# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number** 74909

**Trade Name** Alprazolam Tablets USP 2mg

**Generic Name** Alprazolam Tablets USP 2mg

**Sponsor** Geneva Pharmaceuticals, Inc.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION 74909

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# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number 74909**

# APPROVAL LETTER

ANDA 74-909

MAR 25 1998

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
Broomfield, CO 80038-0446

Dear Madam:

This is in reference to your abbreviated new drug application dated May 31, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Alprazolam Tablets USP, 2 mg.

Reference is also made to your amendments dated July 1, and August 26, 1996; and February 19, and March 16, 1998.

The listed drug product referenced in your application is subject to a period of patent protection which expires on October 29, 2008 (Patent No. 5,061,494, [the '494 patent]). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Alprazolam Tablets USP, 2 mg will not infringe on the '494 patent. Section 505(j)(4)(B)(iii) of the Act provides that " . . . approval shall be made effective immediately unless an action is brought for infringement of a patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received." You have notified the Agency that Geneva Pharmaceuticals, Inc. (Geneva) has complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Geneva within the statutory forty-five day period.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Alprazolam Tablets USP, 2 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Xanax Tablets, 2 mg, of Pharmacia and Upjohn Company). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

Post-marketing reporting requirements for this abbreviated application 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 this drug.

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 be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

3/25/98

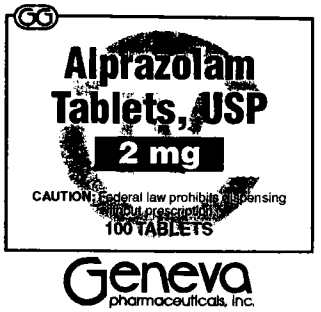
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 74909

## FINAL PRINTED LABELING

MARGO
N/FPL

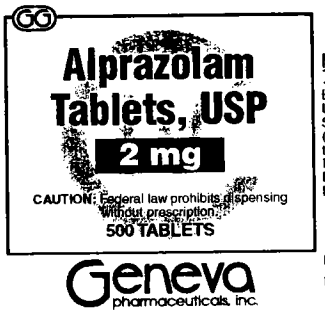



N 3 0781-1329-01 7

Each tablet contains: Alprazolam, USP 2 mg
**Usual Dosage:** See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in a tight, light-resistant container. Keep tightly closed.
**KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
ISS 94-10M Manufactured By N95/7
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:
EXP.:

25 1998
APPROVED




N 3 0781-1329-05 5

Each tablet contains: Alprazolam, USP 2 mg
**Usual Dosage:** See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in a tight, light-resistant container. Keep tightly closed.
**KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
ISS 94-10M Manufactured By N95/7
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:
EXP.:

25 1998
APPROVED

18c

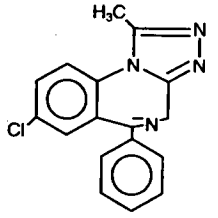
7194

# ALPRAZOLAM TABLETS, USP (C-IV)

7194-2

25 1998

**DESCRIPTION:** Alprazolam 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-α] [1,4] benzodiazepine. The structural formula is:



$C_{17}H_{13}ClN_4$ 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 tablet, for oral administration, contains 2 mg of alprazolam.

Alprazolam tablets, 2 mg, are multi-scored and may be divided as shown below:

Complete 2 mg Tablet

Two 1 mg segments

Four 0.5 mg segments

Inactive ingredients: docusate sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and sodium benzoate.

**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, 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 protein.

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. In patients with alcoholic liver disease the half-life of alprazolam ranged between 5.8 and 65.3 hours (mean: 19.7 hours, n = 17) as compared to between 6.3 and 26.9 hours (mean = 11.4 hours, n = 17) in healthy subjects. In an obese group of subjects the half-life of alprazolam ranged between 9.9 and 40.4 hours (mean = 21.8 hours, n = 12) as compared to between 6.3 and 15.8 hours (mean = 10.6 hours, n = 12) 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 tablets are 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*

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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 tablets are 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.

Alprazolam is contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP 3A) (see WARNINGS and PRECAUTIONS - Drug Interactions).

**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 (i.e., 0.75 to 4 mg per day), there is some risk of dependence. Post-marketing 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 8 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 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.

*Alprazolam Interaction With Drugs That Inhibit Metabolism Via Cytochrome P450 3A:* The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP 3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP 3A. With drugs inhibiting CYP 3A to a lesser but still significant degree, alprazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with alprazolam has been quantified with clinical data; for other drugs, interactions are predicted from *in vitro* data and/or experience with similar drugs in the same pharmacologic class.

The following are examples of drugs known to inhibit the metabolism of alprazolam and/or related benzodiazepines, presumably through inhibition of CYP 3A.

*Potent CYP 3A Inhibitors:* Azole antifungal agents – Although *in vivo* interaction data with alprazolam are not available, ketoconazole and itraconazole are potent CYP 3A inhibitors and the coadministration of alprazolam with them is not recommended. Other azole-type antifungal agents should also be considered potent CYP 3A inhibitors and the coadministration of alprazolam with them is not recommended (see CONTRAINDICATIONS).

*Drugs Demonstrated to be CYP 3A Inhibitors on the Basis of Clinical Studies Involving Alprazolam (caution and consideration of appropriate alprazolam dose reduction are recomended during coadministration with the following drugs):*

Nefazodone – Coadministration of nefazodone increased alprazolam concentration two-fold.

Fluvoxamine – Coadministration of fluvoxamine approximately doubled the maximum plasma concentration of alprazolam, decreased clearance by 49%, increased half-life by 71%, and decreased measured psychomotor performance.

Cimetidine – Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%.

*Other Drugs Possibly Affecting Alprazolam Metabolism:* Other drugs possibly affecting alprazolam metabolism by inhibition of CYP 3A are discussed in the PRECAUTIONS section (see PRECAUTIONS-Drug Interactions).

**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 medicine

Alprazolam 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.

*Alprazolam Interaction With Drugs That Inhibit Metabolism Via Cytochrome P450 3A:* The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP 3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP 3A. With drugs inhibiting CYP 3A to a lesser but still significant degree, alprazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with alprazolam has been quantified with clinical data; for other drugs, interactions are predicted from *in vitro* data and/or experience with similar drugs in the same pharmacologic class.

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**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).

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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 medicine 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, antihistaminics, 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.

*Drugs that Inhibit Alprazolam Metabolism Via Cytochrome P450 3A:* The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP 3A). Drugs which inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam (see CONTRAINDICATIONS and WARNINGS for additional drugs of this type).

*Drugs Demonstrated to be CYP 3A Inhibitors of Possible Clinical Significance on the Basis of Clinical Studies Involving Alprazolam (caution is recommended during coadministration with alprazolam):*

Fluoxetine – Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased half-life by 17%, and decreased measured psychomotor performance.

Propoxyphene – Coadministration of propoxyphene decreased the maximum plasma concentration of alprazolam by 6%, decreased clearance by 38%, and increased half-life by 58%.

Oral Contraceptives – Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.

*Drugs and Other Substances Demonstrated to be CYP 3A Inhibitors on the Basis of Clinical Studies Involving Benzodiazepines Metabolized Similarly to Alprazolam or on the Basis of In Vitro Studies with Alprazolam or Other Benzodiazepines (caution is recommended during coadministration with alprazolam):* Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from *in vitro* studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. Data from *in vitro* studies of benzodiazepines other than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during the coadministration of any of these with alprazolam (see WARNINGS).



**(See Reverse)**

**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 of alprazolam in individuals 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, eg, 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, 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 all 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 | * |

patients may require an even slower dosage reduction.

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| 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 abrupt 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 the 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 tablets have 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 Overdose:** Overdosage reports with alprazolam tablets 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 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

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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 if 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.

**HOW SUPPLIED:** Alprazolam tablets, USP for oral administration are supplied as:

**2 mg:** Rectangular white multi-scored tablets debossed GG 249 on one side and plain on the reverse side in bottles of 100 and 500.

Store at controlled room temperature 15°-30°C (59°-86°F).

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.

Rev. 96-12M C97/4
7194-2

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 74909

## CHEMISTRY REVIEW(S)

# OFFICE OF GENERIC DRUGS

## ABBREVIATED NEW DRUG APPLICATION
## CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

**1. CHEMIST'S REVIEW NUMBER**
3 (THREE)

**2. ANDA NUMBER**
74-909

**3. NAME AND ADDRESS OF APPLICANT**
Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
Broomfield, Colorado 80038-0446

**4. LEGAL BASIS for ANDA SUBMISSION**
The reference listed drug is Xanax® manufactured by Upjohn (NDA 18276).
Two patents currently cover this drug.

A. U.S. Patent No. 5061494 covers an elongated tri-scored tablet and will expire on Oct. 29, 2008. The Geneva certifies that U.S. Patent No. 5061494 will not be infringed by the manufacture, use or sale of the Alprazolam 2 mg Tablets for which this application is submitted.

B. U.S. Patent No. 4508726 is limits to the treatment of panic disorder and will expire on Apr. 2, 2002. The method of treatment using Geneva's Alprazolam Tablets USP, 2 mg for which Geneva seeks approval in this ANDA is a method of treatment for the management of anxiety disorder.

**5. SUPPLEMENT(s)**
None

**6. NAME OF DRUG**
None

**7. NONPROPRIETARY NAME**
Alprazolam Tablets USP

**8. SUPPLEMENT(s) PROVIDE(s) FOR**
None

**9. AMENDMENTS AND OTHER DATES**

| | |
|---|---|
| 5/31/96 | Original submission |
| 5/16/97 | Major amendment |
| 2/19/98 | Minor amendment |

**10. PHARMACOLOGICAL CATEGORY**
Sedative

**11. HOW DISPENSED**

Prescription (℞)

**12. RELATED DMF(s)**

(b)(4)(TS)

[redacted]

**13. DOSAGE FORM**

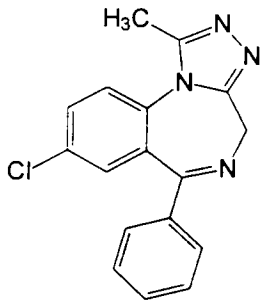
Tablets

**14. POTENCY**

2 mg

**15. CHEMICAL NAME AND STRUCTURE**

Alprazolam. 4*H*-[1,2,4]Triazolo[4,3-α][1,4]benzodiazepine, 8-chloro-1-methyl-6-phenyl-. $C_{17}H_{13}ClN_4$. 308.77. 28981-97-7.




**16. RECORDS AND REPORTS**

None

**17. COMMENTS**

None

**18. CONCLUSIONS AND RECOMMENDATIONS**

The application is approvable.

**19. REVIEWER AND DATE COMPLETED**

Naiqi Ya, Ph.D./February 25, 1998

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 74909

## BIOEQUIVALENCE REVIEW(S)

B96-131

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE : June 11, 1996

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch 6/11/96
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Alprazolam Tablets USP to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355(4)(B)(iv).

Geneva Pharmaceuticals, Inc. has submitted ANDA 74-909 for Alprazolam Tablets USP, 2 mg. The ANDA contains a certification pursuant to 21 USC 355(j)(2)(A)(vii)(iv) stating that a patent expiring October 29, 2008 will not be infringed by the manufacture or sale of the proposed product. In order to accept an ANDA for filing that contains such a patent certification, the Agency must formally make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the study submitted by Geneva on June 5, 1996 for its Alprazolam product satisfies the statutory requirements of "completeness" so that the ANDA may be filed and that a period of six months of market exclusivity can be granted to the applicant who submitted the first substantially complete ANDA under 21 USC 355(j)(4)(B)(iv).

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

---

DIVISION OF BIOEQUIVALENCE:

__✓__ Study meets statutory requirements /S/ [redacted] 6/13/96

_____ Study does **NOT** meet statutory requirements

Reason:

for [redacted]
Director, Division of Bioequivalence

6/17/96
Date

ANDA 74-909

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2655 W. Midway Blvd.
P.O. BOX 446
Broomfield CO 80038-0446

OCT -3 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Alprazolam Tablets USP, 2 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/ [redacted]

for Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

# OFFICE OF GENERIC DRUGS
# DIVISION OF BIOEQUIVALENCE

ANDA # 74-909 SPONSOR : Geneva Pharmaceuticals
DRUG & DOSAGE FORM : Alprazolam Tablets USP
STRENGTH (s) : 2 mg
TYPE OF STUDY: SD fasting
STUDY SITE: CLINICAL : (b)(4)(CC) ANALYTICAL : (b)(4)(CC)

STUDY SUMMARY :

| Parameter | test | ref | ratio | 90% CI (log). |
|---|---|---|---|---|
| Cmax(ng/ml) | 30.21 | 30.02 | 1.01 | 0.94;1.08 |
| AUC(0-T) ngxhr/ml | 435 | 441 | 0.99 | 0.94;1.04 |
| AUC(0-Inf) ngxhr/ml | 488.2 | 491.6 | 0.99 | 0.94;1.05 |
| Tmax hr | 1.23 | 1.28 | | |
| Half-life hr | 14.6 | 14.0 | | |

DISSOLUTION : USP method (Basket 100rpm, 500 mL pH 6.0 phosphate buffer)
Conditions

| Time(min) | Test Mean(range) | Ref. Mean(range) |
|---|---|---|
| 10 | 101 (b)(4)(CC) | 104 (b)(4)(CC) |
| 20 | 100 | 106 |
| 30 | 101 | 106 |
| 40 | 101 | 106 |

Q = NLT (b)(4)(C (Q) in 30 minutes

PRIMARY REVIEWER : Larry A. Ouderkirk BRANCH : 1

INITIAL : /S/ DATE : 3/5/98

Team Leader : Yih-Chain Huang BRANCH : 1

INITIAL : /S/ DATE : 3/5/98

DIRECTOR
DIVISION OF BIOEQUIVALENCE: Dale P. Conner

INITIAL : /S/ DATE : 3/5/98

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : _____ DATE : _____

SEP 30 1996

Alprazolam
Tablets, 2 mg
ANDA #74-909
Reviewer: L.A. Ouderkirk
WP #74909sd.596

Geneva Pharmaceuticals, Inc.
Broomfield, Colorado
Submission Date:
May 31, 1996
August 27, 1996

# Review of An In-Vivo Bioequivalence Study And Dissolution Data

## BACKGROUND:

Alprazolam is a triazolobenxodiazepine widely used in the treatment of generalized anxiety, panic disorder, societal phobia, and depression. It is an analog of the 1,4 benzodiazepine class of compounds acting on the central nervous system. The exact mechanism of action is unknown.

Peak plasma levels following oral dosing occur within one to two hours. Drug half-life has been found to average about 11 hours, but may vary considerably, even in healthy subjects. In diseased or geriatric subjects, the elimination half-life of the drug may double. The usual dosage for treatment of anxiety is 0.75 to 4.0 mg per day, whereas treatment of panic disorder may require that the subject be titrated to a dose of up to 10 mg per day.

Alprazolam is available as oral tablets in strengths of 2.0 mg, 1.0 mg, 0.5 mg, and 0.25 mg. The innovator product is Xanax® Tablets, marketed by The Upjohn Company.

## I. IN-VIVO BIOEQUIVALENCE STUDY #005-34-11034:

### A. STUDY INVESTIGATORS AND CONTRACT LABORATORY:

(b)(4)(CC)

### B. INFORMED CONSENT AND IRB APPROVAL:

Subjects gave written, informed consent before they were accepted into the study. The study protocol was reviewed and approved by an IRB before the study began.

### C. STUDY OBJECTIVE:

The objective of the study was to compare the bioavailability of Geneva's formulation of alprazolam tablets, 2 mg, with that of a marketed reference formulation, Xanax® Tablets, 2 mg , manufactured by The Upjohn Company.

**D. STUDY DESIGN:**

The study was designed as a random, two-period, two-treatment, two-sequence crossover. Twenty-six healthy male subjects were entered into the study.

**E. SUBJECT SELECTION CRITERIA:**

Subjects selected for the study met the following acceptance criteria:

1. Aged 18-60 years.
2. Healthy, as determined by physical examination, medical history and clinical laboratory diagnostic tests (blood chemistry, hematology, urinalysis).
3. No concurrent illness, acute or chronic diseases or history of asthma, serious cardiovascular, neurological, renal, G.I., hepatic, or hematopoietic disease. No history of alcohol or drug abuse or allergy to the drug under test or related compounds.
4. Acceptable electrocardiogram.
5. Weight within 15% of ideal for height (Metropolitan Life Insurance Company Bulletin, 1983).
6. Normal glucose 6-phosphate dehydrogenase (G6PD) levels.
7. Minimum blood pressure of 100/60 mm Hg.
8. Negative HIV 1, hepatitis B surface antigen, and urine drug screen within 30 days of the study.

**F. SUBJECT RESTRICTIONS:**

1. No alcohol consumption beginning 48 hours before dosing.
2. No Rx drugs beginning fourteen days or OTC drugs (excluding analgesics, vitamins, medicated lozenges, dietary supplements, and non-ingested medications) beginning seven days before the study.
3. No caffeine beginning 12 hours before dosing, each phase.
4. No smoking beginning 1 hour pre-dose until 4 hours post-dose.

**G. STUDY SCHEDULES:**

Subjects were housed in the clinic live-in facility for 12 hours before until 24 hours after drug administration. Subjects were fasted for ten hours overnight before dosing. The volunteers were randomly numbered and divided into two dosing groups of equal number. A 2 mg oral dose of the test or reference product was administered with 240 ml of water to each subject according to a randomization schedule. Subjects continued to fast until five hours post-dose, when a standard lunch was served. Water intake was unrestricted, except for one hour before and after drug administration, when no fluid was permitted other than that needed to administer the dosage form.

Venous blood samples (10 ml) were drawn pre-dose (0 hours) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16,

24, 36, and 48 hours post-dose. The serum was separated by refrigerated centrifugation and was stored frozen at -20°C pending assay. Standardized meals were served at regularly scheduled intervals and the same menus were used during both study phases. Subjects were prohibited from smoking beginning one hour before dosing until four hours after. A one-week washout period was observed between Phase 1 and 2 dosing.

Blood pressure and pulse measurements were obtained predose, and at 2, 4, 6, and 24 hours postdose.

**H. DRUG TREATMENTS:**

1. **Test Product A:** Alprazolam Tablets, 2 mg; (Geneva Pharmaceuticals, Inc.); Lot #6495094, Assayed Potency = 101% , Batch Net Yield = (b)(4)(CC) tablets; Manf. Date = 12/1/95, Exp. Date = 12/97

2. **Reference Product B:** Xanax® Tablets, 2 mg, (The Upjohn Company); Lot #235JT, Assayed Potency = 105.2%, Exp. Date = 8/00

**I. ANALYTICAL:**

(b)(4)(CC)

**K. STATISTICAL ANALYSIS:**

The study data were analyzed by ANOVA and the F-test to determine statistically significant ($p \leq 0.05$) differences between treatments, dosing sequences, subjects within sequence, and study phase for areas under the curve (AUCT, AUCI), maximum serum drug concentration (Cmax), time to maximum drug concentration (Tmax), elimination rate constants (KE) and half-life values ($T_{1/2}$). The KE was estimated by linear least squares fitting of the logarithms of the last five concentrations versus time. The arithmetic mean and

standard deviation were calculated for each of these parameters and for the alprazolam concentrations at each time point. The geometric means were also calculated for AUCT, AUCI, Cmax, and Cmax/AUCI. The power of the study to detect a 20% difference in parameters as statistically significant and the 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means and the standard error of the difference in formulations from the ANOVA. ANOVA was performed for subject serum drug concentrations at each sampling time and included all sums of squares (Types I-IV). The ESTIMATE option of SAS GLM was used to generate linear estimates of adjusted treatment mean differences.

## L. CLINICAL NOTES:

Study Phase 1 and 2 dosing was conducted on February 10, 1996 and February 17, 1996, respectively. Of the 26 subjects who began the study, 25 completed both Phases. The 25 male subjects completing the study consisted of 13 Caucasians, 11 Blacks, and 1 Asian. All were between the ages of 19 and 49. Fourteen of the 25 subjects were smokers. Subject #25 (Black, non-smoker) experienced flu-like symptoms before the start of Period 2 and withdrew prior to Period 2 dosing.

A total of 61 adverse medical events (**Table 3**) were experienced by 26 subjects during the study. Feelings of sleepiness, sluggishness or relaxation were the most frequently reported events (50 events). Of the events reported, 47 were judged to be probably related to the study medications and 14 were judged possibly related. All of the events were mild or moderate in intensity. Both products appeared to be equally well tolerated.

Samples obtained at times that deviated significantly from the scheduled time were reported. A significant deviation was defined as being greater than 5% for blood samples collected up to 10 hours and greater than 30 minutes for samples obtained thereafter (SOP #(b)(4)(CC) . There was only one deviation meeting this definition - the 48 hour sample for subject #10 in study phase 2 was obtained 1 hour 54 minutes late. The AUCT was calculated using the actual time to determine whether it would differ appreciably from the AUCT calculated using the scheduled time. Since the difference was only 1.6%, the scheduled phlebotomy time was used to calculate the AUC.

Interphase use of alcohol by 8 subjects was reported. All events occurred at least 48 hours after the first dosing and at least 48 hours before the second dosing. There were no reports of interphase medication use.

## M. ANALYTICAL NOTES:

Of the 899 samples assayed for this study, 29 (3.22%) were re-assayed. **Table 4** lists these samples, the original concentration, the re-assayed concentration, and the reported concentration, along with the reason for the reported concentration.

## N. RESULTS OF BIOEQUIVALENCE STUDY:

All serum samples from the 25 subjects who completed the study were assayed and the data obtained were statistically analyzed.

The mean serum concentration-versus-time data for the test and reference products are summarized as mean ± standard deviation in **Table 5** and represented graphically in **Figure 1**. There were no significant ($\alpha$=0.05) differences in mean concentrations between the formulations at any time after dosing. The blood sampling schedule proved suitable for this bioequivalence study. The AUCT/AUCI ratio was >0.8 for 46 of 50 estimates of AUCI obtained. The first measurable post-dose sample did not represent the Cmax for any dose. Four post-dose samples were obtained before the average time of the maximum concentration.

Summaries of the arithmethic mean and least-squares means study results for pharmacokinetic parameters are summarized in **Tables 6 and 7**, respectively. Based on the least squares means of the logarithmically-transformed parameters, the AUCT and AUCI for the test product were 2% and 1% lower, respectively, than were those for the reference product. The CMAX for the test product was 1% higher than that for the reference product and occurred 4% earlier (3 minutes). Based on the logarithmic transformation, the 90% confidence intervals about the ratios of test/reference means for AUCT and AUCI were within the 0.80 - 1.25 limit when the Geneva product was compared to the Upjohn product (AUCT [0.94-1.04], AUCI [0.94-1.05], and CMAX [0.94-1.08]).

There was no statistically significant sequence effect ($\alpha$=0.10) for any analysis of AUC and CMAX.

## II. IN-VITRO DISSOLUTION TESTING RESULTS:

The firm conducted dissolution testing on its 2 mg strength test product versus the reference Xanax® Tablets, 2 mg, manufactured by Upjohn. The results of the dissolution testing and the method used are given in **Table 8**.

## III. PRODUCT FORMULATION:

The formulation of the product, as supplied by the manufacturer, is given in **Table 9**.

## COMMENTS:

1. The elimination half-life of alprazolam averaged approximately 14 hours and ranged from about 8-22 hours. In light of this, it is recommended that in any future studies conducted on this drug, the firm should extend the subject blood collection period to 72 hours, as recommended in the Alprazolam Tablets Guidance (issued 11/27/92).

2. The firm has prohibited the subjects from smoking

beginning one hour before dosing until four hours after. It is the general policy of the Division of Bioequivalence that use of tobacco products should be prohibited beginning at the time of subject confinement (usually 10-12 hours pre-dose) until the end of the study period. Any future deviation from this policy will require advance approval by the Division.

3. The firm has prohibited the subjects from ingesting OTC medications for seven days before the studies begin, with the exception of OTC analgesics, vitamins, medicated lozenges, dietary supplements, and non-ingested medications. The Division of Bioequivalence recommends that the subjects be prohibited from using any OTC medication for seven days before the study, with the exception of non-ingested, non-absorbed products.

**RECOMMENDATIONS:**

1. The in vivo bioequivalence study #005-34-11034, conducted by Geneva Pharmaceuticals, Inc., on its Alprazolam Tablets, 2 mg, lot #6495094, versus the listed reference product, Xanax® Tablets, 2 mg, Lot #235JT, manufactured by The Upjohn Company, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Geneva's Alprazolam Tablets, 2 mg, are bioequivalent to the listed reference product, Xanax® Tablets, 2 mg, manufactured by The Upjohn Company.

2. The dissolution testing conducted by the firm on its Alprazolam Tablets, 2 mg, versus the reference Xanax® Tablets, 2 mg, is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 ml pH 6.0 phosphate buffer at 37C (made per USP 23 alprazolam tablet monograph) using USP 23 apparatus 1 (basket) at 100 rpm. The test products should meet the following tolerance:

Not less than (b)(4)((Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

3. From the Bioequivalence viewpoint, the firm has met the in-vivo bioequivalence and in-vitro dissolution requirements, and the ANDA #74-909 is acceptable.

The firm should be informed of the Comments and Recommendations, above.

/S/ [redacted]

9-27-96

Larry A. Ouderkirk
Division of Bioequivalence
Review Branch 1

RD INITIALED YCHuang /S/ [redacted]
FT INITIALED YCHuang

Date: 9/27/96

/S/ [redacted]

Concur:

Date: 9/30/96

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 74-909 (original, duplicate), Ouderkirk, HFD-652 (Huang), Drug File, Division File

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**TABLE 3 - ADVERSE EVENTS**
**ALPRAZOLAM TABLETS, 2 MG**
**STUDY #005-34-11034**

| SUBJ# | DATE | TIME | EVENT | SEVERITY [1] | RESOLUTION | RELATIONSHIP TO DRUG[2] | RX | PRODUCT UNDER STUDY[3] |
|---|---|---|---|---|---|---|---|---|
| 1 | 02/10/96 | 0820 | SLEEPY | 1 | 02/10/96 0915 | 3 | MONITOR | B |
| | 02/17/96 | 0904 | SLEEPY | 1 | 02/17/96 1345 | 3 | MONITOR | A |
| 2 | 02/10/96 | 0815 | SLEEPY | 1 | 02/10/96 1800 | 3 | MONITOR | A |
| | 02/17/96 | 0904 | SLEEPY | 1 | 02/17/96 1800 | 3 | MONITOR | B |
| 3 | 02/10/96 | 0816 | SLEEPY | 1 | 02/10/96 1800 | 3 | MONITOR | A |
| | 02/17/96 | 0906 | SLEEPY | 1 | 02/17/96 1143 | 3 | MONITOR | B |
| 4 | 02/10/96 | 0820 | SLEEPY | 1 | 02/10/96 1315 | 3 | MONITOR | B |
| | 02/17/96 | 0636 | INCREASED BP (DIASTOLIC) | 1 | 02/17/96 0951 | 2 | MONITOR | B |
| | 02/17/96 | 0905 | SLEEPY | 1 | 02/17/96 0947 | 3 | MONITOR | A |
| 5 | 02/10/96 | 0835 | SLEEPY | 1 | 02/10/96 1320 | 3 | MONITOR | A |
| | 02/17/96 | 0905 | SLEEPY | 1 | 02/17/96 1600 | 3 | MONITOR | B |
| 6 | 02/10/96 | 0840 | SLEEPY | 1 | 02/10/96 1602 | 3 | MONITOR | B |
| | 02/17/96 | 0640 | INCREASED BP (DIASTOLIC) | 1 | 02/17/96 0957 | 2 | MONITOR | B |
| | 02/17/96 | 0905 | SLEEPY | 1 | 02/18/96 0900 | 3 | MONITOR | A |
| 7 | 02/10/96 | 0842 | SLEEPY | 1 | 02/10/96 1800 | 3 | MONITOR | B |
| | 02/17/96 | 0905 | SLEEPY | 1 | 02/17/96 1401 | 3 | MONITOR | A |
| 8 | 02/10/96 | 0840 | SLEEPY | 1 | 02/10/96 1110 | 3 | MONITOR | A |
| | 02/17/96 | 0905 | SLEEPY | 1 | 02/17/96 1254 | 3 | MONITOR | B |

UNK. = UNKNOWN
[1] 1=MILD 2=MODERATE 3=SEVERE
[2] 1=NONE 2=POSSIBLE 3=PROBABLE
[3] A=TEST PRODUCT B=REFERENCE PRODUCT

**TABLE 3 [CON'T]- ADVERSE EVENTS**
**ALPRAZOLAM TABLETS, 2 MG**
**STUDY #005-34-11034**

| SUBJ# | DATE | TIME | EVENT | SEVERITY [1] | RESOLUTION | RELATIONSHIP TO DRUG[2] | RX | PRODUCT UNDER STUDY[3] |
|---|---|---|---|---|---|---|---|---|
| 9 | 02/10/96 | 0845 | SLEEPY | 1 | 02/10/96 1200 | 3 | MONITOR | B |
| | 02/17/96 | 0906 | SLEEPY | 1 | 02/17/96 1800 | 3 | MONITOR | A |
| 10 | 02/10/96 | 0845 | SLEEPY | 1 | 02/10/96 1340 | 3 | MONITOR | A |
| | 02/17/96 | 0900 | SLEEPY | 1 | 02/17/96 2000 | 3 | MONITOR | B |
| 11 | 02/10/96 | 0900 | SLUGGISH | 1 | 02/10/96 1604 | 2 | MONITOR | B |
| | 02/17/96 | 0910 | SLUGGISH | 1 | 02/17/96 1800 | 2 | MONITOR | A |
| 12 | 02/10/96 | 0847 | SLEEPY | 1 | 02/10/96 2000 | 3 | MONITOR | A |
| | 02/17/96 | 0913 | SLEEPY | 1 | 02/17/96 1600 | 3 | MONITOR | B |
| 13 | 02/10/96 | 0848 | SLEEPY | 1 | 02/10/96 1602 | 3 | MONITOR | A |
| | 02/17/96 | 0914 | SLEEPY | 1 | 02/17/96 1400 | 3 | MONITOR | B |
| 14 | 02/10/96 | 0908 | SLEEPY | 1 | 02/10/96 1600 | 3 | MONITOR | B |
| | 02/17/96 | 0906 | SLEEPY | 1 | 02/17/96 1415 | 3 | MONITOR | A |
| 15 | 02/10/96 | 0932 | SLEEPY | 1 | 02/10/96 1345 | 3 | MONITOR | A |
| | 02/17/96 | 0906 | SLEEPY | 1 | 02/17/96 1345 | 3 | MONITOR | B |
| 16 | 02/10/96 | 0900 | SLEEPY | 1 | 02/10/96 1330 | 3 | MONITOR | B |
| | 02/17/96 | 0907 | SLEEPY | 1 | 02/17/96 1400 | 3 | MONITOR | A |

UNK. = UNKNOWN
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[2] 1=NONE 2=POSSIBLE 3=PROBABLE
[3] A=TEST PRODUCT B=REFERENCE PRODUCT

**TABLE 3 [CON'T]- ADVERSE EVENTS**
**ALPRAZOLAM TABLETS, 2 MG**
**STUDY #005-34-11034**

| SUBJ# | DATE | TIME | EVENT | SEVERITY [1] | RESOLUTION | RELATIONSHIP TO DRUG[2] | RX | PRODUCT UNDER STUDY[3] |
|---|---|---|---|---|---|---|---|---|
| 17 | 02/10/96 | 0900 | SLEEPY | 1 | 02/10/96 2000 | 3 | MONITOR | B |
| | 02/10/96 | 0900 | LIGHTHEADED | 1 | 02/10/96 0930 | 2 | MONITOR | B |
| | 02/17/96 | 0907 | SLEEPY | 1 | 02/18/96 0100 | 3 | MONITOR | A |
| 18 | 02/10/96 | 0900 | SLEEPY | 1 | 02/10/96 1700 | 3 | MONITOR | A |
| | 02/17/96 | 0907 | SLEEPY | 1 | 02/17/96 2100 | 3 | MONITOR | B |
| 19 | 02/10/96 | 0915 | SLEEPY | 1 | 02/10/96 1200 | 3 | MONITOR | A |
| | 02/17/96 | 0915 | SLEEPY | 1 | 02/17/96 1330 | 3 | MONITOR | B |
| 20 | 02/10/96 | 0910 | LIGHTHEADED | 1 | 02/10/96 0930 | 2 | MONITOR | B |
| | 02/17/96 | 0915 | SLEEPY | 1 | 02/17/96 1204 | 3 | MONITOR | A |
| 21 | 02/10/96 | 0911 | SLEEPY | 1 | 02/10/96 1340 | 3 | MONITOR | B |
| | 02/17/96 | 0915 | SLEEPY | 1 | 02/17/96 1800 | 3 | MONITOR | A |
| * | 02/18/96 | UNK. | RASH ON CHEST | 1 | UNKNOWN | 2 | NONE | A |
| 22 | 02/10/96 | 0911 | SLEEPY | 1 | 02/10/96 1700 | 3 | MONITOR | A |
| | 02/17/96 | 0910 | RELAXED | 1 | 02/17/96 1205 | 2 | MONITOR | B |
| 23 | 02/10/96 | 0912 | SLEEPY | 1 | 02/10/96 1350 | 3 | MONITOR | A |
| | 02/17/96 | 0916 | SLEEPY | 1 | 02/17/96 1800 | 3 | MONITOR | B |
| | 02/17/96 | 1450 | OCCIPITAL HEADACHE | 1 | 02/17/96 2300 | 2 | MONITOR | B |

* - At the 48 hour return blood draw, subject informed staff that he developed a rash on his chest after discharge of Period I and Period II. Subject was advised to be evaluated by the physician, however, there is no documentation indicating the subject was seen or evaluated. Attempts to contact the subject are continuing.

UNK. = UNKNOWN
[1] 1=MILD 2=MODERATE 3=SEVERE
[2] 1=NONE 2=POSSIBLE 3=PROBABLE
[3] A=TEST PRODUCT B=REFERENCE PRODUCT

**TABLE 3 [CON'T]- ADVERSE EVENTS**
**ALPRAZOLAM TABLETS, 2 MG**
**STUDY #005-34-11034**

| SUBJ# | DATE | TIME | EVENT | SEVERITY [1] | RESOLUTION | RELATIONSHIP TO DRUG[2] | RX | PRODUCT UNDER STUDY[3] |
|---|---|---|---|---|---|---|---|---|
| 24 | 02/10/96 | 0910 | SLEEPY | 1 | 02/10/96 1600 | 3 | MONITOR | B |
| | 02/16/96 | 2040 | BILATERAL ARM RASH | 1 | 03/29/96 UNK. | 2 | MONITOR | B |
| | 02/17/96 | 0910 | SLEEPY | 1 | 02/17/96 1800 | 3 | MONITOR | A |
| | 02/17/96 | 1254 | LIGHTHEADED | 1 | 02/17/96 1302 | 2 | MONITOR | A |
| 25 | 02/10/96 | 0927 | SLEEPY | 1 | 02/10/96 2300 | 3 | MONITOR | A |
| | 02/16/96 | 0545 | SORE THROAT | 1 | 02/23/96 AM | 2 | NONE | A |
| | 02/16/96 | 0545 | FLU SYMPTOMS | 1 | 02/23/96 AM | 2 | NONE | A |
| 26 | 02/10/96 | 0929 | SLEEPY | 1 | 02/10/96 1414 | 3 | MONITOR | B |
| | 02/10/96 | 1255 | LIGHTHEADED, FAINTED | 2 | 02/10/96 1257 | 2 | MONITOR/$H_2O$/ SUPINE W/ FEET ELEVATED | B |
| | 02/17/96 | 0917 | SLEEPY | 1 | 02/17/96 1414 | 3 | MONITOR | A |

UNK. = UNKNOWN
[1] 1=MILD 2=MODERATE 3=SEVERE
[2] 1=NONE 2=POSSIBLE 3=PROBABLE
[3] A=TEST PRODUCT B=REFERENCE PRODUCT

# Table 4 - Reassay Samples

| Subj. | Per. | Time No.[1] | Reason for Reassay | Initial Value | Repeat Value(s) | Value Used | Comments[2] |
|---|---|---|---|---|---|---|---|
| 1 | 2 | 12 | INTERFERENCE | -- | 13.745 | 13.745 | B |
| 1 | 2 | 14 | INTERFERENCE | -- | 9.086 | 9.086 | B |
| 2 | 2 | 14 | INTERFERENCE | -- | 8.070 | 8.070 | B |
| 3 | 2 | 9 | INTERFERENCE | -- | 19.765 | 19.765 | B |
| 3 | 2 | 13 | INTERFERENCE | -- | 9.882 | 9.882 | B |
| 4 | 1 | 0 | CONFIRM INTERFERENCE | 0.000 | 0.000 | 0.000 | E1 |
| 4 | 1 | 2 | CONFIRM INTERFERENCE | 23.807 | 25.162 | 23.807 | E1 |
| 4 | 1 | 4 | CONFIRM INTERFERENCE | 25.666 | 27.444 | 25.666 | E1 |
| 4 | 1 | 6 | CONFIRM INTERFERENCE | 25.725 | 27.936 | 25.725 | E1 |
| 4 | 2 | 15 | INTERFERENCE | -- | 8.422 | 8.422 | B |
| 6 | 1 | 0 | CONFIRM PEAK IN 0 HR | 0.000 | 0.000 | 0.000 | E2 |
| 6 | 2 | 0 | CONFIRM PEAK IN 0 HR | 0.000 | 0.000 | 0.000 | E2 |
| 7 | 1 | 0 | CONFIRM PEAK IN 0 HR | 2.016 | 0.000 | 0.000 | E2 |
| 7 | 2 | 0 | CONFIRM PEAK IN 0 HR | 1.091 | 0.000 | 0.000 | E2 |
| 8 | 1 | 1 | INTERFERENCE | -- | 1.651 | 1.651 | B |
| 8 | 1 | 11 | INTERFERENCE | -- | 12.682 | 12.682 | B |
| 8 | 2 | 17 | INTERFERENCE | -- | 1.006 | 1.006 | B |
| 9 | 1 | 13 | INTERFERENCE | -- | 11.884 | 11.884 | B |
| 9 | 2 | 16 | INTERFERENCE | -- | 3.017 | 3.017 | B |
| 11 | 1 | 2 | PK ANOMALY | 17.394 | 16.860 | 16.933 | A |
| 11 | 1 | 2 | PK ANOMALY | 17.394 | 16.933 | 16.933 | A |
| 14 | 1 | 2 | PK ANOMALY | 34.913 | 32.732 | 32.929 | A |
| 14 | 1 | 2 | PK ANOMALY | 34.913 | 32.929 | 32.929 | A |
| 16 | 1 | 16 | INTERFERENCE | -- | -- | -- | E3 |
| 16 | 2 | 16 | INTERFERENCE | -- | -- | -- | E3 |
| 16 | 2 | 17 | INTERFERENCE | -- | -- | -- | E3 |
| 17 | 1 | 13 | INTERFERENCE | -- | 16.519 | 16.519 | B |
| 17 | 2 | 15 | INTERFERENCE | -- | 6.781 | 6.781 | B |
| 23 | 1 | 11 | INTERFERENCE | -- | 16.803 | 16.803 | B |
| 23 | 1 | 12 | INTERFERENCE | -- | 14.469 | 14.469 | B |
| 24 | 2 | 16 | INTERFERENCE | -- | 1.979 | 1.979 | B |

1 Sampling Times Numbered Consecutively (0=0 Hours, 1=0.25 Hours, 2=0.5 Hours, etc.)

2 A - Median Value
B - First Analytically Valid Concentration
E1 - Interference Confirmed, Original Value Reported
E2 - Peak Not Present, Reassay Value Reported
E3 - No Analytically Valid Value

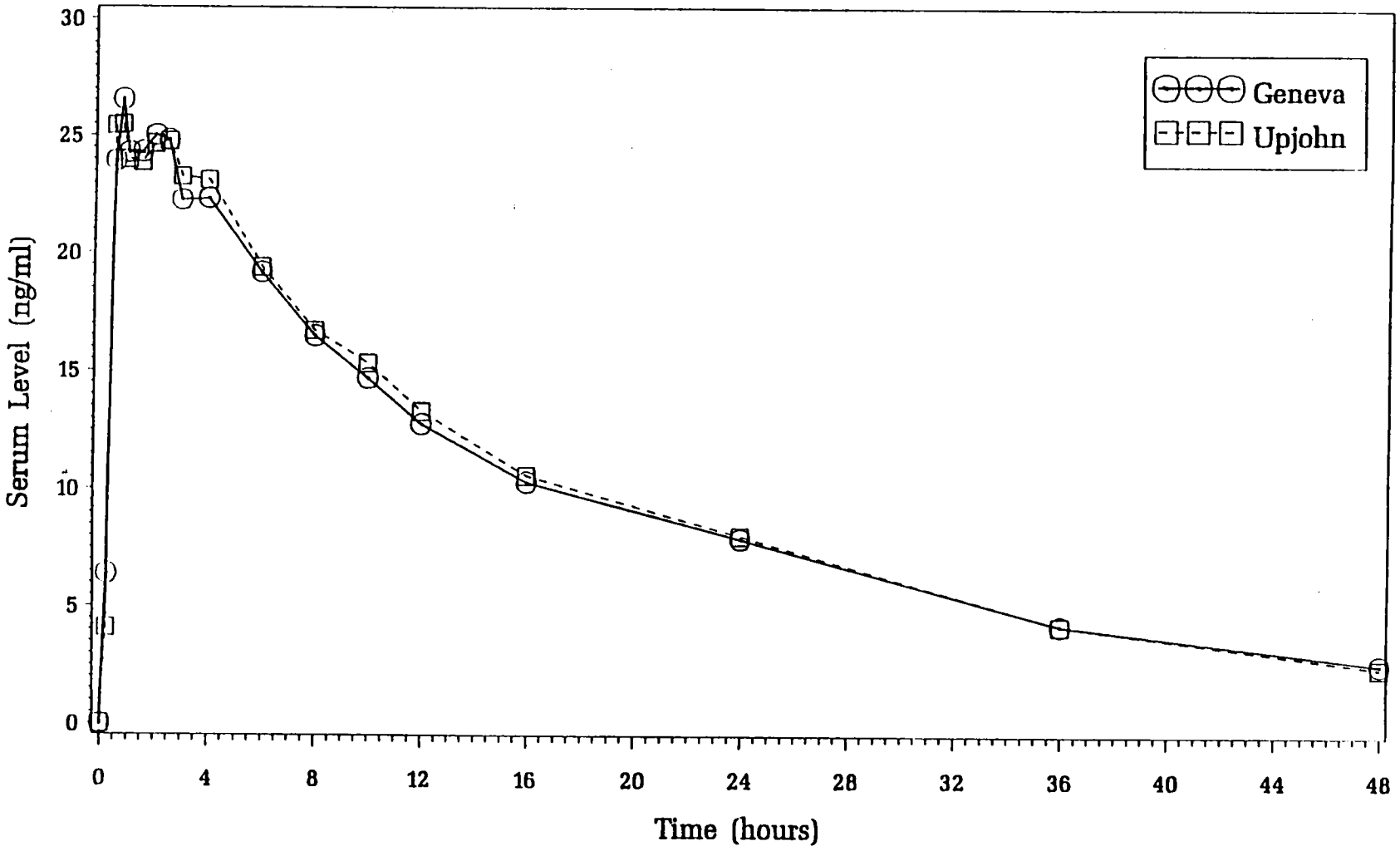
TABLE 5 - ALPRAZOLAM SERUM CONCENTRATIONS (ng/ml)
ARITHMETIC MEANS ± STANDARD DEVIATION (N = 25)
STUDY #005-34-11034

| Time (Hours) | Geneva Test Product | Upjohn Reference Product | Ratio Test/Ref. | Signif. |
|---|---|---|---|---|
| 0 | 0.0000 | 0.0000 | -- | -- |
| 0.25 | 6.374 ± 8.467 | 4.087 ± 5.415 | 1.56 | N.S. |
| 0.5 | 23.92 ± 14.19 | 25.42 ± 13.22 | 0.94 | N.S. |
| 0.75 | 26.53 ± 9.167 | 25.47 ± 10.12 | 1.04 | N.S. |
| 1 | 24.28 ± 7.244 | 23.98 ± 7.384 | 1.01 | N.S. |
| 1.5 | 24.30 ± 6.172 | 23.86 ± 6.066 | 1.02 | N.S. |
| 2 | 25.01 ± 5.658 | 24.65 ± 4.540 | 1.01 | N.S. |
| 2.5 | 24.80 ± 5.041 | 24.76 ± 4.418 | 1.00 | N.S. |
| 3 | 22.25 ± 5.030 | 23.26 ± 3.691 | 0.96 | N.S. |
| 4 | 22.31 ± 4.170 | 23.12 ± 3.510 | 0.96 | N.S. |
| 6 | 19.16 ± 4.006 | 19.39 ± 3.414 | 0.99 | N.S. |
| 8 | 16.48 ± 3.778 | 16.71 ± 3.304 | 0.99 | N.S. |
| 10 | 14.68 ± 3.289 | 15.32 ± 3.486 | 0.96 | N.S. |
| 12 | 12.74 ± 3.518 | 13.28 ± 3.269 | 0.96 | N.S. |
| 16 | 10.30 ± 2.959 | 10.57 ± 2.738 | 0.98 | N.S. |
| 24 | 7.891 ± 3.198 | 8.013 ± 3.134 | 0.98 | N.S. |
| 36 | 4.213 ± 2.248 | 4.197 ± 2.164 | 1.00 | N.S. |
| 48 | 2.564 ± 1.+710 | 2.411 ± 1.663 | 1.06 | N.S. |

Figure 1: Mean Alprazolam Serum Levels

#005 – 11034

N = 25




15A

**TABLE 6: PHARMACOKINETIC PARAMETERS FOR SERUM ALPRAZOLAM**
**ARITHMETIC MEANS ± STANDARD DEVIATION (N = 25)**
**STUDY #005-34-11034**

| Parameter | Test: Geneva N | Mean ± SD | (CV) | Reference: Upjohn N | Mean ± SD | (CV) | Ratio T/R |
|---|---|---|---|---|---|---|---|
| AUC 0-T (ng $ml^{-1}hr$) | 25 | 452.7 ± 137.4 | 30.3 | 25 | 458.2 ± 129.3 | 28.2 | 0.99 |
| Ln AUC 0-T (Geometric Mean) | 25 | 6.0728 ± 0.2953 (433.9) | | 25 | 6.0900 ± 0.2777 (441.4) | | 0.98 |
| AUC 0-Inf (ng $ml^{-1}hr$) | 25 | 516.2 ± 188.7 | 36.6 | 25 | 518.5 ± 174.0 | 33.6 | 1.00 |
| Ln AUC 0-Inf (Geometric Mean) | 25 | 6.1879 ± 0.3421 (486.8) | | 25 | 6.1989 ± 0.3268 (492.2) | | 0.99 |
| Cmax (ng/ml) | 25 | 31.26 ± 7.933 | 25.4 | 25 | 31.03 ± 8.081 | 26.0 | 1.01 |
| Ln Cmax (Geometric Mean) | 25 | 3.4091 ± 0.2675 (30.24) | | 25 | 3.4021 ± 0.2629 (30.03) | | 1.01 |
| Tmax (hr) | 25 | 1.230 ± 0.9268 | 75.3 | 25 | 1.290 ± 0.9887 | 76.6 | 0.95 |
| Rate Constant (hr) | 25 | 0.05100 ± 0.01358 | 26.6 | 25 | 0.05346 ± 0.01495 | 28.0 | 0.95 |
| Half-Life (hr) | 25 | 14.60 ± 4.063 | 27.8 | 25 | 14.03 ± 4.082 | 29.1 | 1.04 |
| Cmax/AUCinf ($hr^{-1}$) | 25 | 0.06550 ± 0.02421 | 37.0 | 25 | 0.06348 ± 0.01954 | 30.8 | 1.03 |
| Ln (Cmax/AUCinf) (Geometric Mean) | 25 | -2.7788 ± 0.3190 (0.06211) | | 25 | -2.7968 ± 0.2794 (0.06100) | | 1.02 |

TABLE 7: PHARMACOKINETIC PARAMETERS FOR SERUM ALPRAZOLAM
LEAST SQUARES MEANS ± STANDARD ERROR (N = 25)
#005-34-11034

| Study Parameter | Test Geneva | Reference Upjohn | Ratio T/R | Signif. | Power | C.V. (%) | 90% CI |
|---|---|---|---|---|---|---|---|
| AUC 0-T ($ng\ ml^{-1}hr$) | 453.9 ± 9.210 | 457.8 ± 9.210 | 0.99 | N.S. | >0.99 | 10.1 | 0.94; 1.04 |
| Ln AUC 0-T (Antiln) | 6.0752 ± 0.0206 (435.0) | 6.0891 ± 0.0206 (441.0) | 0.99 | N.S. | >0.99 | 10.3 | 0.94; 1.04 |
| AUC 0-I ($ng\ ml^{-1}hr$) | 517.9 ± 11.39 | 518.0 ± 11.39 | 1.00 | N.S. | >0.99 | 11.0 | 0.95; 1.05 |
| Ln AUC 0-Inf (Antiln) | 6.1907 ± 0.0219 (488.2) | 6.1977 ± 0.0219 (491.6) | 0.99 | N.S. | >0.99 | 11.0 | 0.94; 1.05 |
| Cmax (ng/ml) | 31.22 ± 0.8905 | 31.02 ± 0.8905 | 1.01 | N.S. | >0.99 | 14.3 | 0.94; 1.08 |
| Ln Cmax (Antiln) | 3.4082 ± 0.0292 (30.21) | 3.4017 ± 0.0292 (30.02) | 1.01 | N.S. | 0.99 | 14.7 | 0.94; 1.08 |
| Tmax (hr) | 1.232 ± 0.1225 | 1.280 ± 0.1225 | 0.96 | N.S. | <0.50 | 47.8 | 0.73; 1.19 |
| KEL (hr) | 0.05092 ± 0.00091 | 0.05346 ± 0.000 | 0.95 | N.S. | >0.99 | 8.5 | 0.91; 0.99 |
| T1/2 (hr) | 14.63 ± 0.1918 | 14.04 ± 0.1918 | 1.04 | p=0.0386 | >0.99 | 6.8 | 1.01; 1.08 |
| Cmax/AUCinf ($hr^{-1}$) | 0.06523 ± 0.00299 | 0.06356 ± 0.00299 | 1.03 | N.S. | 0.82 | 23.5 | 0.91; 1.14 |
| Ln (Cmax/AUCinf) (Antiln) | -2.7825 ± 0.0346 (0.06188) | -2.7959 ± 0.0346 (0.06106) | 1.01 | N.S. | 0.97 | 17.4 | 0.93; 1.10 |

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

## Table 8 - In Vitro Dissolution Testing

Drug (Generic Name): Alprazolam Tablets
Dose Strength: 2 mg
ANDA No.: 74-909
Firm: Geneva Pharmaceuticals, Inc.
Submission Date: May 31, 1996
File Name: 74909sd.596

### I. Conditions for Dissolution Testing:

USP 23 Apparatus: Basket
RPM: 100
No. Units Tested: 12
Medium: pH 6.0 Phosphate Buffer (Prepared per USP 23 Monograph)
Volume: 500 mL
Specifications: NLT [redacted](Q) in 30 minutes
Reference Drug: Xanax® Tablets, Upjohn
Assay Methodology: [redacted](b)(4)

### II. Results of In Vitro Dissolution Testing:

| Sampling Times (Minutes) | Test Product Lot #6495094 Strength: 2.0 mg | | | Reference Product Lot #235JT Strength: 2.0 mg | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 10 | 101 | [redacted](b)(4)(CC) | 2.2 | 104 | [redacted](b)(4)(CC) | 0.9 |
| 20 | 100 | | 2.1 | 106 | | 0.7 |
| 30 | 101 | | 2.3 | 106 | | 0.6 |
| 40 | 101 | | 2.3 | 106 | | 0.8 |
| Cont. Unif. | Ave. (N=10) = 101.0%, CV=0.2% | | | Ave. (N=10) = 105.9%, CV=0.9% | | |

## TABLE 9

## QUANTITATIVE FORMULATION OF ALPRAZOLAM TABLET, 2.0 MG

| INGREDIENT | MG/TABLET |
|---|---|
| ALPRAZOLAM USP | 2.000 |
| DOCUSATE SODIUM USP | (b)(4)(TS) |
| SODIUM BENZOATE NF | |
| LACTOSE NF | |
| FD&C BLUE #2 ALUMINUM LAKE | |
| FD&C YELLOW #6 ALUMINUM LAKE | |
| MICROCRYSTALLINE CELLULOSE NF | |
| PREGELATINIZED STARCH NF | |
| SD-3A ALCOHOL | |
| MAGNESIUM STEARATE NF | |
| TOTAL TABLET WEIGHT | 260.000 |

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 74909

## ADMINISTRATIVE DOCUMENTS

# ANDA APPROVAL SUMMARY

| ANDA: | CHEMIST: | DATE: |
|---|---|---|
| 74-909 | Naiqi Ya, Ph.D. | February 25, 1998 |

**DRUG PRODUCT:**
Alprazolam Tablets USP

**FIRM:**
Geneva Pharmaceuticals, Inc.

| DOSAGE FORM: | STRENGTH: |
|---|---|
| Tablets | 2 mg |

**cGMP:**
EER was found acceptable on Febraury 19, 1998.

**BIO:**
Reviewed by L. Ouderkirk and found acceptable on September 30, 1996.

**VALIDATION - *(Description of dosage form same as firm's):***
Not required because of a compendial drug.

**STABILITY:**
The containers in the stability studies are identical to those in the container section.

**LABELING:**
Container, carton, and insert labeling were approved by L. Golson on October 22, 1997.

**STERILIZATION VALIDATION *(If applicable)*:**
Not applicable.

**SIZE OF BIO BATCH *(Firm's source of NDS ok?)*:**
It was used for bio studies. This batch (6495094) record was included.

**SIZE OF STABILITY BATCHES *(If different from bio batch, were they Manufactured via the same process?)*:**
The exhibit batch size was (b)(4)(CC) tablets. The tablet weight is 260 mg.

**PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:**
The proposed production batches is (b)(4)(CC) tablets. The manufacturing processes and size are identical to the exhibit batches.

| Signature of chemist: | Signature of supervisor: |
|---|---|
| /S/ [redacted] 2/25/98 | /S/ [redacted] 2/26/98 |

X:\NEW\FIRMSAM\GENEVA\LTRS&REV\74909SU[redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74909

CORRESPONDENCE

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400

FEDERAL EXPRESS

FEB 19 1998

**MINOR AMENDMENT**

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

**ORIG AMENDMENT**
NC

RE: ANDA #74-909 Alprazolam Tablets USP, 2 mg
Amendment - Chemistry

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application ANDA #74-909 Alprazolam Tablets USP, 2 mg in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96 (a).

Reference is made to your communication of November 4, 1997

We would like to inform you that the Denver District completed the inspection of our manufacturing site on February 9, 1998 and based on discussions at the wrap up meeting the Denver District will be recommending approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan

Beth Brannan, Director
Drug Regulatory Affairs

BB/kak

**RECEIVED**
FEB 20 1998
**GENERIC DRUGS**

2-24-98

GP™

GP097

Geneva pharmaceuticals, Inc.
2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446
(303) 466-2400

/s/ [redacted]

FEDERAL EXPRESS

May 31, 1996

Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855



RE: Alprazolam Tablets USP, 2 mg

Dear Sir:

Geneva Pharmaceuticals, Inc. is hereby submitting an Abbreviated New Drug Application for Alprazolam Tablets USP, 2 mg as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.92 and 314.94.

A comprehensive table of contents is provided which shows the volume and page number of our submission's contents, as required by the regulations Part 314.94(a)(1).

The blue archival copy (6 volumes) contains the complete application (Chemistry, Labeling, Manufacturing, and Controls). The Methods Validation packet is also provided in a blue archival binder.

The red chemistry section copy (2 volumes) contains the complete application (Chemistry, Labeling, Manufacturing, and Controls). The orange pharmacokinetic section copy (3 volumes) contains bioequivalence information. A bioequivalence study has been completed comparing Geneva's, Alprazolam Tablets USP, 2 mg to Xanax® Tablets, 2 mg.

This information is submitted for your review and approval.

als, Inc.
2 mg

Please acknowledge receipt of this document by signing and dating t
cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan

Beth Brannan, Director
Drug Regulatory Affairs

Enclosures

BB/slc

NDA ORIG AMENDMENT

Geneva
pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400

**FEDERAL EXPRESS**

**MAJOR AMENDMENT**

MAY 16 1997

N/AC

Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North, Room 150
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 74-909 Alprazolam Tablets USP, 2 mg
Major Amendment - Chemistry, Labeling and Manufacturing Controls

Dear Director:

We are submitting an amendment to our unapproved Abbreviated New Drug Application for Alprazolam Tablets USP, 2 mg in accordance with Section 505(j) of the Food, Drug and Cosmetic Act and with 21 CFR 314.96(a).

Reference is made to your written communication of November 8, 1996. Response to your comments is provided in order of appearance in your communication.

**A. Chemistry Deficiencies**

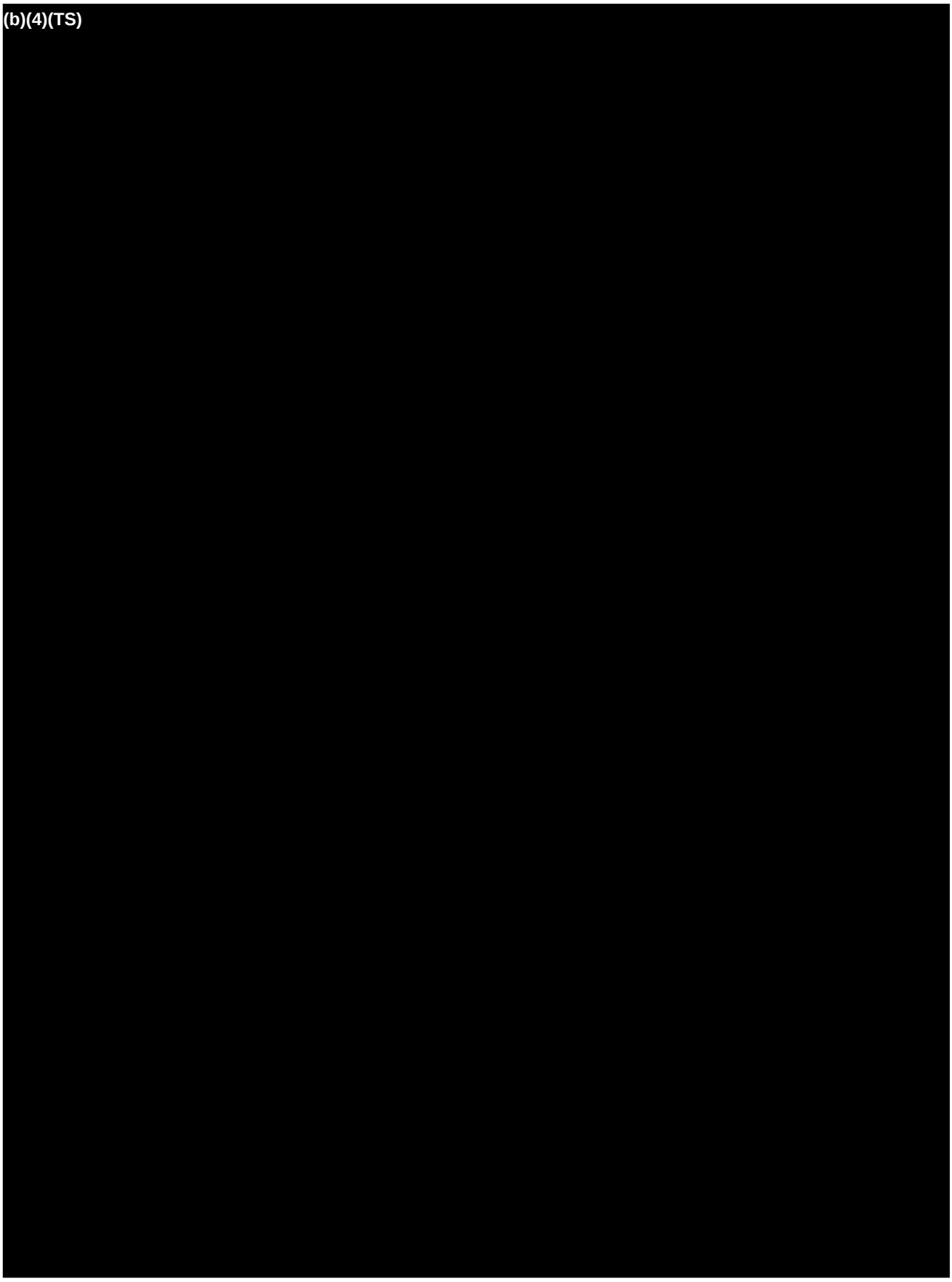
(b)(4)(TS)

[redacted]

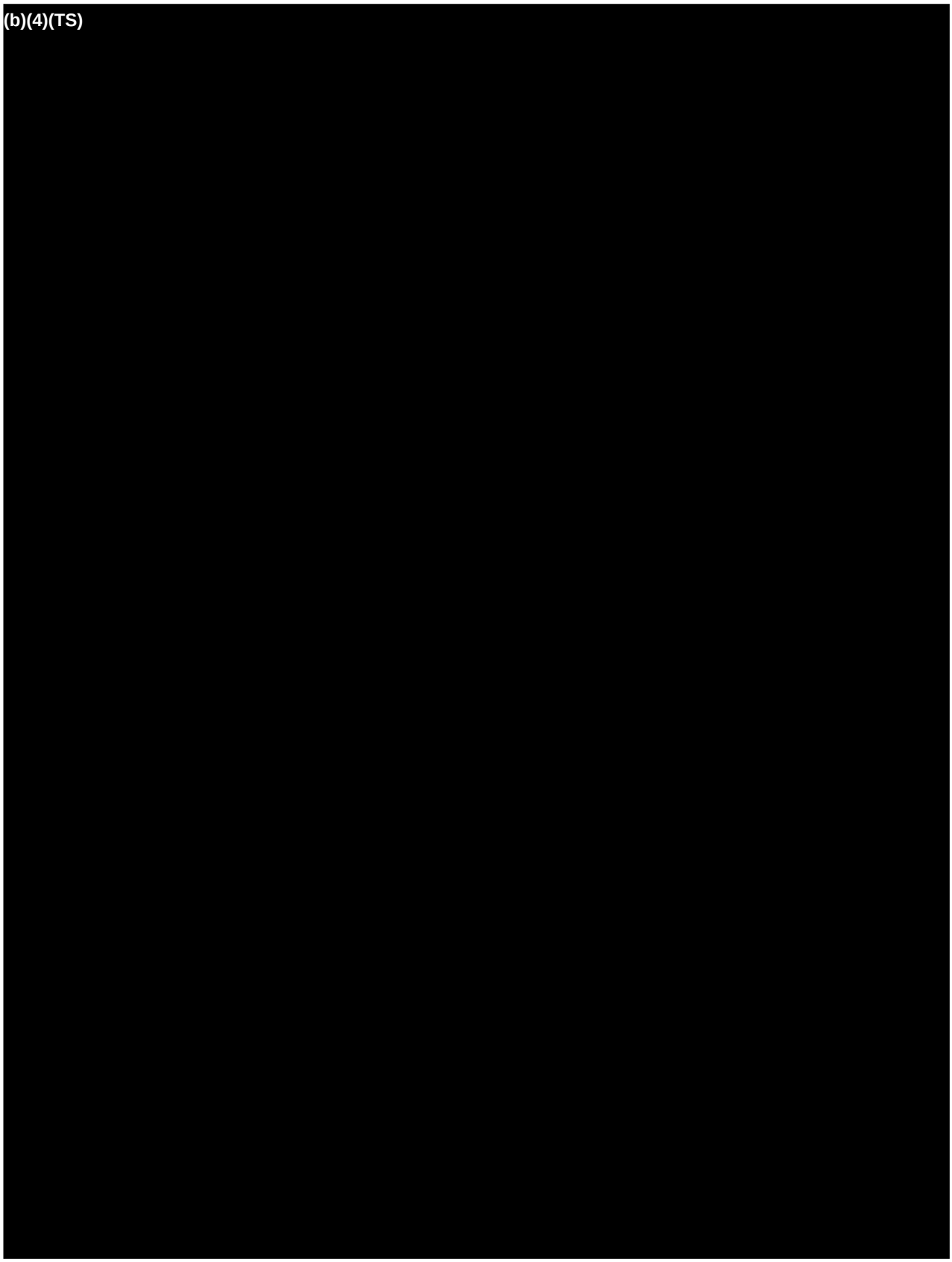
MAY 19 1997

[redacted]

(b)(4)(TS)



(b)(4)(TS)



9. We acknowledge that (b)(4)(CC) was inadequate. We have contacted the DMF holder (b)(4)(CC) and learned that they have responded to your inquiry with an updated DMF dated December 18, 1996. The current DMF referral letter referencing the update is provided in Attachment 5.

**B. Labeling Deficiencies**

1. Container:

The 2 mg container label presentation is different from the other approved strengths as indicated below:

0.25 mg- black reverse
0.5 mg- black with border
1 mg- black
2 mg- red reverse

2. Insert

a. The insert labeling has been revised as requested.

b. The scoring configuration of the "multiscored" tablet is described as requested in the insert.

Final print container and inset labeling are provided in Attachment 6.

**C. Acknowledgments**

(b)(4)(TS)

2. We acknowledge that the manufacturers of the drug substance, finished product and testing laboratories must be in compliance with cGMP's at the time of approval.

**D. Additional Updates**

**3059 Alprazolam**

Changes:

(b)(4)(TS)

[redacted]

**2035 Magnesium Stearate NF**

Changes:

(b)(4)(TS)

[redacted]

**2027 Lactose Monohydrate NF (Modified)**

Changes:

(b)(4)(TS)

[redacted]

Attachment 3:

**1516 SDA 3A 190 Proof**

Changes:

(b)(4)(TS)

[redacted]

**Changes to the Master Manufacturing Form**

Page 11 of 12, Tableting section, added "average" to hardness specification to better describe how the value is obtained. The updated Master Manufacturing Form is provided in Attachment 10.

**Accumulated Room Temperature Data**

Accumulated Room Temperature Data (12 months) is provided in Attachment 11.

The information is provided for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

BB:kk