

*Less than 1%

When treatment with alprazolam is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during therapy with alprazolam and are of no known significance.

Post Introduction Reports: Various adverse drug reactions have been reported in association with the use of alprazolam since market introduction. The majority of these reactions were reported through the medical event voluntary reporting system. Because of the spontaneous nature of the reporting of medical events and the lack of controls, a causal relationship to the use of alprazolam cannot be readily determined. Reported events include: liver enzyme elevations, gynecomastia and galactorrhea.

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence: Withdrawal symptoms similar in character to those noted with sedative/hypnotics and alcohol have occurred following discontinuance of benzodiazepines, including alprazolam. The symptoms can range from mild dysphoria and insomnia to a major syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors and convulsions. Distinguishing between withdrawal emergent signs and symptoms and the recurrence of illness is often difficult in patients undergoing dose reduction. The long term strategy for treatment of these phenomena will vary with their cause and the therapeutic goal. When necessary, immediate management of withdrawal symptoms requires re-institution of treatment at doses of alprazolam sufficient to suppress symptoms. There have been reports of failure of other benzodiazepines to fully suppress these withdrawal symptoms. These failures have been attributed to incomplete cross-tolerance but may also reflect the use of an inadequate dosing regimen of the substituted benzodiazepine or the effects of concomitant medications.

While it is difficult to distinguish withdrawal and recurrence for certain patients, the time course and the nature of the symptoms may be helpful. A withdrawal syndrome typically includes the occurrence of new symptoms, tends to appear toward the end of taper or shortly after discontinuation, and will decrease with time.

While the severity and incidence of withdrawal phenomena appear to be related to dose and duration of treatment, withdrawal symptoms, including seizures, have been reported after only brief therapy with alprazolam at doses within the recommended range for the treatment of anxiety (e.g., 0.75 to 4 mg/day). Signs and symptoms of withdrawal are often more prominent after rapid decrease of dosage or abrupt discontinuance. The risk of withdrawal seizures may be increased at doses above 4 mg/day (See WARNINGS).

Patients, especially individuals with a history of seizures or epilepsy, should not be abruptly discontinued from any CNS depressant agent, including alprazolam. It is recommended that all patients on alprazolam who require a dosage reduction be gradually tapered under close supervision (See WARNINGS and DOSAGE AND ADMINISTRATION).

Psychological dependence is a risk with all benzodiazepines, including alprazolam. The risk of psychological dependence may also be increased at higher doses and with longer term use, and this risk is further increased in patients with a history of alcohol or drug abuse. Some patients have experienced considerable difficulty in tapering and discontinuing from alprazolam, especially those receiving higher doses for extended periods. Addiction-prone individuals should be under careful surveillance when receiving alprazolam. As with all anxiolytics, repeat prescriptions should be limited to those who are under medical supervision.

Controlled Substance Class: Alprazolam is a controlled substance under the Controlled Substance Act by the Drug Enforcement Administration and alprazolam Intensol™ has been assigned to Schedule IV.

OVERDOSAGE

Manifestations of alprazolam overdosage include somnolence, confusion, impaired coordination, diminished reflexes and coma. Death has been reported in association with overdoses of alprazolam by itself, as it has with other benzodiazepines. In addition, fatalities have been reported in patients who have overdosed with a combination of a single benzodiazepine, including alprazolam, and alcohol; alcohol levels seen in some of these patients have been lower than those usually associated with alcohol-induced fatality.

The acute oral LD_{50} in rats is 331 to 2171 mg/kg. Other experiments in animals have indicated that cardiopulmonary collapse can occur following massive intravenous doses of alprazolam (over 195 mg/kg; 975 times the maximum recommended daily human dose of 10 mg/day). Animals could be resuscitated with positive mechanical ventilation and the intravenous infusion of norepinephrine bitartrate.

Animal experiments have suggested that forced diuresis or hemodialysis are probably of little value in treating overdosage.

General Treatment of Overdosage: Overdosage reports with alprazolam is limited. As in all cases of drug overdosage, respiration, pulse rate, and blood pressure should be monitored. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. If hypotension occurs, it may be combated by the use of vasopressors. Dialysis is of limited value. As with the management of intentional overdosing 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 re-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. The complete flumazenil package insert including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS should be consulted prior to use.

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 require higher doses. In such cases, dosage should be increased cautiously to avoid adverse effects.

Anxiety disorders and transient symptoms of anxiety:

Treatment for patients with anxiety should be initiated with a dose of 0.25 to 0.5 mg given three times daily. The dose may be increased to achieve a maximum therapeutic effect, at intervals of 3 to 4 days, to a maximum daily dose of 4 mg, given in divided doses. The lowest possible effective dose should be employed and the need for continued treatment reassessed frequently. The risk of dependence may increase with dose and duration of treatment.

In elderly patients, in patients with advanced liver disease or in patients with debilitating disease, the usual starting dose is 0.25 mg, given two or three times daily. This may be gradually increased as needed and tolerated. The elderly may be especially sensitive to the effects of benzodiazepines.

If side effects occur at the recommended starting dose, the dose may be lowered.

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every three days. Some patients may require an even slower dosage reduction.

Proper Use of an Intensol™

An Intensol is a concentrated oral solution as compared to standard oral liquid medications. It is recommended that an Intensol be mixed with liquid or semi-solid food such as water, juices, soda or soda-like beverages, applesauce and puddings.

Use only the calibrated dropper provided with this product. Draw into the dropper the amount prescribed for a single dose. Then squeeze the dropper contents into a liquid or semi-solid food. Stir the liquid or food gently for a few seconds. The Intensol formulation blends quickly and completely. The entire amount of the mixture, of drug and liquid or drug and food, should be consumed immediately. Do not store for future use.

HOW SUPPLIED

Alprazolam Intensol™ Oral Solution (Concentrate) for oral administration is available as:

1 mg per mL (flavorless, colorless solution)
NDC 0054-3069-44: Bottles of 30 mL with calibrated dropper (graduations of 0.25 mL (0.25 mg), 0.5 mL (0.5 mg), 0.75 mL (0.75 mg), and 1 mL (1 mg) on the dropper).

Store at Controlled Room Temperature
15°-30°C (59°-86°F)

Protect from Light

Dispense in a tight, light-resistant container.

Caution: Federal law prohibits dispensing without prescription.

ANIMAL PHARMACOLOGY

ANIMAL STUDIES

When rats were treated with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended human dose) orally for 2 years, a tendency for a dose related increase in the number of cataracts was observed in females and a tendency for a dose related increase in corneal vascularization was observed in males. These lesions did not appear until after 11 months of treatment.

CLINICAL STUDIES

Alprazolam was compared to placebo in double blind clinical studies (doses up to 4 mg/day) in patients with a diagnosis of anxiety or anxiety with associated depressive symptomatology. Alprazolam was significantly better than placebo at each of the evaluation periods of these four week studies as judged by the following psychometric instruments: Physician's Global Impressions, Hamilton Anxiety Rating Scale, Target Symptoms, Patient's Global Impressions and Self-Rating Symptom Scale.

[illegible] Revised September 1993
[illegible]

Roxane Laboratories, Inc.
Columbus, Ohio 43216

C H E M I S T ' S R E V I E W

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-312

3. NAME AND ADDRESS OF APPLICANT

Roxane Laboratories, Inc.
P.O. Box 165:2
Columbus, Ohio 43216

4. BASIS OF SUBMISSION

Roxane Laboratories, Inc. certifies that the existing patents for Alprazolam are patent No.3987052 (expiration 10-19-93), patent No.3980789 (expiration 9-14-93) and patent No.4508726 (expiration 4-2-2002). In addition the firm certify the existence of an exclusivity with an expiration date of 11-6-93.
Roxane will not market the product for which this application is submitted until after patents 3987052 and 3980789 have expired.
Roxane Laboratories, Inc. states that the use patent no.4508726 and the exclusivity do not claim any of the proposed indications in the labeling of this application.
The reference listed drug,according to the available information for the uses claimed in this application, is not entitled to any period of exclusivity under section 505(j)(4)(D) of the act. The existing exclusivity(expiration 11-6-93) is for panic Disorder, for which this application does not claim.

7. NONPROPRIETARY NAME

Alprazolam oral solution concentrate (Intensol)

9. AMENDMENTS AND OTHER DATES:

Original application January 6, 1993
Amendment 2/1/93
Amendment 8/19/93
Amendment 9/15/93
Amendment 9/23/93
Amendment 10/15/93
Amendment 10/18/93

10. PHARMACOLOGICAL CATEGORY

Anti-anxiety

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's

13. DOSAGE FORM

Concentrated oral solution

14. POTENCY

1 mg/mL

15. CHEMICAL NAME AND STRUCTURE

4H-[1,2,4]Triazolo[4,3-a][1,4]benzodiazepine, 8-chloro-1-methyl-6-phenyl.

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER:

Nashed E. Nashed, Ph.D.

Endorsed by P.Schwartz, Ph.D.

DATE COMPLETED:

10/18/93

10/19/93

cc: ANDA #74-312
ANDA #74-312/Division File

Endorsements:

HFD-630/N.Nashed/10-18-93 NN 10/20/93

HFD-630/P.Schwartz, Ph.D./10-19-93 PS 10/20/93
X:\Majors\Nashed\74-312.2
F/T MM 10-19-93

BIO/DISSOLUTION

REVIEW

AUG 6 1993

Alprazolam Solution/Concentrate
ANDA #74-312, 1 mg/mL, Intensol[R] (Concentrate)
ANDA #74-314, 0.1 mg/mL, Oral Solution
Reviewer: S. P. Shrivastava
WP 74312S.193

Roxane Laboratories, Inc.
Columbus, Ohio
Submission Date:
January 6, 1993
January 11, 1993

Review of *in vivo* Bioequivalence Study

I. Objective

The firm has submitted a three-way crossover bioavailability study comparing Roxane's alprazolam, 0.1 mg/mL oral solution and 1 mg/mL Intensol[R] (concentrate) comparing them with Xanax[R] (Upjohn Co.), 1 mg tablets. Since there is no approved alprazolam solution on the market, these ANDAs represent the first generic products. The firm is requesting approval of the products under Section 505(j)(2)(C) FFD&CA. Roxane has two separate approved petitions, Docket # 92P-0050/CP2 and 92P-0050/CP1, dated December 15/21, 1992, for the two products.

II. Introduction

Alprazolam is triazolo-analog of 1,4-benzodiazepine class of central nervous system active compounds. It is white crystalline powder, which is soluble in methanol, or ethanol but has no appreciable solubility in water at physiological pH.

The product presumably exerts its effect by binding at stereospecific receptors at several sites within the CNS system. Its mechanism of action is unknown. Clinically, all benzodiazepines cause a dose related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Following oral administration, alprazolam is readily absorbed. Peak concentrations in plasma occurs in 1-2 hours post-dosing. Plasma levels are proportionate to the dose given. Over the dose range of 0.5-3 mg, 8-37 ng/mL were observed. The half-life of alprazolam has been found to be 11.2 hrs. (range: 6.3-26.9 hrs) in healthy adults. An initial dose of 0.25-0.5 mg TID is recommended for anxiety patients.

Major metabolites of alprazolam are: α-hydroxy-alprazolam and benzophenone. Biologically, α-hydroxy-alprazolam is only 50% active and benzophenone is inactive. Plasma levels of these metabolites are extremely low, and their half-lives are similar to the alprazolam (PDR, 1992).

III. Protocol

10327: Dated 1/7/92. The document was initialed 1/17/92 by the PI.

Laboratory/Site
Clinical:
Analytical:

Investigator(s)
Principal Investigator:
IRB Approval: Document was approved by IRB on 1/30/92 with modifications.
Written Informed Consent Forms: Dated 4/1/92; approved by IRB 4/6/92.
Study Design: Single dose, three-way, randomized, cross-over design, with three period and six phases, under fasting conditions. **Subjects:** 30; there were no additions, and 29 subjects completed the study. Healthy male subjects with ideal body weight ± 10%. and ages between 19-50 years were recruited.

Subjects were without any medication, including aspirin or OTC for at least two weeks prior to the study and until after the completion of the study. The subjects fasted for 10 hours prior to dosing, and for 5 hours post-dosing. A standardized meals were served and continued until 36 hours post-dosing. Water was provided *ad libitum* during the 10 hour fast and the one hour post-dosing period. The wash-out period was 7 days.

Restrictions
- No drugs including OTC preparations or aspirin.
- No alcoholic beverages from 48 hours pre-dosing until 48 hours post-dosing.
- No xanthine or caffeine containing foods and beverages for 24 hours prior to dosing until after the completion of the study.

Exclusion Criteria
- Subjects with history of epilepsy or seizures, glaucoma, psychosis, mental depression, or asthma; serious cardiovascular, pulmonary, hepatic, renal, hematopoietic, or GI tract disease; and alcohol or drug abuse as evidenced by medical examination within 30 days.
- Minimum screening/check-in blood pressure of 100/60 mm Hg.
- Subjects with pertinent clinical test results outside the normal range.
- Subjects with history of allergic response to alprazolam or any other benzodiazepines.

Treatment

Test Drug: Test A. Orai solution, 0.1 mg/mL: Lot # 929003 Lot size:
Date of Manuf. 4/92; Potency: 100.7%
Test B. Intensol® (Concentrate), 1 mg/mL, Lot #919076,
Lot Size - ; Date of Manuf. 1/92, Potency - 100.9%
Dose: 1 mg active ingredient; Oral solution 10 mL and Intensol® 1 mL administered orally.

Reference Drug: C. Xanax®, 1 mg tablets; Lot # 204YH; Exp.Date 1/92
Manufacturer: Upjohn Co. Dose: one tablet/patient.

2 Page(s)

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V. Results

Pharmacokinetic Parameters

- Pharmacokinetic parameters are given in Tables 1-6.

- ANOVA analysis did not show any significant treatment or sequence effect on AUC_{0-t}, and $AUC_{0-\infty}$. However, there was a significant sequence effect on C_{max}, and treatment effect on T_{max}. The firm has not offered any explanation for these effects.

- The test/reference ratios for all PK parameters (average) for the products were within 0.95-1.16 (Tables 2-3). The T_A/R and T_B/R ratios for T_{max} were 0.63 and 0.65, respectively.

- The 90% CIs for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within 80-120% (Tables 1-3).

- Data for all 29 subjects were used in the computation of PK parameters. Subject # 3 did not return for phase II of the study and was dropped out.

- Ratios of individual $AUC_{0-t}/AUC_{0-\infty}$ averaged 0.94 (range: 0.90-0.96), 0.94 (0.84-0.97), and 0.94 (0.88-0.97) for alprazolam oral solution, alprazolam concentrate (Intensol®), and Xanax®, respectively.

- A reanalysis of data on SAS indicated correctly reported elimination constants, AUCs, $T_{1/2}$, and Cmax values (Tables 4-6).

- The individual T/R ratios for AUCs and C_{max} were between 0.57-1.47.

- The individual T/R ratios for T_{max} for oral solution and concentrate were 0.8 hour (range, 0.2-2.0 hours) and 0.9 hour (range, 0.25-2.0 hours), respectively. It indicates a shorter T_{max} for both test products as compared to the reference product.

Table 1. Mean (%CV) Pharmacokinetic Parameters (n = 29)

Parameter	Test-A*	Test-B*	Ratio, T_A/T_B	90% CI
AUC_{0-T}, ng.Hr/mL	217.3 (30.5)	222.9 (28.6)	0.98	92.8-102.2
AUC_{0-Inf}, ng.Hr/mL	229.9 (29.8)	236.7 (27.6)	0.97	92.6-101.9
C_{max}, ng/mL	16.9 (14.4)	16.9 (16.3)	1.00	94.4-105.8
T_{max}, Hr	0.73 (61.8)	0.75 (54.9)	0.98	
$T_{1/2}$, Hr	11.3 (23.9)	11.6 (23.8)	0.97	
K_{el}, Hr^{-1}	0.064 (22.3)	0.062 (20.2)	1.03	

Table 2. Mean (%CV) Pharmacokinetic Parameters (n = 29)

Parameter	Test-A*	Reference (C*)	Ratio, T_A/R_C	90% CI
AUC_{0-T}, ng.Hr/mL	217.3 (30.5)	221.4 (30.7)	0.98	93.4-102.9
AUC_{0-Inf}, ng.Hr/mL	229.9 (29.8)	235.7 (31.0)	0.98	92.9-102.2
C_{max}, ng/mL	16.9 (14.4)	17.1 (20.5)	0.99	93.0-104.3
T_{max}, Hr	0.73 (61.8)	1.15 (64.2)	0.63	
$T_{1/2}$, Hr	11.3 (23.9)	11.3 (30.0)	1.00	
K_{el}, Hr^{-1}	0.064 (22.3)	0.065 (22.8)	0.98	

* Test-A = Oral solution; Test B = Concentrates Solution (Intensol®); Reference (C) = Xanax® tablets.

Table 3. Mean (%CV) Pharmacokinetic Parameters (n = 29)

Parameter	Test-B	Reference (C)	Ratio, T_B/R_C	90% CI
AUC_{0-T}, ng.Hr/mL	222.9 (28.6)	221.4 (30.7)	1.01	95.9-105.3
AUC_{0-Inf}, ng.Hr/mL	236.7 (27.6)	235.7 (31.0)	1.00	95.7-104.9
C_{max}, ng/mL	16.9 (16.3)	17.1 (20.5)	0.99	92.9-104.1
T_{max}, Hr	0.75 (54.9)	1.15 (64.2)	0.65	
$T_{1/2}$, Hr	11.6 (23.8)	11.3 (30.0)	1.03	
K_{el}, Hr^{-1}	0.062 (20.2)	0.065 (22.8)	0.95	

Table 4. Test Product/Reference Product PK Parameter Ratios

			RAUCT 1 2	RAUCI 1 2	RCMAX 1 2	RTMAX 1 2	RAUCT 1 3	RAUCI 1 3	RCMAX 1 3	RTMAX 1 3	RAUCT 2 3	RAUCI 2 3	RCMAX 2 3	RTMAX 2 3
1	1	4	1.00	1.01	0.91	1.00	0.99	1.00	1.12	0.25	1.00	0.98	1.23	0.25
2	2	1	0.96	0.92	1.16	0.50	0.91	0.92	0.96	0.67	0.95	1.00	0.83	1.33
3	4	3	0.89	0.87	1.00	0.50	0.90	0.90	0.84	0.67	1.01	1.03	0.84	1.33
4	5	6	1.38	1.32	1.36	0.67	1.17	1.14	1.25	0.67	0.84	0.86	0.92	1.00
5	6	5	1.07	1.08	0.93	1.00	1.15	1.09	0.81	0.67	1.08	1.01	0.87	0.67
6	7	1	1.18	1.11	1.39	0.25	1.13	1.21	0.96	1.00	0.95	1.08	0.69	4.00
7	8	3	0.65	0.67	0.91	2.00	0.76	0.78	0.97	1.00	1.18	1.15	1.06	0.50
8	9	2	0.83	0.85	1.16	0.50	0.86	0.88	1.11	0.20	1.04	1.03	0.95	0.40
9	10	5	0.90	0.90	1.23	1.00	0.89	0.89	0.70	1.00	0.98	0.99	0.5	1.00
10	11	4	1.01	1.02	0.97	0.67	0.96	0.97	0.88	1.00	0.95	0.95	0.91	1.50
11	12	6	1.00	1.01	1.06	0.67	1.02	1.01	1.01	0.67	1.02	1.01	0.95	1.00
12	13	1	0.94	0.95	0.96	1.50	0.97	0.96	1.16	0.33	1.03	1.02	1.21	0.25
13	14	2	0.99	1.00	0.73	1.50	1.11	1.02	1.08	1.50	1.12	1.02	1.47	1.00
14	15	4	0.93	0.92	0.85	1.00	1.03	1.03	0.93	1.00	1.11	1.13	1.10	1.00
15	16	3	1.06	1.06	1.14	1.00	0.96	0.96	1.29	0.25	0.90	0.90	1.13	0.25
16	17	6	0.81	0.82	1.01	1.00	0.98	0.96	1.17	0.25	1.21	1.17	1.16	0.25
17	18	5	0.83	0.82	1.09	0.67	1.02	1.01	1.08	0.67	1.23	1.22	0.98	1.00
18	19	6	0.87	0.87	0.99	1.00	0.87	0.87	1.01	1.00	1.00	1.00	1.02	1.00
19	20	5	1.31	1.29	1.20	1.60	1.20	1.18	1.04	1.00	0.92	0.91	0.87	0.63
20	21	1	0.99	0.98	0.91	4.00	0.98	0.98	0.95	0.80	1.00	1.01	1.05	0.20
21	22	3	1.08	1.11	1.09	1.00	1.10	1.12	1.39	0.40	1.02	1.01	1.27	0.40
22	23	4	0.99	0.98	0.92	1.00	1.10	1.11	0.95	1.00	1.12	1.13	1.03	1.00
23	24	2	1.06	1.08	0.86	2.33	1.06	1.07	0.99	0.88	0.99	0.99	1.16	0.38
24	25	5	1.27	1.28	0.91	1.00	1.06	1.07	0.72	1.00	0.83	0.83	0.80	1.00
25	26	6	0.90	0.91	1.06	2.50	0.78	0.80	0.99	1.25	0.87	0.88	0.93	0.50
26	27	3	0.96	0.95	1.01	1.00	1.14	1.14	0.90	1.00	1.19	1.19	0.89	1.00
27	28	4	0.91	0.89	1.05	1.00	0.95	0.94	0.96	2.00	1.04	1.05	0.92	2.00
28	29	2	0.81	0.81	0.75	0.50	0.95	0.95	1.08	0.40	1.17	1.17	1.44	0.80
29	30	1	0.80	0.77	0.84	0.67	0.66	0.62	0.86	0.40	0.83	0.81	1.03	0.60

1=Test-A 2=Test-B 3=Ref-C
The format,1_2 or 12, denotes Trt #1 vs. Trt #2

Table 5. Statistics on the Test/Reference PK Parameter Ratios

N Obs	Variable	N	Minimum	Maximum	Mean	Std Dev
29	RAUCT12	29	0.6472674	1.3846518	0.9787714	0.1596839
	RAUCI12	29	0.6746981	1.3205672	0.9743327	0.1521540
	RCMAX12	29	0.7317073	1.3867925	1.0161918	0.1595368
	RTMAX12	29	0.2500000	4.0000000	1.1385057	0.7664739
	RAUCT13	29	0.6595321	1.1978358	0.9883847	0.1273695
	RAUCI13	29	0.6248399	1.2059469	0.9846257	0.1274049
	RCMAX13	29	0.6972112	1.3875969	1.0058372	0.1566181
	RTMAX13	29	0.2000000	2.0000000	0.7913793	0.4040315
	RAUCT23	29	0.8274353	1.2291335	1.0197262	0.1127492
	RAUCI23	29	0.8089281	1.2216172	1.0187910	0.1074991
	RCMAX23	29	0.5657371	1.4748201	1.0092207	0.2009585
	RTMAX23	29	0.2000000	4.0000000	0.9045977	0.7378338

1=Test-A 2=Test-B 3=Ref-C
The format,1_2 or 12, denotes Trt #1 vs. Trt #2

TABLE 6. 90% Confidence Intervals

	LOUCI1_2	UPPCI1_2	LOUCI1_3	UPPCI1_3	LOUCI2_3	UPPCI2_3
NAME						
AUCI	92.50	101.85	92.88	102.15	95.66	104.93
AUCT	92.84	102.24	93.40	102.85	95.88	105.33
CMAX	94.44	105.84	93.04	104.27	92.90	104.13
LAUCI	92.42	100.54	93.57	101.79	97.07	105.59
LAUCT	92.62	101.00	93.85	102.34	97.03	105.81
LCMAX	95.14	106.08	94.23	105.07	93.80	104.59

1=Test-A 2=Test-B 3=Ref-C
The format,1_2 or 12, denotes Trt #1 vs. Trt #2

Blood/Plasma/Serum

- The lower limit of quantitation 0.5 ng/mL was properly validated.
- The average test/reference ratios for plasma concentration during 0.5-48 hours varied between 0.91-1.22 and 0.96-1.12), respectively, for oral solution and concentrate (Table 7). The ratios are normally higher for the initial samples and lower for the final samples, indicating a shift in the test plasma concentration-time curve towards left.

TABLE 7. Mean Plasma Concentration at Each Sampling Time Point (n = 29)

OBS	TIME	M_CONC1 Test A	SD1	M_CONC2 Test B	SD2	M_CONC3 Ref. (C)	SD3	RATIO1_2 T_A/T_B	RATIO1_3 T_A/R	RATIO2_3 T_B/R
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	.	.	.
2	0.25	6.27	4.59	4.94	3.97	3.26	4.03	1.27	1.92	1.52
3	0.50	15.77	3.69	14.51	4.91	12.98	6.53	1.09	1.22	1.12
4	0.75	15.00	2.34	15.22	2.90	14.61	4.62	0.99	1.03	1.04
5	1.00	14.26	2.58	14.45	2.53	13.81	3.90	0.99	1.03	1.05
6	1.25	13.61	2.63	13.55	2.56	13.53	3.02	1.00	1.01	1.00
7	1.50	13.26	2.72	13.43	2.28	13.19	2.43	0.99	1.01	1.02
8	1.75	12.88	2.36	13.10	1.97	13.64	2.06	0.98	0.94	0.96
9	2.00	12.76	2.34	13.60	2.53	13.94	2.14	0.94	0.92	0.98
10	2.50	12.29	2.38	12.98	2.02	13.47	2.10	0.95	0.91	0.96
11	3.00	11.70	2.20	12.42	1.99	12.70	2.30	0.94	0.92	0.98
12	4.00	11.55	2.79	11.49	1.89	11.79	1.99	1.01	0.98	0.97
13	6.00	9.61	1.85	9.76	1.84	9.84	1.86	0.99	0.98	0.99
14	9.00	7.79	1.85	7.74	1.66	8.07	1.61	1.01	0.96	0.96
15	12.00	6.35	1.64	6.51	1.70	6.41	1.69	0.97	0.99	1.02
16	24.00	3.14	1.22	3.32	1.30	3.31	1.34	0.95	0.95	1.00
17	36.00	1.49	0.85	1.57	0.81	1.48	0.87	0.95	1.00	1.06
18	48.00	0.67	0.68	0.68	0.67	0.68	0.77	0.98	0.99	1.01
19	60.00	0.24	0.39	0.25	0.45	0.24	0.48	0.97	1.03	1.07
20	72.00	0.06	0.22	0.09	0.26	0.10	0.32	0.66	0.57	0.87

M_Conc1=Test A, M_Conc2=Test B, and M_Conc3=Reference (Trt C) plasma concentration, in ng/mL. Ratios1_2, 1_3, and 2_3 denote ratios for Trt A/B, Trt A/C, and Trt B/C, respectively.

Adverse Reactions

Adverse reactions are given in Table 8. Drowsiness definitely appears to be related to the test product, and it appears to be equally common to all three products.

Table 8 Adverse Reactions

REACTION	TEST ORAL SOL.	TEST INTENSOL[R]	REF.
Tired	0	0	1
Frontal Headache	1	0	1
Headache	1	1	1
Dizzy	1	0	0
Sleepy	0	0	1
Drowsy	10	17	13

Formulation: See Table 9.

TABLE 9. Comparison of Test and Reference Product Formulations (Not for release under FOI)

Ingredients	Amount (mg/mL)		Amount, mg/Tablet
	Oral Sol	Intensol[R]	Ref.
Strength (mg)	0.1	1.0	1.0
Alprazolam	0.1	1.0	1.0

* Listed as ingredients without quantitative or purity information.
** May be varied from 0.75 - 2.0% (w/w) to facilitate compression

Labeling:

Intensol[R] is a concentrated oral liquid, and the directions for administration call for mixing measured volume of Intensol[R] with unspecified volume/amount of liquid or semi-solid food, e.g.,

water, juice, soda, soda-like beverages, other liquid, applesauce, pudding, or other semi-solid food. In the current study, the weighed volume of the dose was administered orally by syringe, followed by 240 mL of water. The firm needs to demonstrate that mixing procedures, and addition of other liquids or semi-solids do not interfere with the equivalent bioavailability of the drug product.

The T_{max} for the test products range between 0.25-2.0 hours. The chemist should note the change in T_{max} values, and incorporate the desired information in the lable. C_{max} and $T_{1/2}$ values for the test products are comparable to the innovator's product, and are correct as labeled.

VI. Comments

1. The 90% CIs for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within 80-120%.

2. There was a significant sequence effect on C_{max}, and treatment effect on T_{max}. The firm has not offered any explanation for these effects.

3. The firm is recommending administration of Intensol[R] with unspecified volume/amount of liquid or semi-solid, e.g., water, juice, soda, other liquids, applesauce, pudding or other semi-solid food. However, the firm should demonstrate or present evidence that the administration of the test product with recommended liquids and semi-solids does not affect its bioavailability.

4. The firm has submitted chromatogram tracings for subjects # 8, 12, 16, 20, 23, and 26. The Agency requires chromatographic raw data for 20% of the subjects in sequence (e.g. first, middle, or last six subjects in sequence). The firm should provide the chromatographic raw data for subjects # 21, 22, 24 and 25 to complete the evaluation.

5. The T_{max} for the test products range between 0.25-2.0 hours. The chemist should note the T_{max} values in the label, and make any modifications to incorporate the desired information.

VII. Recommendations

1. The single dose bioavailability study conducted by Roxane Laboratories on alprazolam 0.1 mg/mL oral solution, Lot # 929003, and alprazolam 1 mg/mL concentrated solution (Intensol[R]), Lot # 919076, comparing them to Upjohn's Xanax[R] tablets, 1 mg, Lot # 204YH, has been found incomplete by the Division of Bioequivalence because of the deficiencies cited in comments #2-4.

The firm should be informed of the comments #2-4, and recommendations.

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

for
RD INITIALED RPATNAIK
FT INITIALED RPATNAIK Date 8/4/1993

Concur: Vasantkant M. Mhatre Date: 8/4/93

R. M. Mhatre, Ph.D.
Acting Director
Division of Bioequivalence

SPS/sps/6-17-93/74312S.193

cc: ANDA #74-312 (Original, Duplicate) HFD-600 (DHare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-655 (Patnaik, Shrivastava), HFD-340, Drug File.

OCT 8 1993

Alprazolam Solution/Concentrate
ANDA #74-312, 1 mg/mL, Intensol[R] (Concentrate)
ANDA #74-314, 0.1 mg/mL, Oral Solution
Reviewer: S. P. Shrivastava
WP 74312O.993

Roxane Laboratories, Inc.
Columbus, Ohio
Submission Date:
September 15, 1993

Review of *in vivo* Bioequivalence Study Correspondence

I. Background

The firm had submitted a three-way crossover bioavailability study comparing Roxane's alprazolam, 0.1 mg/mL oral solution and 1 mg/mL Intensol[R] (concentrate) with Xanax[R] (Upjohn Co.), 1 mg tablets (Submission dates, January 6 and 11, 1993). Since there is no approved alprazolam solution on the market, these ANDAs represented the first generic products. The firm had requested approval of the products under Section 505(j)(2)(C) FFD&CA.

The review was completed (Re: review by Shrivastava, 8/6/93), and deficiencies were cited. The firm has responded to the deficiencies.

II. Response to Agency's Comments

Comment 1: **There was a significant sequence effect on C_{max}, and treatment effect on T_{max}. The firm has not offered any explanation for these effects.**

Response: The significant sequence effect for C_{max} apparently resulted from differences in extent of absorption for the subjects that were randomized into different sequence groups. Statistical analyses showed no sequence effect due to age, race, frame size, height, or smoking status. A significant sequence effect was observed for body weight (α=0.05). There was an inverse relationship between mean body weight, and mean C_{max} for the sequence.

The mean T_{max} for the solution, concentrate and tablets were 0.75, 0.76, and 1.16 hours, respectively. The tablet dose (Upjohn) had a significantly longer T_{max} than either solution or concentrate (Roxane). This probably is due to dissolution time required for the tablets.

Reviewer: The explanation is acceptable.

Comment 2: **The firm is recommending administration of Intensol[R] with unspecified volume/amount of liquid or semi-solid, e.g., water, juice, soda, other liquids, applesauce, pudding or other semi-solid food. However, the firm should demonstrate or present evidence that the administration**

of the test product with recommended liquids and semi-solids does not affect its bioavailability.

Response: Although no evidence of bioavailability with recommended liquids or semi-solids was provided, the water soluble nature of the drug and ingredients, and the fact that the product is to be administered immediately after mixing, would not affect the bioavailability.

Reviewer: Alprazolam is not appreciably soluble in water at physiological pH (PDR), and is **practically insoluble** in water (Remington's Pharmaceutical Sciences). Other pertinent information are: Alprazolam is readily absorbed. The absorption is slower when taken with food, however, the total absorption is unchanged. *In vitro*, alprazolam is 80% bound to protein, and protein binding is independent of concentration. In the biostudy, the administration of product was followed by 240 mL of water.

The Division of Labeling Review may look into the issue concerning the dosage administration portion of labeling for this product.

Comment 3: The firm has submitted chromatogram tracings for subjects # 8, 12, 16, 20, 23, and 26. The Agency requires chromatographic raw data for 20% of the subjects in sequence (e.g. first, middle, or last six subjects in sequence). The firm should provide the chromatographic raw data for subjects # 21, 22, 24 and 25 to complete the evaluation.

Response: The firm has enclosed the chromatograms for subjects #21, 22, 24, & 25.

Reviewer: The data is appropriate and acceptable.

III. Recommendations

The single dose bioavailability study conducted by Roxane Laboratories on alprazolam 0.1 mg/mL oral solution, Lot # 929003, and 1 mg/mL concentrated solution (Intensol®), Lot # 919076, comparing it to Upjohn's Xanax® tablets, 1 mg, Lot # 204YH, has been found acceptable by the Division of Bioequivalence.

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED NTRAN
FT INITIALED NTRAN Date 10/1/93

Concur: Date: 10/6/93

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

SPS/sps/9-28-93/74312O.993

cc: ANDA #74-312 (Original, Duplicate), HFD-600 (DHare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-655 (Tran, Shrivastava), HFD-340, Drug File.

APPENDIX - 1

TABLE 1: ALPRAZOLAM SERUM CONCENTRATIONS
ARITHMETIC MEANS ± STANDARD DEVIATION
(ng/ml)

Time (Hours)	ROXANE SOLUTION Test Product 1	ROXANE CONCENTRATE Test Product 2	UPJOHN TABLET Reference	Ratio Test-1/Test-2	Ratio Test-1/Ref.	Ratio Test-2/Ref.	Significance*
0	0.000	0.000	0.000	--	--	--	--
0.25	6.27 ± 4.59	4.77 ± 3.94	3.26 ± 4.03	1.31	1.92+	1.46	p<0.05
0.5	15.8 ± 3.69	14.5 ± 4.91	13.0 ± 6.53	1.09	1.22	1.12	N.S.
0.75	15.0 ± 2.34	15.2 ± 2.90	14.6 ± 4.62	0.99	1.03	1.04	N.S.
1	14.3 ± 2.58	14.4 ± 2.53	13.8 ± 3.90	0.99	1.04	1.04	N.S.
1.25	13.6 ± 2.63	13.5 ± 2.56	13.5 ± 3.07	1.01	1.01	1.00	N.S.
1.5	13.3 ± 2.72	13.4 ± 2.30	13.2 ± 2.43	0.99	1.01	1.02	N.S.
1.75	12.9 ± 2.36	13.1 ± 2.00	13.6 ± 2.06	0.98	0.95+	0.96	p<0.05
2	12.7 ± 2.34	13.6 ± 2.33	13.9 ± 2.14	0.93	0.91+	0.98	p<0.05
2.5	12.3 ± 2.38	13.0 ± 2.02	13.5 ± 2.10	0.95	0.91+	0.96	p<0.05
3	11.7 ± 2.20	12.4 ± 1.99	12.7 ± 2.33	0.94+	0.92+	0.98	p<0.05
4	11.5 ± 2.79	11.5 ± 1.89	11.8 ± 1.99	1.00	0.97	0.97	N.S.
6	9.61 ± 1.85	9.76 ± 1.84	9.84 ± 1.86	0.98	0.98	0.99	N.S.
9	7.79 ± 1.85	7.74 ± 1.66	8.07 ± 1.61	1.01	0.97	0.96	N.S.
12	6.35 ± 1.64	6.51 ± 1.70	6.41 ± 1.69	0.98	0.99	1.02	N.S.
24	3.14 ± 1.22	3.32 ± 1.30	3.31 ± 1.34	0.95	0.95	1.00	N.S.
36	1.49 ± 0.846	1.57 ± 0.807	1.48 ± 0.875	0.95	1.01	1.06	N.S.
48	0.653 ± 0.690	0.682 ± 0.669	0.701 ± 0.769	0.96	0.93	0.97	N.S.
60	0.244 ± 0.390	0.253 ± 0.453	0.211 ± 0.492	0.96	1.16	1.20	N.S.
72	0.059 ± 0.225	0.086 ± 0.265	0.103 ± 0.324	0.69	0.57	0.83	N.S.

*Based on Type III test from the analysis of variance, not evaluating pair-wise comparisons (α=0.05).
+Significant difference with Bonferroni multiple comparisons t-test (α=0.05).

APPENDIX-2

TABLE 2: PHARMACOKINETIC PARAMETERS
ARITHMETIC MEANS ± STANDARD DEVIATION
ALPRAZOLAM - SERUM

Parameter	Test 1 ROXANE SOLUTION	Test 2 ROXANE CONCENTRATE	Reference UPJOHN TABLET	Test 1/ Test 2	Test 1/ Ref.	Test 2/ Ref.	Significance*
AUC 0-T (ng ml^{-1} hr)	217	223	221	0.97	0.98	1.01	N.S.
Std. Dev.	66.2	63.7	68.0				
Cmax (ng/ml)	16.9	16.9	17.1	1.00	0.99	0.99	N.S.
Std. Dev.	2.43	2.74	3.51				
Tmax (hr)	0.733	0.750	1.15	0.98	0.64+	0.65+	p=0.0018
Std. Dev.	0.453	0.412	0.757				
AUC 0-Inf (ng ml^{-1} hr)	230	237	236	0.97	0.97	1.00	N.S.
Std. Dev.	68.6	65.4	73.0				
Rate Constant (hr^{-1})	0.0645	0.0622	0.0653	1.04	0.99	0.95	N.S.
Std. Dev.	0.0143	0.0125	0.0148				
Half-Life (hr)	11.3	11.6	11.3	0.97	1.00	1.03	N.S.
Std. Dev.	2.71	2.77	3.39				
Ln AUC 0-T (antiln)	5.34 (209)	5.37 (215)	5.36 (213)	0.97	0.98	1.01	N.S.
Std. Dev.	0.308	0.274	0.299				
Ln Cmax (antiln)	2.81 (16.6)	2.81 (16.6)	2.82 (16.8)	1.00	0.99	0.99	N.S.
Std. Dev.	0.154	0.175	0.200				
Ln AUC 0-Inf (antiln)	5.39 (219)	5.43 (228)	5.42 (226)	0.96	0.97	1.01	N.S.
Std. Dev.	0.300	0.266	0.298				

*Based on Type III test from the analysis of variance, not evaluating pairwise comparisons (α=0.05).
+Significant difference with Bonferroni multiple comparisons t-test (α=0.05).

APPENDIX 5

TABLE 3: PHARMACOKINETIC PARAMETERS
LEAST SQUARES MEANS ± STANDARD ERROR
ALPRAZOLAM - SERUM

Parameter	Test 1 ROXANE SOLUTION	Test 2 ROXANE CONCENTRATE	Reference UPJOHN TABLET	Test 1/ Test 2	Test 1/ Ref.	Test 2/ Ref.	Significance*
AUC 0-T (ng ml^{-1} hr)	217	222	221	0.98	0.98	1.00	N.S.
Std. Error	4.41	4.41	4.41				
Cmax (ng/ml)	16.8	16.8	17.1	1.00	0.98	0.98	N.S.
Std. Error	0.405	0.405	0.405				
Tmax (hr)	0.746	0.763	1.16	0.98	0.64+	0.66+	p=0.0018
Std. Error	0.0888	0.0888	0.0888				
AUC 0-Inf (ng ml^{-1} hr)	229	236	235	0.97	0.97	1.00	N.S.
Std. Error	4.61	4.61	4.61				
Rate Constant (hr^{-1})	0.0646	0.0623	0.0653	1.04	0.99	0.95	N.S.
Std. Error	0.00126	0.00126	0.00126				
Half-Life (hr)	11.3	11.6	11.3	0.97	1.00	1.03	N.S.
Std. Error	0.244	0.244	0.244				
Ln AUC 0-T (antiln)	5.33 (206)	5.37 (215)	5.35 (211)	0.96	0.98	1.02	N.S.
Std. Error	0.0183	0.0183	0.0183				
Ln Cmax (antiln)	2.81 (16.6)	2.81 (16.6)	2.82 (16.8)	1.00	0.99	0.99	N.S.
Std. Error	0.0230	0.0230	0.0230				
Ln AUC 0-Inf (antiln)	5.39 (219)	5.43 (228)	5.42 (226)	0.96	0.97	1.01	N.S.
Std. Error	0.0178	0.0178	0.0178				

*Based on Type III test from the analysis of variance, not evaluating pair-wise comparisons (α=0.05).
+Significant difference with Bonferroni multiple comparisons t-test (α=0.05).

APPENDIX-4

TABLE 4: ALPRAZOLAM SERUM
PHARMACOKINETIC PARAMETERS
STUDY POWER AND 90% CONFIDENCE INTERVALS

ROXANE SOLUTION vs. UPJOHN TABLET

Measured Parameters	Study Power	Confidence Interval
AUC 0-T	>0.99	[0.93; 1.03]
Cmax	>0.99	[0.93; 1.04]
Tmax	<0.50	[0.46; 0.82]
AUC 0-Inf	>0.99	[0.93; 1.02]
Rate Constant	>0.99	[0.94; 1.04]
Half-Life (hr)	>0.99	[0.95; 1.05]
Ln AUC 0-T	>0.99	[0.94; 1.02]
Ln Cmax	>0.99	[0.94; 1.05]
Ln AUC 0-Inf	>0.99	[0.94; 1.02]

ROXANE CONCENTRATE vs. UPJOHN TABLET

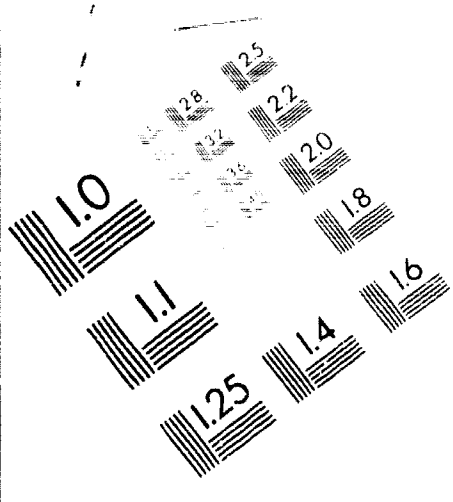
Measured Parameters	Study Power	Confidence Interval
AUC 0-T	>0.99	[0.96; 1.05]
Cmax	>0.99	[0.93; 1.04]
Tmax	<0.50	[0.48; 0.84]
AUC 0-Inf	>0.99	[0.96; 1.05]
Rate Constant	>0.99	[0.91; 1.00]
Half-Life (hr)	>0.99	[0.98; 1.08]
Ln AUC 0-T	>0.99	[0.97; 1.06]
Ln Cmax	>0.99	[0.94; 1.05]
Ln AUC 0-Inf	>0.99	[0.97; 1.06]

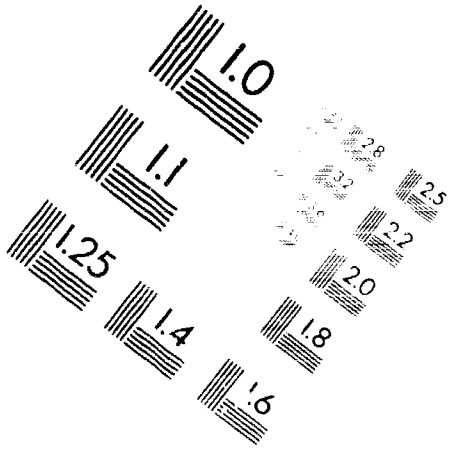
ROXANE SOLUTION vs. ROXANE CONCENTRATE

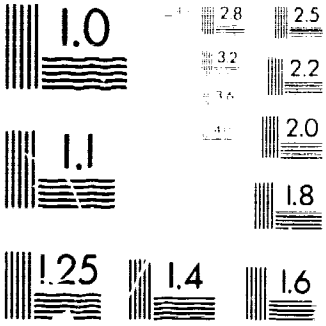
Measured Parameters	Study Power	Confidence Interval
AUC 0-T	>0.99	[0.93; 1.02]
Cmax	>0.99	[0.94; 1.06]
Tmax	<0.50	[0.70; 1.25]
AUC 0-Inf	>0.99	[0.93; 1.02]
Rate Constant	>0.99	[0.99; 1.08]
Half-Life (hr)	>0.99	[0.92; 1.02]
Ln AUC 0-T	>0.99	[0.93; 1.01]
Ln Cmax	>0.99	[0.95; 1.06]
Ln AUC 0-Inf	>0.99	[0.92; 1.01]

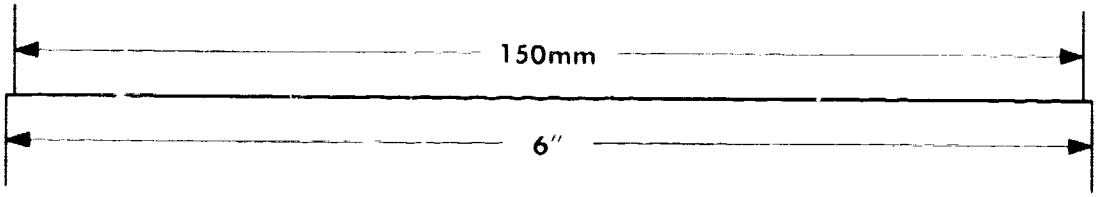
The power of the study to detect a 20% difference in parameters as statistically significant (α=0.05) and the 90% confidence intervals about the ratios of the test/reference means were calculated using least squares means from the analysis of variance.

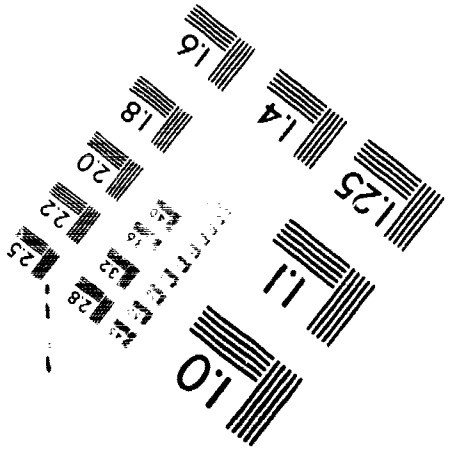
IMAGE EVALUATION
TEST TARGET (MT-3)

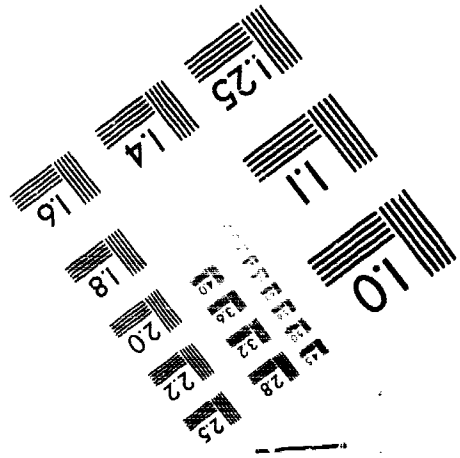












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