CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-434/S-001

Name: Xanax XR Tablets

Generic Name: alprazolam extended-release

Sponsor: Pharmacia & Upjohn Company

Approval Date: 04/02/2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-434/S-001

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Approvable Letter(s)	
Final Printed Labeling	X
Medical Review(s)	X
Chemistry Review(s)	
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Administrative Document(s)	X
Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-434/S-001

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 18-276/S-038, 039
NDA 21-434/S-001

Pfizer, Inc.
c/o Pharmacia and Upjohn Company
Attention: Alan Dunbar, Director
235 East 42nd Street
150/7/16
New York, NY 10017

Dear Mr. Dunbar:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Application	Drug Name	Submission Date	Receipt Date	Provides For:
NDA 21-434/ SLR-001	Xanax XR (alprazolam) Extended-Release Tablets	March 11, 2003	March 12, 2003	Update to PRECAUTIONS/Drug Interactions section of labeling to include additional guidance to the physician regarding potential drug interactions of alprazolam with sertraline and paroxetine.
NDA 18-276/ SLR-038	Xanax (alprazolam) Tablets	April 2, 2003	April 3, 2003	
NDA 18-276/ SLR-039	Xanax (alprazolam) Tablets	October 1, 2003	October 2, 2003	Revisions to various sections of the current Xanax labeling to be consistent with the recently approved Xanax XR labeling.

We have completed our review of these applications and they are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

We remind you of your email communication on April 1, 2004 in which you committed to the following labeling language under the section entitled, "Drug Interactions":

Drugs and other substances demonstrated to be CYP3A 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. However, data from an in vivo drug interaction study involving a single dose of alprazolam 1 mg and steady state doses of sertraline (50 to 150 mg/day) did not reveal any clinically significant changes in the pharmacokinetics of alprazolam. 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).

The final printed labeling (FPL) must be identical to the labeling text submitted for the package inserts including the agreed upon labeling listed above.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 18-276/S-038, 039 and NDA 21-434/S-001." Approval of these submissions by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Richardae Taylor, Pharm.D., Regulatory Health Project Manager, at (301) 594-5793.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
4/2/04 10:30:14 AM
Signed for Russell Katz, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-434/S-001

FINAL PRINTED LABELING

Xanax XR®

alprazolam extended-release tablets

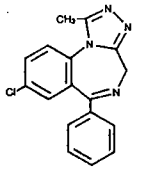
C IV

PHARMACIA

DESCRIPTION

XANAX XR Tablets contain 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-α] [1,4] benzodiazepine. The molecular formula is $C_{17}H_{13}ClN_4$ which corresponds to a molecular weight of 308.76.



The structural formula is represented to the right:

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

Each XANAX XR extended-release tablet, for oral administration, contains 0.5 mg, 1 mg, 2 mg, or 3 mg of alprazolam. The inactive ingredients are lactose, magnesium stearate, colloidal silicon dioxide, and hypromellose. In addition, the 1 mg and 3 mg tablets contain D & C yellow No. 10 and the 2 mg and 3 mg tablets contain FD&C blue No. 2.

CLINICAL PHARMACOLOGY

Pharmacodynamics

CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereospecific 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.

Pharmacokinetics

Absorption

Following oral administration of XANAX (immediate-release) Tablets, alprazolam is readily absorbed.

XANAX XR®

brand of alprazolam extended-release tablets

Peak concentrations in the plasma occur in one to two hours following administration. Plasma levels are proportional to the dose given; over the dose range of 0.5 to 3.0 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: 6.3–26.9 hours) in healthy adults.

The mean absolute bioavailability of alprazolam from XANAX XR Tablets is approximately 90%, and the relative bioavailability compared to XANAX Tablets is 100%. The bioavailability and pharmacokinetics of alprazolam following administration of XANAX XR Tablets are similar to that for XANAX Tablets, with the exception of a slower rate of absorption. The slower absorption rate results in a relatively constant concentration that is maintained between 5 and 11 hours after the dosing. The pharmacokinetics of alprazolam and two of its major active metabolites (4-hydroxyalprazolam and α-hydroxyalprazolam) are linear, and concentrations are proportional up to the recommended maximum daily dose of 10 mg given once daily. Multiple dose studies indicate that the metabolism and elimination of alprazolam are similar for the immediate-release and the extended-release products.

Food has a significant influence on the bioavailability of XANAX XR Tablets. A high-fat meal given up to 2 hours before dosing with XANAX XR Tablets increased the mean C_{max} by about 25%. The effect of this meal on T_{max} depended on the timing of the meal, with a reduction in T_{max} by about 1/3 for subjects eating immediately before dosing and an increase in T_{max} by about 1/3 for subjects eating 1 hour or more after dosing. The extent of exposure (AUC) and elimination half-life ($t_{1/2}$) were not affected by eating.

There were significant differences in absorption rate for the XANAX XR Tablet, depending on the time of day administered, with the C_{max} increased by 30% and the T_{max} decreased by an hour following dosing at night, compared to morning dosing.

Distribution

The apparent volume of distribution of alprazolam is similar for XANAX XR and XANAX Tablets. In vitro, alprazolam is bound (80%) to human serum protein. Serum albumin accounts for the majority of the binding.

Metabolism

Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4), to two major metabolites in the plasma: 4-hydroxyalprazolam and α-hydroxyalprazolam. A benzophenone derived from alprazolam is also found in humans. Their half-lives appear to be similar to that of alprazolam. The pharmacokinetic parameters at steady-state for the two hydroxylated metabolites of alprazolam (4-hydroxyalprazolam and α-hydroxy-alprazolam) were similar for XANAX and XANAX XR Tablets, indicating that the metabolism of alprazolam is not affected by absorption rate. The plasma concentrations of 4-hydroxyalprazolam and α-hydroxyalprazolam relative to unchanged alprazolam concentration after both XANAX XR and XANAX Tablets were always less than 10% and 4%, respectively. The reported relative potencies in benzodiazepine receptor binding experiments and in animal models of induced seizure inhibition are 0.20 and 0.66, respectively, for 4-hydroxyalprazolam and α-hydroxyalprazolam. Such low concentrations and the lesser potencies of 4-hydroxyalprazolam and α-hydroxyalprazolam suggest that they are unlikely to contribute much to the pharmacological effects of alprazolam. The benzophenone metabolite is essentially inactive.

Elimination

Alprazolam and its metabolites are excreted primarily in the urine. The mean plasma elimination half-life of alprazolam following administration of XANAX XR Tablet ranges from 10.7-15.8 hours in healthy adults.

Special Populations

While pharmacokinetic studies have not been performed in special populations with XANAX XR Tablets, the factors (such as age, gender, hepatic or renal impairment) that would affect the pharmacokinetics of alprazolam after the administration of XANAX

Tablets would not be expected to be different with the administration of XANAX XR Tablets.

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: 9.0–26.9 hours, n=16) compared to 11.0 hours (range: 6.3–15.8 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.

Race — Maximal concentrations and half-life of alprazolam are approximately 15% and 25% higher in Asians compared to Caucasians.

Pediatrics — The pharmacokinetics of alprazolam after administration of the XANAX XR Tablet in pediatric patients have not been studied.

Gender — Gender has no effect on the pharmacokinetics of alprazolam.

Cigarette Smoking — Alprazolam concentrations may be reduced by up to 50% in smokers compared to non-smokers.

Drug-Drug Interactions

Alprazolam is primarily eliminated by metabolism via cytochrome P450 3A (CYP3A). Most of the interactions that have been documented with alprazolam are with drugs that inhibit or induce CYP3A4.

Compounds that are potent inhibitors of CYP3A would be expected to increase plasma alprazolam concentrations. Drug products that have been studied in vivo, along with their effect on increasing alprazolam AUC, are as follows: ketoconazole, 3.98 fold; itraconazole, 2.70 fold; nefazodone, 1.98 fold; fluvoxamine, 1.96 fold; and erythromycin, 1.61 fold (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS–Drug Interactions).

CYP3A inducers would be expected to decrease alprazolam concentrations and this has been observed in vivo. The oral clearance of alprazolam (given in a 0.8 mg single dose) was increased from 0.90±0.21 mL/min/kg to 2.13±0.54 mL/min/kg and the elimination $t_{1/2}$ was shortened (from 17.1±4.9 to 7.7±1.7 h) following administration of 300 mg/day carbamazepine for 10 days (see PRECAUTIONS–Drug Interactions). However, the carbamazepine dose used in this study was fairly low compared to the recommended doses (1000-1200 mg/day); the effect at usual carbamazepine doses is unknown.

The ability of alprazolam to induce or inhibit human hepatic enzyme systems has not 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.

CLINICAL EFFICACY TRIALS

The efficacy of XANAX XR Tablets in the treatment of panic disorder was established in two 6-week, placebo-controlled studies of XANAX XR in patients with panic disorder.

In two 6-week, flexible-dose, placebo-controlled studies in patients meeting DSM-III criteria for panic disorder, patients were treated with XANAX XR in a dose range of 1 to 10 mg/day, on a once-a-day basis. The effectiveness of XANAX XR was assessed on the basis of changes in various measures of panic attack frequency, on various measures of the Clinical Global Impression, and on the Overall Phobia Scale. In all, there were seven primary efficacy measures in these studies, and XANAX XR was superior to placebo on all seven outcomes in both studies. The mean dose of XANAX XR at the last treatment visit was 4.2 mg/day in the first study and 4.6 mg/day in the second.

XANAX XR®
brand of alprazolam extended-release tablets

In addition, there were two 8-week, fixed-dose, placebo-controlled studies of XANAX XR in patients with panic disorder, involving fixed XANAX XR doses of 4 and 6 mg/day, on a once-a-day basis, that did not show a benefit for either dose of XANAX XR.

The longer-term efficacy of XANAX XR in panic disorder has not been systematically evaluated.

Analyses of the relationship between treatment outcome and gender did not suggest any differential responsiveness on the basis of gender.

INDICATIONS AND USAGE

XANAX XR Tablets are indicated for the treatment of panic disorder, with or without agoraphobia.

This claim is supported on the basis of two positive studies with XANAX XR conducted in patients whose diagnoses corresponded closely to the DSM-III-R/IV criteria for panic disorder (see CLINICAL STUDIES).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, ie, a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

The longer-term efficacy of XANAX XR has not been systematically evaluated. Thus, the physician who elects to use this drug for periods longer than 8 weeks should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

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

XANAX XR is contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A) (see CLINICAL PHARMACOLOGY, 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 doses of ≤4 mg/day, there is some risk of dependence. Spontaneous reporting system data suggest that the risk of dependence and its severity appear to be greater in patients treated with doses greater than 4 mg/day and for long periods (more than 12 weeks). However, in a controlled postmarketing discontinuation study of panic disorder patients who received XANAX Tablets, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. In contrast, patients treated with doses of XANAX Tablets greater than 4 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day.

Relapse or return of illness was defined as a return of symptoms characteristic of panic disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active treatment was initiated. Rebound refers to a return of symptoms of panic disorder to a level substantially greater in frequency, or more severe in intensity than seen at baseline. Withdrawal symptoms were identified as those which were generally not characteristic of panic disorder and which occurred for the first time more frequently during discontinuation than at baseline.

The rate of relapse, rebound, and withdrawal in patients with panic disorder who received XANAX XR

XANAX XR®
brand of alprazolam extended-release tablets

Tablets has not been systematically studied. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder who received XANAX Tablets showed a high rate of rebound and withdrawal symptoms compared to placebo treated patients.

In a controlled clinical trial in which 63 patients were randomized to XANAX Tablets and where withdrawal symptoms were specifically sought, the following were identified as symptoms of withdrawal: heightened sensory perception, impaired concentration, dysosmia, clouded sensorium, paresthesias, muscle cramps, muscle twitch, diarrhea, blurred vision, appetite decrease, and weight loss. Other symptoms, such as anxiety and insomnia, were frequently seen during discontinuation, but it could not be determined if they were due to return of illness, rebound, or withdrawal.

In two controlled trials of 6 to 8 weeks duration where the ability of patients to discontinue medication was measured, 71%-93% of patients treated with XANAX Tablets tapered completely off therapy compared to 89%-96% of placebo treated patients. In a controlled postmarketing discontinuation study of panic disorder patients treated with XANAX Tablets, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose.

Seizures were reported for three patients in panic disorder clinical trials with XANAX XR. In two cases, the patients had completed 6 weeks of treatment with XANAX XR 6 mg/day before experiencing a single seizure. In one case, the patient abruptly discontinued XANAX XR, and in both cases, alcohol intake was implicated. The third case involved multiple seizures after the patient completed treatment with XANAX XR 4 mg/day and missed taking the medication on the first day of taper. All three patients recovered without sequelae.

Seizures have also been observed in association with dose reduction or discontinuation of XANAX Tablets, the immediate release form of alprazolam. Seizures attributable to XANAX were seen after drug discontinuance or dose reduction in 8 of 1980 patients with panic disorder or in patients participating in clinical trials where doses of XANAX greater than 4 mg/day for over 3 months were permitted. Five of these cases clearly occurred during abrupt dose reduction, or discontinuation from daily doses of 2 to 10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt dose reduction or discontinuation. In one instance, seizure occurred after discontinuation from a single dose of 1 mg after tapering at a rate of 1 mg every three days from 6 mg daily. In two other instances, the relationship to taper is indeterminate; in both of these cases the patients had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8 cases ranged from 4 to 22 weeks. There have been occasional voluntary reports of patients developing seizures while apparently tapering gradually from XANAX. The risk of seizure seems to be greatest 24-72 hours after discontinuation (see DOSAGE AND ADMINISTRATION for recommended tapering and discontinuation schedule).

Status Epilepticus

The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of XANAX Tablets. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well.

Interdose Symptoms

Early morning anxiety and emergence of anxiety symptoms between doses of XANAX Tablets have been reported in patients with panic disorder taking prescribed maintenance doses. These symptoms may reflect the development of tolerance or a time interval between doses which is longer than the duration of clinical action of the administered dose. In either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels above those needed to prevent relapse, rebound, or withdrawal symptoms over the entire course of the interdosing interval.

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). Therefore, the dosage of XANAX XR should be reduced or discontinued gradually (see DOSAGE AND ADMINISTRATION).

CNS Depression and Impaired Performance

Because of its CNS depressant effects, patients receiving XANAX XR 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 XANAX XR.

Risk of Fetal Harm

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 (CYP3A). 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 CYP3A. With drugs inhibiting CYP3A 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 CYP3A.

Potent CYP3A Inhibitors

Azole antifungal agents — Ketoconazole and itraconazole are potent CYP3A inhibitors and have been shown in vivo to increase plasma alprazolam concentrations 3.98 fold and 2.70 fold, respectively. The coadministration of alprazolam with these agents is not recommended. Other azole-type antifungal agents should also be considered potent CYP3A inhibitors and the coadministration of alprazolam with them is not recommended (see CONTRAINDICATIONS).

Drugs demonstrated to be CYP3A inhibitors on the basis of clinical studies involving alprazolam (caution and consideration of appropriate alprazolam dose reduction are recommended 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 metabo-

lism by inhibition of CYP3A are discussed in the PRECAUTIONS section (see PRECAUTIONS–Drug Interactions).

PRECAUTIONS

General

Suicide

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. Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients.

Mania

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

Uricosuric Effect

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.

Use in Patients with Concomitant Illness

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 XANAX Tablets. A decreased systemic alprazolam elimination rate (eg, increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving XANAX Tablets (see CLINICAL PHARMACOLOGY).

Information for Patients

To assure safe and effective use of XANAX XR, the physician should provide the patient 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.
7. Some patients may find it very difficult to discontinue treatment with XANAX XR due to severe emotional and physical dependence. Discontinuation symptoms, including possible seizures, may occur following discontinuation from any dose, but the risk may be increased with extended use at doses greater than 4 mg/day, especially if discontinuation is too abrupt. It is important that you seek advice from your physician to discontinue treatment in a careful and safe manner. Proper discontinuation will help to decrease the possibility of withdrawal reactions that can range from mild reactions to severe reactions such as seizure.

Laboratory Tests

Laboratory tests are not ordinarily required in otherwise healthy patients. However, when treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable in keeping with good medical practice.

XANAX XR®
brand of alprazolam extended-release tablets

Drug Interactions

Use with Other CNS Depressants

If XANAX XR Tablets are 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. The benzodiazepines, including alprazolam, produce additive CNS depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression.

Use with Imipramine and Desipramine

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 XANAX Tablets 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 (CYP3A). 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 CYP3A 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 CYP3A 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. However, data from formal drug interactions studies suggest that neither compound has significant effects on the clearance of CYP3A substrates in vivo; clinically significant interactions with alprazolam are therefore unlikely. Two in vivo studies examined a single dose of alprazolam 1 mg and steady state doses of sertraline 50 mg in one study and 50 to 150 mg in the second study. Another in vivo study examined alprazolam 1 mg and paroxetine 20 mg, each given once daily for 15 days. None of the studies demonstrated any clinically significant changes in the pharmacokinetics or pharmacodynamics of alprazolam. 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).

Drugs demonstrated to be inducers of CYP3A

Carbamazepine can increase alprazolam metabolism and therefore can decrease plasma levels of alprazolam.

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 18 years of age have not been established.

Geriatric Use

The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. The smallest effective dose of alprazolam should be used in the elderly to preclude the development of ataxia and oversedation (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The information included in the subsection on Adverse Events Observed in Short-Term, Placebo-Controlled Trials with XANAX XR Tablets is based on pooled data of five 6- and 8-week placebo-controlled clinical studies in panic disorder.

Adverse event reports were elicited either by general inquiry or by checklist, and were recorded by clinical investigators using terminology of their own choosing. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened during therapy following baseline evaluation. In the tables and tabulations that follow, standard MedDRA terminology (version 4.0) was used to classify reported adverse events.

Adverse Events Observed in Short-Term, Placebo-Controlled Trials of XANAX XR

Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials

Approximately 17% of the 531 patients who received XANAX XR in placebo-controlled clinical trials for panic disorder had at least one adverse event that led to discontinuation compared to 8% of 349 placebo-treated patients. The most common events leading to discontinuation and considered to be drug-related (ie, leading to discontinuation in at least 1% of the patients treated with XANAX XR at a rate at least twice that of placebo) are shown in the following table.

XANAX XR®
brand of alprazolam extended-release tablets

Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled Trials

System Organ Class/Adverse Event	Percentage of Patients Discontinuing Due to Adverse Events	
	XANAX XR (n=531)	Placebo (n=349)
Nervous system disorders		
Sedation	7.5	0.6
Somnolence	3.2	0.3
Dysarthria	2.1	0
Coordination abnormal	1.9	0.3
Memory impairment	1.5	0.3
General disorders/administration site conditions		
Fatigue	1.7	0.6
Psychiatric disorders		
Depression	2.5	1.2

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated with XANAX XR

The prescriber should be aware that adverse event incidence cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with event incidence obtained from other clinical investigations involving different treatments, uses, and investigators. The cited values, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The following table shows the incidence of treatment-emergent adverse events that occurred during 6- to 8-week placebo-controlled trials in 1% or more of patients treated with XANAX XR where the incidence in patients treated with XANAX XR was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in panic disorder patients treated with XANAX XR (incidence of 5% or greater and at least twice the incidence in placebo patients) were: sedation, somnolence, memory impairment, dysarthria, coordination abnormal, ataxia, libido decreased (see table).

Treatment-Emergent Adverse Events: Incidence in Short-Term, Placebo-Controlled Clinical Trials with XANAX XR

System Organ Class/Adverse Event	Percentage of Patients Reporting Adverse Event	
	XANAX XR (n=531)	Placebo (n=349)
Nervous system disorders		
Sedation	45.2	22.6
Somnolence	23.0	6.0
Memory impairment	15.4	6.9
Dysarthria	10.9	2.6
Coordination abnormal	9.4	0.9
Mental impairment	7.2	5.7
Ataxia	7.2	3.2
Disturbance in attention	3.2	0.6
Balance impaired	3.2	0.6
Paresthesia	2.4	1.7
Dyskinesia	1.7	1.4
Hypoesthesia	1.3	0.3
Hypersomnia	1.3	0
General disorders/administration site conditions		
Fatigue	13.9	9.2
Lethargy	1.7	0.6
Infections and infestations		
Influenza	2.4	2.3
Upper respiratory tract infections	1.9	1.7

(continued)

XANAX XR®
brand of alprazolam extended-release tablets

(continued)

Treatment-Emergent Adverse Events: Incidence in Short-Term, Placebo-Controlled Clinical Trials with XANAX XR

Psychiatric disorders		
Depression	12.1	9.2
Libido decreased	6.0	2.3
Disorientation	1.5	0
Confusion	1.5	0.9
Depressed mood	1.3	0.3
Anxiety	1.1	0.6
Metabolism and nutrition disorders		
Appetite decreased	7.3	7.2
Appetite increased	7.0	6.0
Anorexia	1.5	0
Gastrointestinal disorders		
Dry mouth	10.2	9.7
Constipation	8.1	4.3
Nausea	6.0	3.2
Pharyngolaryngeal pain	3.2	2.6
Investigations		
Weight increased	5.1	4.3
Weight decreased	4.3	3.7
Injury, poisoning, and procedural complications		
Road traffic accident	1.5	0
Reproductive system and breast disorders		
Dysmenorrhea	3.6	2.9
Sexual dysfunction	2.4	1.1
Premenstrual syndrome	1.7	0.6
Musculoskeletal and connective tissue disorders		
Arthralgia	2.4	0.6
Myalgia	1.5	1.1
Pain in limb	1.1	0.3
Vascular disorders		
Hot flushes	1.5	1.4
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	1.5	0.3
Rhinitis allergic	1.1	0.6
Skin and subcutaneous tissue disorders		
Pruritis	1.1	0.9

Other Adverse Events Observed During the Premarketing Evaluation of XANAX XR Tablets

Following is a list of MedDRA terms that reflect treatment-emergent adverse events reported by 531 patients with panic disorder treated with XANAX XR. All potentially important reported events are included except those already listed in the above table or elsewhere in labeling, those events for which a drug cause was remote, those event terms that were so general as to be uninformative, and those events that occurred at rates similar to background rates in the general population. It is important to emphasize that, although the events reported occurred during treatment with XANAX XR, they were not necessarily caused by the drug. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Cardiac disorders: *Frequent:* palpitation; *Infrequent:* sinus tachycardia

Ear and Labyrinth disorders: *Frequent:* Vertigo; *Infrequent:* tinnitus, ear pain

Eye disorders: *Frequent:* blurred vision; *Infrequent:* mydriasis, photophobia

Gastrointestinal disorders: *Frequent:* diarrhea, vomiting, dyspepsia, abdominal pain; *Infrequent:* dysphagia, salivary hypersecretion

General disorders and administration site conditions: *Frequent:* malaise, weakness, chest pains; *Infrequent:* fall, pyrexia, thirst, feeling hot and cold, edema, feeling jittery, sluggishness, asthenia, feeling drunk, chest tightness, increased energy, feeling of relaxation, hangover, loss of control of legs, rigors

Musculoskeletal and connective tissue disorders: *Frequent:* back pain, muscle cramps, muscle twitching

Nervous system disorders: *Frequent:* headache, dizziness, tremor; *Infrequent:* amnesia, clumsiness, syncope, hypotonia, seizures, depressed level of consciousness, sleep apnea syndrome, sleep talking, stupor

Psychiatric system disorders: *Frequent:* irritability, insomnia, nervousness, derealization, libido increased, restlessness, agitation, depersonalization, nightmare; *Infrequent:* abnormal dreams, apathy, aggression, anger, bradyphrenia, euphoric mood, logorrhea, mood swings, dysphonia, hallucination, homicidal ideation, mania, hypomania, impulse control, psychomotor retardation, suicidal ideation

Renal and urinary disorders: *Frequent:* difficulty in micturition; *Infrequent:* urinary frequency, urinary incontinence

Respiratory, thoracic, and mediastinal disorders: *Frequent:* nasal congestion, hyperventilation; *Infrequent:* choking sensation, epistaxis, rhinorrhea

Skin and subcutaneous tissue disorders: *Frequent:* sweating increased; *Infrequent:* clamminess, rash, urticaria

Vascular disorders: *Infrequent:* hypotension

The categories of adverse events reported in the clinical development program for XANAX Tablets in the treatment of panic disorder differ somewhat from those reported for XANAX XR Tablets because the clinical trials with XANAX Tablets and XANAX XR Tablets used different standard medical nomenclature for reporting the adverse events. Nevertheless, the types of adverse events reported in the clinical trials with XANAX Tablets were generally the same as those reported in the clinical trials with XANAX XR Tablets.

Discontinuation-Emergent Adverse Events Occurring at an Incidence of 5% or More Among Patients Treated with XANAX XR

The following table shows the incidence of discontinuation-emergent adverse events that occurred during short-term, placebo-controlled trials in 5% or more of patients treated with XANAX XR where the incidence in patients treated with XANAX XR was two times greater than the incidence in placebo-treated patients.

Discontinuation-Emergent Symptoms: Incidence in Short-Term, Placebo-Controlled Trials with XANAX XR

System Organ Class/Adverse Event	Percentage of Patients Reporting Adverse Event	
	XANAX XR (n=422)	Placebo (n=261)
Nervous system disorders		
Tremor	28.2	10.7
Headache	26.5	12.6
Hypoesthesia	7.8	2.3
Paresthesia	7.1	2.7
Psychiatric disorders		
Insomnia	24.2	9.6
Nervousness	21.8	8.8
Depression	10.9	5.0
Derealization	8.0	3.8
Anxiety	7.8	2.7
Depersonalization	5.7	1.9
Gastrointestinal disorders		
Diarrhea	12.1	3.1
Respiratory, thoracic and mediastinal disorders		
Hyperventilation	8.5	2.7
Metabolism and nutrition disorders		
Appetite decreased	9.5	3.8
Musculoskeletal and connective tissue disorders		
Muscle twitching	7.4	2.7
Vascular disorders		
Hot flushes	5.9	2.7

XANAX XR®
brand of alprazolam extended-release tablets

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

To discontinue treatment in patients taking XANAX XR Tablets, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of XANAX XR Tablets be decreased by no more than 0.5 mg every three days (see DOSAGE AND ADMINISTRATION). Some patients may benefit from an even slower dosage reduction. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome.

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.

Post Introduction Reports

Various adverse drug reactions have been reported in association with the use of XANAX Tablets 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 XANAX Tablets cannot be readily determined. Reported events include: liver enzyme elevations, hepatitis, hepatic failure, Stevens-Johnson syndrome, hyperprolactinemia, 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. In recurring panic disorder, symptoms similar to those observed before treatment may recur either early or late, and they will persist.

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 doses greater than 4 mg/day 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 XANAX XR Tablets have been assigned to Schedule IV.

OVERDOSAGE

Clinical Experience

Overdosage reports with XANAX Tablets are limited. 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.

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

General Treatment of Overdose

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

XANAX XR Tablets may be administered once daily, preferably in the morning. The tablets should be taken intact; they should not be chewed, crushed, or broken.

The suggested total daily dose ranges between 3 to 6 mg/day. Dosage should be individualized for maximum beneficial effect. While the suggested total daily dosages given will meet the needs of most patients, there will be some patients who require doses greater than 6 mg/day. In such cases, dosage should be increased cautiously to avoid adverse effects.

Dosing in Special Populations

In elderly patients, in patients with advanced liver disease, or in patients with debilitating disease, the usual starting dose of XANAX XR is 0.5 mg once daily. This may be gradually increased if needed and tolerated (see Dose Titration). The elderly may be especially sensitive to the effects of benzodiazepines.

Dose Titration

Treatment with XANAX XR may be initiated with a dose of 0.5 mg to 1 mg once daily. Depending on the response, the dose may be increased at intervals of 3 to 4 days in increments of no more than 1 mg/day. Slower titration to the dose levels may be advisable to allow full expression of the pharmacodynamic effect of XANAX XR.

Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses in patients especially sensitive to the drug. Dose should be advanced until an acceptable therapeutic response (ie, a substantial reduction in or total elimination of panic attacks) is achieved, intolerance occurs, or the maximum recommended dose is attained.

Dose Maintenance

In controlled trials conducted to establish the efficacy of XANAX XR Tablets in panic disorder, doses in the range of 1 to 10 mg/day were used. Most patients showed efficacy in the dose range of 3 to 6 mg/day. Occasional patients required as much as 10 mg/day to achieve a successful response.

The necessary duration of treatment for panic disorder patients responding to XANAX XR is unknown. However, periodic reassessment is advised. After a period of extended freedom from attacks, a carefully supervised tapered discontinuation may be attempted, but there is evidence that this may often be difficult to accomplish without recurrence of symptoms and/or the manifestation of withdrawal phenomena.

Dose Reduction

Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided (see WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE).

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.

In any case, reduction of dose must be undertaken under close supervision and must be gradual. If significant withdrawal symptoms develop, the previous dosing schedule should be reinstituted and, only after stabilization, should a less rapid schedule of discontinuation be attempted. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome. It is suggested that the dose be reduced by no more than 0.5 mg every three days, with the understanding that some patients may benefit from an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens.

Switch from XANAX (immediate-release) Tablets to XANAX XR (extended-release) Tablets

Patients who are currently being treated with divided doses of XANAX (immediate-release) Tablets, for example 3 to 4 times a day, may be switched to XANAX XR Tablets at the same total daily dose taken once daily. If the therapeutic response after switching is inadequate, the dosage may be titrated as outlined above.

XANAX XR®
brand of alprazolam extended-release tablets

HOW SUPPLIED

XANAX XR (extended-release) Tablets are available as follows:

0.5 mg (white, pentagonal-shaped tablets debossed with an "X" on one side and "0.5" on the other side)
Bottles of 60 NDC 0009-0057-07

1 mg (yellow, square-shaped tablets debossed with an "X" on one side and "1" on the other side)
Bottles of 60 NDC 0009-0059-07

2 mg (blue, round-shaped tablets debossed with an "X" on one side and "2" on the other side)
Bottles of 60 NDC 0009-0066-07

3 mg (green, triangular-shaped tablets debossed with an "X" on one side and "3" on the other side)
Bottles of 60 NDC 0009-0068-07

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

℞ only

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.

Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, Michigan 49001, USA

Revised March 2003 819 612 001B
692842

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-434/S-001

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA:	18,276 (SLR-038) 21,434 (SLR-001)
Sponsor:	Pharmacia & Upjohn Company
Drug:	Xanax (alprazolam)- 18,276 Xanax XR (alprazolam extended-release)- 21,434
Material Submitted:	Changes Being Effected (CBE); labeling supplement
Correspondence Date:	March 11, 2003; April 2, 2003
Formulation & strength:	IR: 0.25 mg, 0.5 mg, 1 mg, and 2 mg tablets XR: 0.5 mg, 1.0 mg, 2 mg, and 3 mg tablets
Clinical Reviewer:	Robert Levin, M.D.
Team Leader:	Thomas Laughren, M.D.
OND Division:	Division of Neuropharmacological Drug Products HFD-120

I. Summary of Submission

The sponsor has submitted a labeling supplement for Xanax and Xanax XR, proposing changes in labeling regarding potential drug interactions between alprazolam and theCYP3A4 inhibitors paroxetine and sertraline. Current alprazolam labeling in the **Drug Interactions** section indicates that data from in *vitro* studies with alprazolam suggests a potential drug interaction with sertraline and paroxetine via inhibition of CYP3A4 activity. The sponsor has proposed a revision in labeling, based on:
1) conclusions of 4 published articles regarding in vivo interaction data for sertraline (Preskorn et. al, 1997), alprazolam and sertraline (Hassan et. al, 2000), alprazolam and paroxetine (Garcia-Gea et. al, and paroxetine and terfenadine (Martin et. al, 1997); and
2) current sertraline and paroxetine labels. Current sertraline and paroxetine labels both indicate that the extent of inhibition of CYP4503A4 inhibition by each drug is not likely to be of clinical significance; thus, the sponsor proposes[redacted]

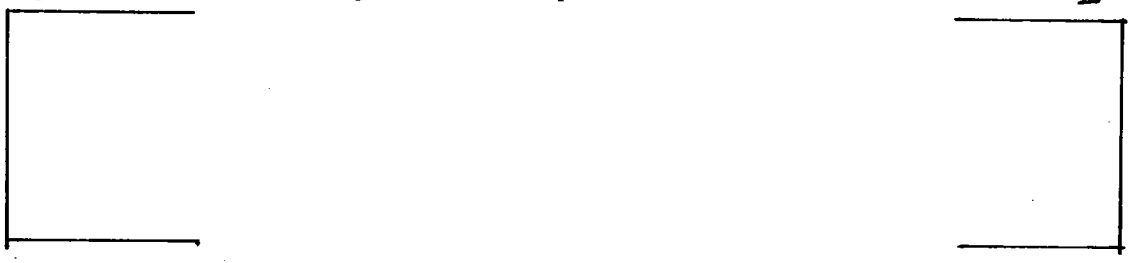
II. Biopharmaceutics Consultant's Conclusions and Recommendations.

Wen-Hwei Chou, Pharm.D., Ph.D. (OCBP) has reviewed the information submitted by the sponsor (consult completed on October 1, 2003). Generally, Dr. Chou does not find the sponsor's proposed labeling changes acceptable, based on the opinion that the data provided do not sufficiently support the proposals regarding potential drug interactions between alprazolam and sertraline and between alprazolam and paroxetine. Dr. Chou has proposed alternative labeling. (For details, please refer to Dr. Chou's consult). The sponsor's proposed labeling changes (in bold, underlined text), along with current labeling (in plain font), are specified below:

Data from in vitro studies of alprazolam suggest a possible interaction with alprazolam for the following: sertraline and paroxetine. [redacted]

Dr. Chou's proposed labeling changes are specified below [with edits by the clinical reviewer]:

~~Data from in vitro studies of alprazolam suggest a possible interaction with alprazolam for the following: sertraline and paroxetine.~~



III. Clinical Reviewer's Conclusions and Recommendations

I agree with Dr. Chou's conclusions and recommendations. I recommend that the Division propose that the sponsor adopt the labeling language suggested by Dr. Chou.

Robert L. Levin, M.D., March 18, 2004
Medical Reviewer,
FDA CDER ODE1 DNDP HFD 120

cc: HFD 120
T Laughren
P Andreason
R Taylor

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Levin
3/18/04 08:39:47 AM
MEDICAL OFFICER

Thomas Laughren
3/22/04 08:47:20 AM
MEDICAL OFFICER
Proposed labeling language needs minor editing before sending to sponsor.--TPL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-434/S-001

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	18,276 (SLR-038) 21,434 (SLR-001)
Submission Dates	03/11/2003, 4/2/03
OCPB consult date	09/05/2003
Brand Name	Xanax (NDA18,276) Xanax Extended-release (XR) tablet (NDA21-434)
Generic Name	Alprazolam
Sponsor	Pharmacia & Upjohn Company
Formulation; Strength	IR: 0.25mg, 0.5mg, 1mg and 2mg XR: 0.5mg, 1mg, 2mg and 3 mg
Indication	IR: Anxiety; Treatment of patients with panic disorder, with or without agoraphobia XR:Treatment of patients with panic disorder, with or without agoraphobia
Sponsor	Pharmacia & Upjohn Company
Submission Type; Code	Changes being effected(CBE): Labeling supplement (electronic submission)
Primary Reviewer	Wen-Hwei Chou, Pharm.D., Ph.D.
Team Leader	Ramana Uppoor, Ph.D.
OCPB Division	HFD-860
OND Division	HFD-120

This review evaluates a labeling supplement for Xanax & Xanax-XR. Current "Drug interaction" section of alprazolam product indicates that data from in-vitro studies with alprazolam suggests a possible drug interaction with sertraline and paroxetine via inhibition of CYP3A4 activity. The sponsor proposed labeling revision based on the published in-vivo interaction data of alprazolam with sertraline, paroxetine with alprazolam or terfenadine (a CYP3A4 substrate), and current sertraline and paroxetine labels. Current sertraline and paroxetine labels both indicate that the extent of inhibition of P450 3A4 activity is not likely to be of clinical significance. The sponsor proposed [redacted]

Overall, we did not find data submitted sufficient to support the proposed labeling text. Specifically,

- We disagree with the proposed labeling text regarding sertraline. Among the two drug interaction articles of alprazolam with sertraline, only 1 study reported both Cmax & AUC. In that study, we noted that there is a trend toward lower Cmax & AUC of alprazolam when single dose alprazolam is coadministered with therapeutic sertraline doses of once daily 50mg, 100mg or 150mg at steady-state. The difference ranged from 4-30% for Cmax and from 11-17% for AUC. The reduction in alprazolam Cmax was statistically significant after a minimum of 2 weeks of daily 50mg dose of sertraline.

- Moreover, the information submitted was insufficient for the proposed labeling revision with regard to paroxetine. No pharmacokinetic measures were reported in the literature upon coadministration of alprazolam and paroxetine. Furthermore, the drug interaction

study of paroxetine and terfenadine (a CYP3A4 substrate) showed high variability in both paroxetine & terfenadine pharmacokinetics. When compared to terfenadine treatment alone, the carboxyterfenadine levels (CYP3A4 mediated) were lower when paroxetine & terfenadine were coadministered. We do not find the results from this study sufficient to support the labeling revision with respect to paroxetine & alprazolam without direct alprazolam & paroxetine data.

- In conclusion, sponsor proposed labeling revision is not acceptable. Agency recommends alternative labeling text based on the available information in current submission. Specifically,

Current Xanax label: Drug interaction (Font in bold indicates where sponsor's revision started)

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).

Sponsor proposed: (Font in bold & underlined indicates addition)

Proposed XANAX Tablets Labeling Change

The proposed text to be added to the current text in the Drug Interactions section of XANAX Tablets package insert is underlined below:

Data from in vitro studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. [redacted]

Agency recommends(strikethrough indicates deletion, underlined text indicated addition):

[redacted]

~~Data from in vitro studies of alprazolam suggest a possible drug interaction with alprazolam for~~

~~the following: sertraline and paroxetine~~.

Recommendation
The Office of Clinical Pharmacology & Biopharmaceutics has reviewed sponsor's proposed labeling supplement and finds it not acceptable. Based on the submitted literature, Agency proposes alternative labeling text. Please forward above Agency's comment to the sponsor.

Signature

Wen-Hwei Chou, Pharm.D., Ph.D. _____

RD/FT Initialed by Ramana Uppoor, Ph.D. _____
Division of Pharmaceutical Evaluation I,
Office of Clinical Pharmacology and Biopharmaceutics

cc: NDA 18,276; NDA21,434
HFD-120 (Taylor)
HFD-860 (Mehta, Sahajwalla, Uppoor, Chou)

Attachment

Individual literature review

1. **Sertraline does not inhibit cytochrome P450 3A-mediated drug metabolism in vivo Preskorn et al. Psychopharmacology Bull 997 33(4)659-665**
   - Open label, noncomparative design
   - Subject received a single dose of alprazolam (1mg) 2 days before sertraline multiple dose administration (50mg/day for 16 days). On day 15 of sertraline dosing, alprazolam was readministered as a single 1mg dose; both drugs were taken at the same time.
   - Bioassay: gas liquid chromatography, lower limit of detection of 1ng/ml
   - PK samples:
     - alprazolam (predose, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours post dose); Alprazolam metabolite levels were not measured.
     - sertraline [0, 1, 2, 4, 6, 8, 12, 24 (trough) on day 14-17].

   - The carbamazepine study employed a double-blind, randomized, placebo-controlled, two-group, parallel design. All subjects were begun on carbamazepine 200 mg every 12 hours for the study duration and then had either placebo or sertraline added on Day 16 to create two groups: carbamazepine plus sertraline or placebo. The doses of sertraline given were 50 mg on Day 16, 100 mg/day on Days 17 to 19, 150 mg/day on Days 20 to 22, and 200 mg/day on Days 23 to 32. Sertraline or placebo were administered with breakfast: carbamazepine was given 2 hours later.

   - The terfenadine studies employed a double-blind, randomized, placebo-controlled, four-group, parallel design. All subjects received terfenadine 60 mg twice a day on Days 2 through 8. Two groups then received sertraline 50 mg/day on Days 11 to 13, 100 mg/day on Days 14 to 16, 150 mg/day on Days 17 to 19, and 200 mg/day on Days 20 to 44. Two groups received placebo on Days 11 to 44. On Days 34 to 44, either terfenadine 60 mg twice a day or placebo terfenadine was added. Therefore, there were four groups (using the two placebo dummies): (a) terfenadine plus sertraline, (b) terfenadine plus placebo sertraline, (c) sertraline plus placebo terfenadine, and (d) placebo sertraline plus placebo terfenadine.

   - For the carbamazepine and terfenadine studies, the plasma concentration-time profile of parent drug and its respective primary metabolite were determined in the absence and in the presence of sertraline. The pharmacokinetic parameters calculated were: Cmax, Tmax, and AUC from 0 to 12 hours.

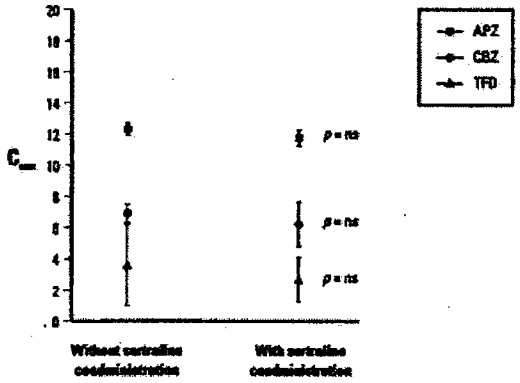


FIGURE 2. C_{max} for alprazolam (APZ), carbamazepine (CBZ), and terfenadine (TFD) with and without sertraline co-administration. C_{max} units are ng/ml for alprazolam and terfenadine and mg/ml for carbamazepine.

The author concluded that there was no significant change in PK parameters for alprazolam as a result of coadministration of sertraline.

Comments:

- The author did not report AUC of alprazolam.
- The result is considered supportive.

2. <u>Dose-response evaluation of the interaction between sertraline and alprazolam in vivo Hassang et al. J Clinical Psychopharmacology 2000, 20(2):150-158</u>

- Randomized, double-blind, placebo-controlled
- 10 healthy volunteers: N=6 (sertraline 50mg), 4 (sertraline 100mg), and 6 (sertraline 150mg); age ranged 20-43 yrs.
- Dose: alprazolam 1mg; sertraline (50mg, 100mg or 150mg /day taken with dinner for 2 weeks)
- PK measures:
- Alprazolam, Sertraline & desmethylsertraline: baseline, 0.5, 1, 1.5, 2, 2.5, 3, 4, 8, 24, and 32 hours post alprazolam dose.

PD measures: sedation, psychomotor impairment, and memory impairment.

Bioassay:

- Alprazolam: gas liquid chromatography-MS; lower limit of detection of 1nM. For concentration of 3 to 50 nM, the coefficient of variation was 4.8%. For concentration <2.5nM, the CV was 27%.

- Sertraline & desmethylsertraline: HPLC; lower limit of detection of 2nM. The coefficient of variation Sertraline & desmethylsertraline were 11.8% and 5.1%, respectively, for concentrations <25nM, and 4.1% and 3.4% for concentration >50nM.

Data analysis: All statistical comparisons within dosage groups were made using paired tests (t-test or Wilcoxon signed rank test) and ANOVA where possible.

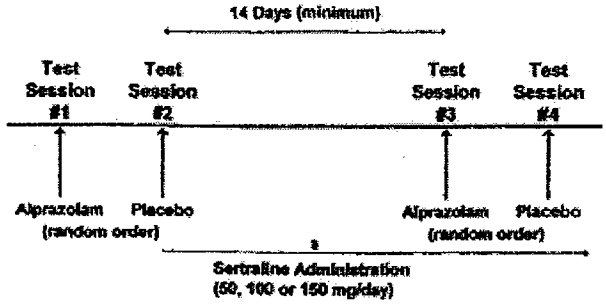


FIG. 1. Study design.

TABLE 1. Mean ± SD values for pharmacokinetic parameters grouped by dosage of sertraline[a]

	50-mg Sertraline Group (N = 6)		100-mg Sertraline Group (N = 4)		150-mg Sertraline Group (N = 6)	
	Alprazolam Alone	Alprazolam + Sertraline	Alprazolam Alone	Alprazolam + Sertraline	Alprazolam Alone	Alprazolam + Sertraline
C_{max} (ng/mL)[b]	12.7[c] ± 7.6	8.5[c] ± 2.3	10.3 ± 1.9	7.6 ± 1.1	11.0 ± 2.2	10.5 ± 3.6
T_{max} (hr)[b]	2.7 ± 1.4	2.5 ± 0.9	2.3 ± 0.5	2.6 ± 1.3	2.4 ± 0.9	2.0 ± 0.8
$t_{1/2}$ (hr)[b]	11.2 ± 2.1	12.2 ± 3.3	12.4 ± 3.1	12.4 ± 5.6	12.2 ± 3.2	14.2 ± 7.1
$AUC_{0-\infty}$ (ng/mL·hr)[b]	166.9 ± 53.0	141.7 ± 26.6	158.1 ± 24.6	130.5 ± 35.0	177.2 ± 53.1	174.9 ± 57.3

[a] C_{max}, peak alprazolam concentration; T_{max}, time to peak alprazolam concentration; $t_{1/2}$, elimination half-life; $AUC_{0-\infty}$, area under the concentration-time curve from baseline to infinity.
[b] Parameters were calculated for each individual subject then averaged. Therefore, values do not correspond to those obtained by examining Figure 2, in which concentrations were averaged at each time point.
[c] Wilcoxon matched pairs significance compared with alprazolam alone ($p = 0.06$).

Sertraline & desmethlysertraline concentrations

	Sertraline	desmethlysertraline
50mg	56±22nM/L	88±45nM/L
100mg	192±6nM/L	215±6nM/L
150mg	224±1082nM/L	298±61nM/L

Author concluded that after a minimum of 2 weeks of daily sertraline administration (50mg, 100mg or 150mg/day), alprazolam concentrations showed no significant changes based on the Cmax, tmax, t1/2 and AUC with the exception of a reduced Cmax in the 50mg/day group.

Comments

- There is a consistent trend toward lower Cmax & AUC of alprazolam when alprazolam is coadministered with sertraline.
  - The % decrease in Cmax: 30% (50mg/day, statistically significant), 26% (100mg), and 4% (150mg)
  - The % decrease in AUC: 15% (50mg/day, statistically significant), 17% (100mg), and 11% (150mg)

- Larger % CV for Cmax was observed at 50mg: 50% (alprazolam alone), 30% (alprazolam +sertraline)

- The observed decreases in Cmax & AUC are opposite to what should be anticipated from in vitro inhibitory data. In vitro data suggest inhibition of alprazolam metabolism by sertraline or paroxetine via CYP3A4.

- The PD measures are not valid clinical endpoints.

3. **Paroxetine Does Not Affect the Cardiac Safety and Pharmacokinetics of Terfenadine in Healthy Adult Men. Martin D et al J Clin Psychopharmacol 1997, 17(6)451-459**
   - 12 healthy male volunteers (age range 21-39 years)
   - randomized, open-label, two-period, steady-state crossover study
   - Treatment:
     - Treatment A: Terfenadine (60mg bid for 8 days) was administered alone
     - Treatment B: Terfenadine with paroxetine at steady-state (20mg qd for 15 days, with terfenadine on day 8 through 15).
     - Dose free interval for at least 14 days.
   - PK measures
     - Plasma terfenadine level: Bioassay-LC/MS/MS; LLOQ: 0.05ng/ml; Between run % CV: 14.7-6.0% over calibration range of 0.05-5.0ng/ml
     - Plasma carboxyterfenadine level (CYP3A4 mediated): Bioassay-HPLC-fluorescence; LLOQ: 10ng/ml; Between run % CV: 12.3-5.2% over calibration range of 10-500ng/ml
     - Plasma paroxetine level: Bioassay-LC/MS/MS; LLOQ: 0.05ng/ml; Between run % CV: <10%
   - Safety: AEs, ECG
   - Statistical analysis:
     - QTc using equivalence approach (90% CI, the equivalence range was arbitrarily set at -40 to +40). The maximum QTc and mean QTc obtained on the final day of terfenadine dosing in each study period were analyzed separately by ANOVA.
     - PK comparison of treatment A versus treatment B: 95% CI

Results:

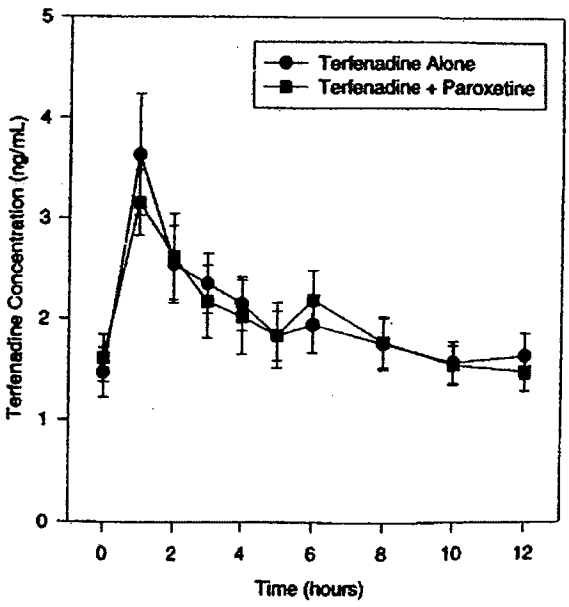


FIG. 1. Mean (SEM) plasma concentrations of terfenadine after repeated oral administration of terfenadine (60 mg twice daily) alone and with paroxetine at steady state (20 mg once daily) in 10 healthy subjects (subject 10 excluded).

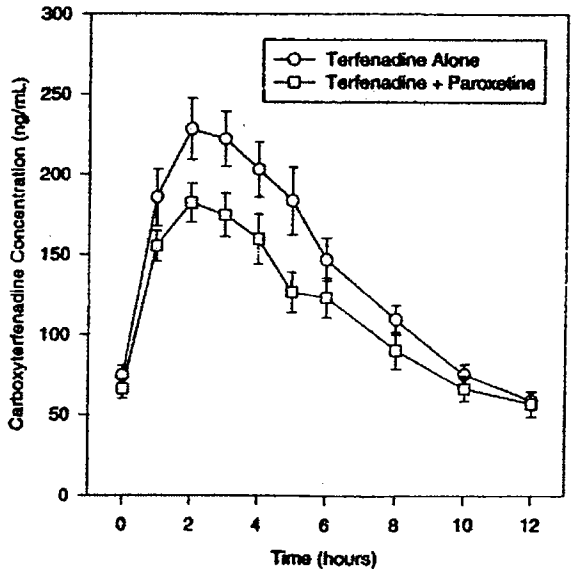


FIG. 2. Mean (SEM) plasma concentrations of carboxyterfenadine after repeated oral administration of terfenadine (60 mg twice daily) alone and with paroxetine at steady state (20 mg once daily) in 11 healthy subjects.

TABLE 2. Average paroxetine steady-state trough concentrations

Subject	Paroxetine Concentration[a] (ng/mL)
1	37.6
3	1.35
4	2.24
5	21.1
6	26.6
7	71.3
8	41.8
9	105.0
10	29.8
11	16.8
12	46.4
Mean	36.4
(SD)	(30.4)

[a]Mean of three consecutive predose values (days 13–15).

TABLE 1. Summary of electrocardiographic changes (mean [SEM]) noted over a 12-hour period on the last day of dosing with terfenadine relative to the predose baseline

	Baseline QT_c (msec)	Mean QT_c[a] (msec)	Maximum QT_c[b] (msec)	Maximum Change From Baseline (msec)
Terfenadine alone (A)	381 (4)	387 (5)	405 (5)	25 (5)
Terfenadine + paroxetine (B)	381 (3)	386 (4)	404 (4)	23 (5)
PE[c] (B−A) (90% CI)		−1.07 (−4.14, 1.99)	−2.07 (−12.54, 8.41)	

[a]Mean QT_c, mean of all QT_c values obtained on the last day of dosing over the 12-hour period.

[b]Maximum QT_c, maximum QT_c value obtained on the last day of dosing over the 12-hour period.

[c]Point estimate.

TABLE 3. Steady-state pharmacokinetic parameters for terfenadine and carboxyterfenadine

	Terfenadine C_{ss} (ng/mL)		Terfenadine AUCτ (ng·hr/mL)		Carboxyterfenadine C_{ss} (ng/mL)		Carboxyterfenadine AUCτ (ng·hr/mL)	
Subject	Terfenadine Alone (Regimen A)	Terfenadine + Paroxetine (Regimen B)	Terfenadine Alone (Regimen A)	Terfenadine + Paroxetine (Regimen B)	Terfenadine Alone (Regimen A)	Terfenadine + Paroxetine (Regimen B)	Terfenadine Alone (Regimen A)	Terfenadine + Paroxetine (Regimen B)
1	0.39	0.84	Not evaluable	Not evaluable	256	196	1,436	1,078
3	2.31	3.86	21.8	31.4	211	176	1,825	1,907
4	5.06	3.94	22.8	34.5	304	146	1,837	1,135
5	4.35	2.85	20.7	11.0	322	232	1,871	1,325
6	5.03	3.32	34.0	22.1	363	206	1,562	1,289
7	5.87	4.45	38.3	30.9	287	245	1,936	1,610
8	2.29	3.84	15.4	23.4	299	245	1,883	1,533
9	4.78	4.55	33.1	36.7	278	246	2,081	1,803
10	40.3	27.3	409	287	269	213	1,724	1,900
11	1.94	2.26	10.8	17.2	216	169	1,623	1,243
12	2.97	2.85	26.0	16.9	111	138	839	956
Geometric mean (range)	3.64 (0.39–40.3)	3.68 (0.84–27.3)	30.8 (10.8–409)	30.0 (11.0–287)	248 (111–363)	197 (138–246)	1,648 (839–2,081)	1,361 (956–1,900)
Point estimate (B:A) (90% CI)	0.98 (0.80, 1.21)		0.97 (0.87, 1.08)		0.80 (0.67, 0.95)		0.83 (0.74, 0.92)	

Conclusion:

- One subject withdrew because of adverse experiences related to paroxetine, but the other 11 subjects completed the study uneventfully.
- On the final day of coadministration, the rate-corrected QT interval (QTc) was unaltered compared with terfenadine dosed alone; maximum QTc values (mean [SEM]) were 404 (4) and 405 (5) msec, respectively.
- Terfenadine PK were unchanged: geometric mean steady-state AUC values were 80.0 ng hr/mL during coadministration with paroxetine; 80.8 ng hr/mL when dosed alone ($p > 0.05$). The corresponding Cmax values were 8.68 and 8.64 ng/mL ($p > 0.05$). There was, however, a small (on average 17-20%), unexplained reduction in the steady- state Cmax and AUC of carboxyterfenadine during coadministration with paroxetine.
- In conclusion, paroxetine does not affect the pharmacokinetics or cardiovascular effects of terfenadine. The small reduction in carboxyterfenadine plasma concentrations is unlikely to be important clinically.

Comments:

- The author did not specified the approach for QT correction.
- The variability of terfenadine & paroxetine are large.

		Terfenadine alone	Terfenadine +paroxetine
Terfenadine	Cmax (range ng/ml)	0.39-40.3	0.84-27.3
	AUC (range, ng h/ml)	10.8-409	11.0-287
Carboxyterfenadine	Cmax (range ng/ml)	111-356	138-246
	AUC (range, ng h/ml)	839-2081	956-1900

Paroxetine Css (ng/ml): 1.35-105.0

4. **PD interaction between paroxetine and alprazolam following a repeated-dose scheme in healthy subjects: Garcia-Gea C et al**

Comments:
No PK measures were reported. The PD measures were not validated in clinical trials.

5. **Current Paroxetine label:**

Drugs Metabolized by Cytochrome P450IIIA4: An in vivo interaction study involving the co-administration under steady- state conditions of paroxetine and terfenadine, a substrate for cytochrome P450IIIA4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of P450IIIA4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine's in vitro Ki and its lack of effect on terfenadine's in vivo clearance predicts its effect on other IIIA4 substrates, paroxetine's extent of inhibition of IIIA4 activity is not likely to be of clinical significance.

6. **Current Sertraline label**

Drugs Metabolized by P450 3A4 – In three separate in-vivo interaction studies, sertraline was coadministered with cytochrome P450 3A4 substrates, terfenadine, carbamazepine, or

cisapride under steady- state conditions. The results of these studies indicated that sertraline did not increase plasma concentrations of terfenadine, carbamazepine, or cisapride. These data indicate that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance. Results of the interaction study with cisapride indicate that sertraline 200 mg (q.d.) induces the metabolism of cisapride (cisapride AUC and Cmax were reduced by about 35%).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wen-Hwei Chou
9/30/03 07:51:56 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
9/30/03 08:05:42 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-434/S-001

ADMINISTRATIVE

Division of Neuropharmacological Drug Products

REGULATORY PROJECT MANAGER
LABELING REVIEW

Sponsor: **Pfizer Inc. for Pharmacia & Upjohn Company**

Supplements	Drug Name	Submission Date	Last Approved Supplement	CBE	Supplement Provides For
NDA 21-434/ SLR-001	Xanax XR (alprazolam) Extended-Release Tablets	March 11, 2003	NDA approved on 1/17/03	Yes	Update to PRECAUTIONS/Drug Interactions section of labeling to include additional guidance to the physician regarding potential drug interactions of alprazolam with sertraline and paroxetine.
NDA 18-276/ SLR-038	Xanax (alprazolam) Tablets	April 2, 2003	SLR-035 on 5/2/00	No	
NDA 18-276/ SLR-039	Xanax (alprazolam) Tablets	October 1, 2003	SLR-035 on 5/2/00	No	Revisions to various sections of the current Xanax labeling to be consistent with the recently approved Xanax XR labeling.

REVIEW

Reviewed by Medical Officer: Yes; The medical officer has completed his review for NDA 18-276/SLR-038 and NDA 21-434/SLR-001 and recommends changes to the sponsors proposed labeling. The sponsor has agreed to the Division's proposed changes and the medical officer recommends an approval action for these supplements. The medical officer has completed his review of NDA 18-276/SLR-039 and recommends approval of this supplement.

Upon receipt of NDA 21-434/SLR-001 submitted as a "Changes Being Effective Supplement (CBE)", the previous Project Manager, Anna Marie Homonnay Weikel, informed the sponsor that the submission did not qualify as a CBE. The sponsor agreed not to implement the changes until an approval action was issued by the Agency.

A side-by-side labeling comparison was performed for each of the above proposed labeling supplements to the Division's last approved labeling for each supplement. Based on this comparison, the above supplements only provide for the changes listed above.

CONCLUSIONS

1. The above labeling supplements only provide for the labeling revisions listed in the table above.
2. Based on the medical officer's review of the above supplements, I recommend issuing an approval letter.

Richardae Taylor, Pharm.D.
Regulatory Health Project Manager

Robbin Nighswander, R.Ph., M.S.
Supervisory Regulatory Health Project Manager

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richardae Taylor
4/9/04 01:50:41 PM
CSO

Robbin Nighswander
4/9/04 01:53:34 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-434/S-001

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-434/S-001

PRIOR APPROVAL SUPPLEMENT

Pharmacia & Upjohn
Attention: Roma Thomas
Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Ms. Thomas:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Xanax XR® Extended-release Tablets

NDA Number: 21-434

Supplement number: S-001

Date of supplement: March 11, 2003

Date of receipt: March 12, 2003

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 12, 2003 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Neuropharmacological Drugs, HFD-120
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drugs
Attention: Document Room
1451 Rockville Pike
Rockville, Maryland 20852

If you should have any questions, please call Ms. Anna Marie H. Weikel, Regulatory Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Robbin Nighswander, R.Ph.
Chief Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Anna-Marie Homonnay
3/24/03 04:19:18 PM

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

March 11, 2003

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

RE: NDA 21-434
Xanax XR® Tablets (alprazolam)
Panic Related Disorders

Changes Being Effected (CBE-30)
Labeling Supplement

Dear Sir / Madam:

As per our e-mail communication to Ms. Anna Marie Weikel, FDA Sr. Regulatory Project Manager, dated February 14, 2003, Pharmacia & Upjohn[1] wishes to submit a labeling supplement for **XANAX® Tablets and XANAX XR Tablets.** The purpose of this supplement is to add to the **PRECAUTIONS** in the Drug Interaction section further guidance to the physician regarding potential drug interactions of alprazolam with sertraline and paroxetine (please refer to 21 CFR 314.70 (c) (2) (i)). The proposed labeling supplement for **XANAX Tablets** immediate release formulation will be addressed in a separate submission to **NDA 18-276.**

Labeling
The current **Drug Interactions** section for XANAX XR indicates that data from in vitro studies with alprazolam suggests a possible drug interaction with sertraline and paroxetine. Included in this supplement are more recent results from clinical studies. The published literature articles contained in this supplement discuss results of in vivo drug interactions studies of alprazolam with sertraline and paroxetine. These studies provide scientific evidence that neither paroxetine nor sertraline will alter the pharmacokinetics or pharmacodynamics of alprazolam in vivo.

In addition please note that the current approved labeling for both sertraline and paroxetine indicate that the extent of inhibition of P450 3A4 activity is not likely to be of clinical significance. Based on the data from in vivo studies and the current approved labeling for paroxetine and sertraline, Pharmacia believes it is appropriate [redacted]

[1] Pharmacia and Upjohn Company is the holder of NDA 21-434 and is a wholly owned subsidiary of the Pharmacia Corporation.

The CD-ROM contains the following files and directory structure:

Main Directory – N21434

- Cover Letter (cover.pdf)
- 356h Form (356h.pdf)
- User Fee Form (userfee.pdf)
- Table of Contents (ndatoc.pdf)
- Justification for Labeling Revision (other.pdf)
- Reference 1 (other1.pdf)
- Reference 2 (other2.pdf)
- Reference 3 (other3.pdf)
- Reference 4 (other4.pdf)
- Reference 5 (other5.pdf)
- Reference 6 (other6.pdf)

Subdirectory – Labeling

- FPL - Composed (copy code 819 612 001) (PI1.pdf)
- FPL - Size adjusted for ease of reading (copy code: 819 612 001) (PI2.pdf)
- Mock up of Proposed Text (PI3.pdf)
- Labeling Table of Contents (labeltoc.pdf)

The enclosed CD-ROM has been scanned with Trend Micro OfficeScan Corporate Edition for Windows NT version 5.02 and found to be virus free.

If you have any questions regarding this submission, please contact me by telephone at 269.833.4379 or by fax at 269.833.8237. Please send all correspondence to Mail-Code 0200-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Roma J. Thomas

Roma J. Thomas
Regulatory Manager
Global Regulatory Affairs

RJT:kmv
Attachments

cc: Anna Marie Weikel, R.Ph., Sr. Regulatory Project Manager
Division of Neuropharmacological Drug Products, HFD-120
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Woodmont II Building 4th floor
1451 Rockville Pike
Rockville, MD 20858