CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 18-276/S-038

Name: Xanax Tablets

Generic Name: alprazolam immediate-release

Sponsor: Pharmacia & Upjohn Company

Approval Date: 04/02/2004

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APPLICATION NUMBER:

NDA 18-276/S-038

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APPLICATION NUMBER:

NDA 18-276/S-038

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 18-276/S-038

FINAL PRINTED LABELING

Xanax®

alprazolam tablets, USP

C IV

PHARMACIA

Xanax
alprazolam tablets

0811557929

Xanax
alprazolam tablets

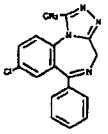
0811557929

DESCRIPTION

XANAX 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-4H-s-triazolo [4,3-α] [1,4] benzodiazepine.

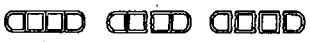
The structural formula is represented to the right:



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 Tablet, for oral administration, contains 0.25, 0.5, 1 or 2 mg of alprazolam.

XANAX Tablets, 2 mg, are multi-scored and may be divided as shown below:



Complete 2 mg Tablet	Two 1 mg segments	Four 0.5 mg segments

Inactive ingredients: Cellulose, corn starch, docusate sodium, lactose, magnesium stearate, silicon dioxide and sodium benzoate. In addition, the 0.5 mg tablet contains FD&C Yellow No. 6 and the 1 mg tablet contains FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereo specific receptors at several sites within the central nervous sys-

Xanax

brand of alprazolam tablets

tem. Their exact mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Following oral administration, alprazolam is readily absorbed. Peak concentrations in the plasma occur in one to two hours following administration. Plasma levels are proportionate to the dose given; over the dose range of 0.5 to 3.0 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 predominant metabolites are α-hydroxy-alprazolam and a benzophenone derived from alprazolam. The biological activity of α-hydroxy-alprazolam is approximately one-half that of alprazolam. The benzophenone metabolite is essentially inactive. Plasma levels of these metabolites are extremely low, thus precluding precise pharmacokinetic description. However, their half-lives appear to be of the same order of magnitude as that of alprazolam. Alprazolam and its metabolites are excreted primarily in the urine.

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

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

Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function and impaired renal function. Changes have also been demonstrated in geriatric patients. A mean half-life of alprazolam of 16.3 hours has been observed in healthy elderly subjects (range: 9.0-26.9 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.

INDICATIONS AND USAGE

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

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

Anxiety associated with depression is responsive to XANAX.

XANAX is also indicated for the treatment of panic disorder, with or without agoraphobia.

Studies supporting this claim were conducted in patients whose diagnoses corresponded closely to the DSM-III-R criteria for panic disorder (see CLINICAL STUDIES).

Panic disorder is an illness characterized by recurrent panic attacks. The panic attacks, at least initially, are unexpected. Later in the course of this disturbance certain situations, eg, driving a car or being in a crowded place, may become associated with having a panic

attack. These panic attacks are not triggered by situations in which the person is the focus of others' attention (as in social phobia). The diagnosis requires four such attacks within a four week period, or one or more attacks followed by at least a month of persistent fear of having another attack. The panic attacks must be characterized by at least four of the following symptoms: dyspnea or smothering sensations; dizziness, unsteady feelings, or faintness; palpitations or tachycardia; trembling or shaking; sweating; choking; nausea or abdominal distress; depersonalization or derealization; paresthesias; hot flashes or chills; chest pain or discomfort; fear of dying; fear of going crazy or of doing something uncontrolled. At least some of the panic attack symptoms must develop suddenly, and the panic attack symptoms must not be attributable to some known organic factors. Panic disorder is frequently associated with some symptoms of agoraphobia.

Demonstrations of the effectiveness of XANAX by systematic clinical study are limited to four months duration for anxiety disorder and four to ten weeks duration for panic disorder; however, patients with panic disorder have been treated on an open basis for up to eight months without apparent loss of benefit. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

XANAX Tablets are contraindicated in patients with known sensitivity to this drug or other benzodiazepines. XANAX 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 is contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP 3A) (see WARNINGS and PRECAUTIONS–Drug Interactions).

WARNINGS

Dependence and withdrawal reactions, including seizures:

Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to XANAX. These include a spectrum of withdrawal symptoms; the most important is seizure (see DRUG ABUSE AND DEPENDENCE). Even after relatively short-term use at the doses recommended for the treatment of transient anxiety and anxiety disorder (ie, 0.75 to 4.0 mg per 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, the duration of treatment (three months compared to six months) had no effect on the ability of patients to taper to zero dose. In contrast, patients treated with doses of XANAX greater than 4 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day.

The importance of dose and the risks of XANAX as a treatment for panic disorder:

Because the management of panic disorder often requires the use of average daily doses of XANAX above 4 mg, the risk of dependence among panic disorder patients may be higher than that among those treated for less severe anxiety. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder showed a high rate of rebound and withdrawal symptoms in patients treated with XANAX compared to placebo treated patients.

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.

In a controlled clinical trial in which 63 patients were randomized to XANAX 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.

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In a larger database comprised of both controlled and uncontrolled studies in which 641 patients received XANAX, discontinuation-emergent symptoms which occurred at a rate of over 5% in patients treated with XANAX and at a greater rate than the placebo treated group were as follows:

DISCONTINUATION-EMERGENT SYMPTOM INCIDENCE

Percentage of 641 XANAX-Treated Panic Disorder Patients Reporting Events

Body System/Event			
Neurologic		**Gastrointestinal**	
Insomnia	29.5	Nausea/Vomiting	16.5
Light-headedness	19.3	Diarrhea	13.6
Abnormal involuntary movement	17.3	Decreased salivation	10.6
Headache	17.0	**Metabolic-Nutritional**	
Muscular twitching	6.9	Weight loss	13.3
Impaired coordination	6.6	Decreased appetite	12.8
Muscle tone disorders	5.9		
Weakness	5.8	**Dermatological**	
Psychiatric		Sweating	14.4
Anxiety	19.2		
Fatigue and Tiredness	18.4	**Cardiovascular**	
Irritability	10.5	Tachycardia	12.2
Cognitive disorder	10.3		
Memory impairment	5.5	**Special Senses**	
Depression	5.1	Blurred vision	10.0
Confusional state	5.0		

From the studies cited, it has not been determined whether these symptoms are clearly related to the dose and duration of therapy with XANAX in patients with panic disorder.

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

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 and its treatment:

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

Interdose Symptoms:

Early morning anxiety and emergence of anxiety symptoms between doses of XANAX have been reported in patients with panic disorder taking prescribed maintenance doses of XANAX. 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. In these situations, it is recommended that the same total daily dose be given divided as more frequent administrations (see DOSAGE AND ADMINISTRATION).

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Risk of dose reduction:

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

XANAX Tablets are not of value in the treatment of psychotic patients and should not be employed in lieu of appropriate treatment for psychosis. Because of its CNS depressant effects, patients receiving XANAX 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.

Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If XANAX 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, XANAX is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

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

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

Potent CYP 3A inhibitors:

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

Drugs demonstrated to be CYP 3A inhibitors on the basis of clinical studies involving alprazolam (caution and consideration of appropriate alprazolam dose reduction are 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 metabolism by inhibition of CYP 3A are discussed in the PRECAUTIONS section (see PRECAUTIONS–Drug Interactions).

PRECAUTIONS

General: If XANAX 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 (see DRUG INTERACTIONS).

As with other psychotropic medications, the usual precautions with respect to administration of the drug and size of the prescription are indicated for severely

depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

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

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

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

Information for Patients:

For all users of XANAX:

To assure safe and effective use of benzodiazepines, all patients prescribed XANAX should be provided with the following guidance. In addition, panic disorder patients, for whom doses greater than 4 mg/day are typically prescribed, should be advised about the risks associated with the use of higher doses.

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.

Additional advice for panic disorder patients:

The use of XANAX at doses greater than 4 mg/day, often necessary to treat panic disorder, is accompanied by risks that you need to carefully consider. When used at doses greater than 4 mg/day, which may or may not be required for your treatment, XANAX has the potential to cause severe emotional and physical dependence in some patients and these patients may find it exceedingly difficult to terminate treatment. In two controlled trials of six to eight weeks duration where the ability of patients to discontinue medication was measured, 7 to 29% of patients treated with XANAX did not completely taper off therapy. In a controlled postmarketing discontinuation study of panic disorder patients, the patients treated with doses of XANAX greater than 4 mg/day had more difficulty tapering to zero dose than patients treated with less than 4 mg/day. In all cases, it is important that your physician help you discontinue this medication in a careful and safe manner to avoid overly extended use of XANAX.

In addition, the extended use at doses greater than 4 mg/day appears to increase the incidence and severity of withdrawal reactions when XANAX is discontinued. These are generally minor but seizure can occur, especially if you reduce the dose too rapidly or discontinue the medication abruptly. Seizure can be life-threatening.

Laboratory Tests: Laboratory tests are not ordinarily required in otherwise healthy patients.

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

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

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

Drugs demonstrated to be CYP 3A inhibitors of possible clinical significance on the basis of clinical studies involving alprazolam (caution is recommended during coadministration with alprazolam):

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

Propoxyphene—Coadministration of propoxyphene decreased the maximum plasma concentration of alprazolam by 6%, decreased clearance by 36%, and increased half-life by 58%.

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

Drugs and other substances demonstrated to be CYP 3A inhibitors on the basis of clinical studies involving benzodiazepines metabolized similarly to alprazolam or on the basis of in vitro studies with alprazolam or other benzodiazepines (caution is recommended during coadministration with alprazolam): Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from *in vitro* studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. Data from *in vitro* studies of benzodiazepines other than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during the coadministration of any of these with alprazolam (see WARNINGS).

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: XANAX 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 XANAX.

Pediatric Use: Safety and effectiveness of XANAX 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 XANAX should be used in the elderly to preclude the development of ataxia and oversedation (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Side effects to XANAX Tablets, if they occur, are gen-

erally observed at the beginning of therapy and usually disappear upon continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of alprazolam, eg, drowsiness or light-headedness.

The data cited in the two tables below are estimates of untoward clinical event incidence among patients who participated under the following clinical conditions: relatively short duration (ie, four weeks) placebo-controlled clinical studies with dosages up to 4 mg/day of XANAX (for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety) and short-term (up to ten weeks) placebo-controlled clinical studies with dosages up to 10 mg/day of XANAX in patients with panic disorder, with or without agoraphobia.

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

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

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

ANXIETY DISORDERS

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

**None reported*

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

In addition to the relatively common (ie, greater than 1%) untoward events enumerated in the table above, the following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritabil-

ity, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

PANIC DISORDER

	Treatment-Emergent Symptom Incidence*	
	XANAX	PLACEBO
Number of Patients	1388	1231
% of Patients Reporting:		
Central Nervous System		
Drowsiness	76.8	42.7
Fatigue and Tiredness	48.6	42.3
Impaired Coordination	40.1	17.9
Irritability	33.1	30.1
Memory Impairment	33.1	22.1
Light-headedness/Dizziness	29.8	36.9
Insomnia	29.4	41.8
Headache	29.2	35.6
Cognitive Disorder	28.8	20.6
Dysarthria	23.3	6.3
Anxiety	16.6	24.9
Abnormal Involuntary Movement	14.8	21.0
Decreased Libido	14.4	8.0
Depression	13.8	14.0
Confusional State	10.4	8.2
Muscular Twitching	7.9	11.8
Increased Libido	7.7	4.1
Change in Libido (Not Specified)	7.1	5.6
Weakness	7.1	8.4
Muscle Tone Disorders	6.3	7.6
Syncope	3.8	4.8
Akathisia	3.0	4.3
Agitation	2.9	2.6
Disinhibition	2.7	1.5
Paresthesia	2.4	3.2
Talkativeness	2.2	1.0
Vasomotor Disturbances	2.0	2.6
Derealization	1.9	1.2
Dream Abnormalities	1.8	1.5
Fear	1.4	1.0
Feeling Warm	1.3	0.5
Gastrointestinal		
Decreased Salivation	32.6	34.2
Constipation	26.2	15.4
Nausea/Vomiting	22.0	31.8
Diarrhea	20.6	22.8
Abdominal Distress	18.3	21.5
Increased Salivation	5.6	4.4
Cardio-Respiratory		
Nasal Congestion	17.4	16.5
Tachycardia	15.4	26.8
Chest Pain	10.6	18.1
Hyperventilation	9.7	14.5
Upper Respiratory Infection	4.3	3.7
Sensory		
Blurred Vision	21.0	21.4
Tinnitus	6.6	10.4
Musculoskeletal		
Muscular Cramps	2.4	2.4
Muscle Stiffness	2.2	3.3
Cutaneous		
Sweating	15.1	23.5
Rash	10.8	8.1
Other		
Increased Appetite	32.7	22.8
Decreased Appetite	27.8	24.1
Weight Gain	27.2	17.9
Weight Loss	22.6	16.5
Micturition Difficulties	12.2	8.6
Menstrual Disorders	10.4	8.7
Sexual Dysfunction	7.4	3.7
Edema	4.9	5.6
Incontinence	1.5	0.6
Infection	1.3	1.7

**Events reported by 1% or more of XANAX patients are included.*

In addition to the relatively common (ie, greater than 1%) untoward events enumerated in the table above, the following adverse events have been reported in association with the use of XANAX: seizures, hallucinations, depersonalization, taste alterations, diplopia, elevated bilirubin, elevated hepatic enzymes, and jaundice.

Xanax

brand of alprazolam tablets

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

To discontinue treatment in patients taking XANAX, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of XANAX 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.

Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients. Therefore, the same precaution must be exercised when using doses of XANAX greater than 4 mg/day in treating patients with panic disorders as is exercised with the use of any psychotropic drug in treating depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

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

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

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

**Less than 1%*

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

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

Post Introduction Reports: Various adverse drug reactions have been reported in association with the use of XANAX 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 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

Xanax

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symptoms similar in character to those noted with sedative/hypnotics and alcohol have occurred following discontinuance of benzodiazepines, including XANAX. 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 XANAX 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 XANAX 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 XANAX. It is recommended that all patients on XANAX 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 XANAX. 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 XANAX, especially those receiving higher doses for extended periods. Addiction-prone individuals should be under careful surveillance when receiving XANAX. 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 Tablets have been assigned to Schedule IV.

OVERDOSAGE

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

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

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

General Treatment of Overdose: Overdosage reports with XANAX Tablets are limited. As in all cases of drug overdosage, respiration, pulse rate, and blood pressure should be monitored. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. If hypotension occurs, it may be combated by the use of vasopressors. Dialysis is

of limited value. As with the management of intentional overdosing with any drug, it should be borne in mind that multiple agents may have been ingested.

Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS should be consulted prior to use.

DOSAGE AND ADMINISTRATION

Dosage should be individualized for maximum beneficial effect. While the usual daily dosages given below will meet the needs of most patients, there will be some who require doses greater than 4 mg/day. In such cases, dosage should be increased cautiously to avoid adverse effects.

Anxiety disorders and transient symptoms of anxiety:

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

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

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

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

Panic disorder:

The successful treatment of many panic disorder patients has required the use of XANAX at doses greater than 4 mg daily. In controlled trials conducted to establish the efficacy of XANAX in panic disorder, doses in the range of 1 to 10 mg daily were used. The mean dosage employed was approximately 5 to 6 mg daily. Among the approximately 1700 patients participating in the panic disorder development program, about 300 received XANAX in dosages of greater than 7 mg/day, including approximately 100 patients who received maximum dosages of greater than 9 mg/day. Occasional patients required as much as 10 mg a day to achieve a successful response.

Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses in patients especially sensitive to the drug. Thereafter, the dose can be increased at intervals equal to at least 5 times the elimination half-life (about 11 hours in young patients, about 16 hours in elderly patients). Longer titration intervals should probably be used because the maximum therapeutic response may not occur until after the plasma levels achieve steady state. 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. For patients receiving doses greater than 4 mg/day, periodic reassessment and consideration of dosage reduction is advised. In a controlled postmarketing dose-response study, patients treated with doses of XANAX greater than 4 mg/day for three months were able to taper to 50% of their total maintenance dose without apparent loss of clinical benefit. Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided. (See WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE).

The following regimen is one that follows the principles outlined above:

Treatment may be initiated with a dose of 0.5 mg three

times 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 per day. Slower titration to the dose levels greater than 4 mg/day may be advisable to allow full expression of the pharmacodynamic effect of XANAX. To lessen the possibility of interdose symptoms, the times of administration should be distributed as evenly as possible throughout the waking hours, that is, on a three or four times per day schedule.

The necessary duration of treatment for panic disorder patients responding to XANAX is unknown. 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.

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.

HOW SUPPLIED

XANAX Tablets are available as follows:

0.25 mg (white, oval, scored, imprinted "XANAX 0.25")	
Bottles of 100	NDC 0009-0029-01
Reverse Numbered Unit Dose (100)	NDC 0009-0029-46
Bottles of 500	NDC 0009-0029-02
Bottles of 1000	NDC 0009-0029-14
0.5 mg (peach, oval, scored, imprinted "XANAX 0.5")	
Bottles of 100	NDC 0009-0055-01
Reverse Numbered Unit Dose (100)	NDC 0009-0055-46
Bottles of 500	NDC 0009-0055-03
Bottles of 1000	NDC 0009-0055-15
1 mg (blue, oval, scored, imprinted "XANAX 1.0")	
Bottles of 100	NDC 0009-0090-01
Bottles of 500	NDC 0009-0090-04
Bottles of 1000	NDC 0009-0090-13
2 mg (white, oblong, multi-scored, imprinted "XANAX" on one side and "2" on the reverse side)	
Bottles of 100	NDC 0009-0094-01
Bottles of 500	NDC 0009-0094-03

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

℞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.

CLINICAL STUDIES

Anxiety Disorders:

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

Panic Disorder:

Support for the effectiveness of XANAX in the treatment of panic disorder came from three short-term, placebo-controlled studies (up to 10 weeks) in patients with diagnoses closely corresponding to DSM-III-R criteria for panic disorder.

The average dose of XANAX was 5-6 mg/day in two of the studies, and the doses of XANAX were fixed at 2 and 6 mg/day in the third study. In all three studies, XANAX was superior to placebo on a variable defined as "the number of patients with zero panic attacks" (range, 37-83% met this criterion), as well as on a global improve-

Xanax
brand of alprazolam tablets

ment score. In two of the three studies, XANAX was superior to placebo on a variable defined as "change from baseline on the number of panic attacks per week" (range, 3.3-5.2), and also on a phobia rating scale. A subgroup of patients who were improved on XANAX during short-term treatment in one of these trials was continued on an open basis up to eight months, without apparent loss of benefit.

Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, Michigan 49001, USA
Revised December 2001

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-276/S-038

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

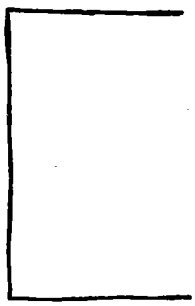
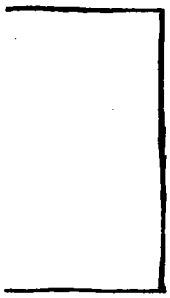
I. Summary of Submission

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:

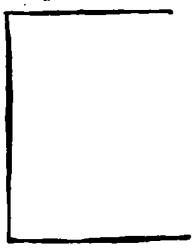
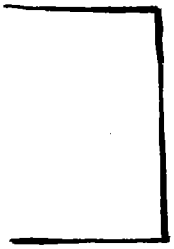
Data from in vitro studies of alprazolam suggest a possible interaction with alprazolam for the following: sertraline and paroxetine. [redacted]

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 18-276/S-038

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.

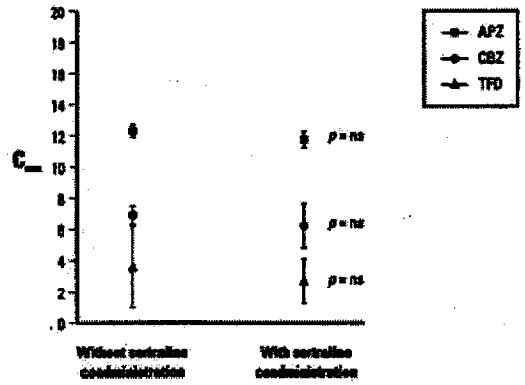


FIGURE 2. C_{max} for alprazolam (APZ), carbamazepine (CBZ), and terfenadine (TFD) with and without sertraline co-administration. C_{max} units are ng/ml for alprazolam and terfenadine and mg/ml for carbamazepine.

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.

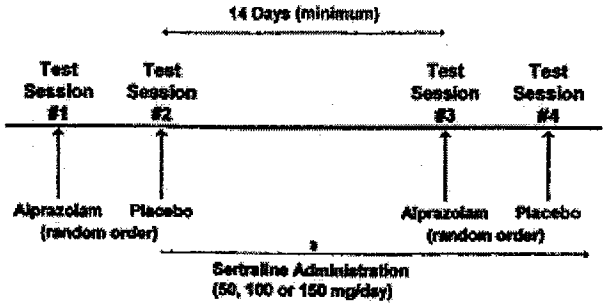


FIG. 1. Study design.

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] ± 7.5	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 ± 52.0	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 ($p = 0.05$).

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:

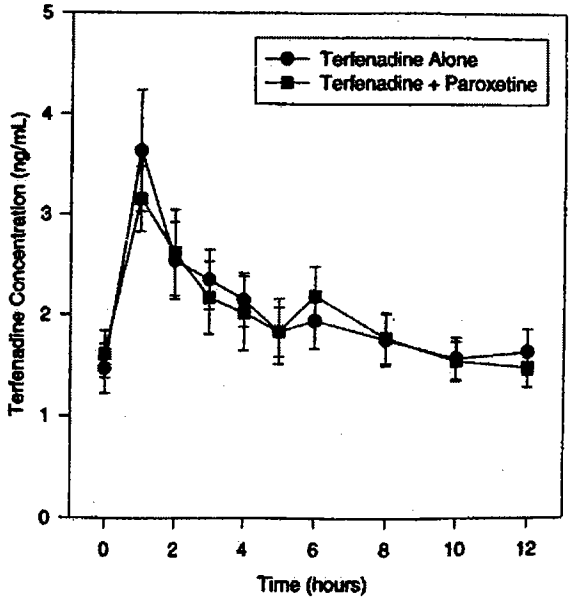


FIG. 1. Mean (SEM) plasma concentrations of terfenadine after repeated oral administration of terfenadine (60 mg twice daily) alone and with paroxetine at steady state (20 mg once daily) in 10 healthy subjects (subject 10 excluded).

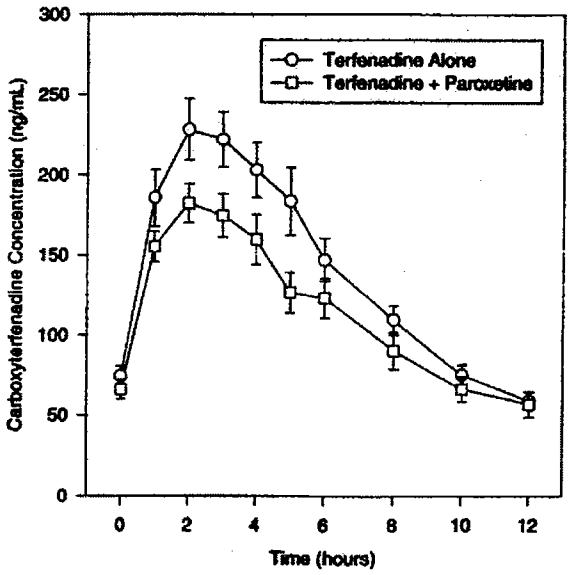


FIG. 2. Mean (SEM) plasma concentrations of carboxyterfenadine after repeated oral administration of terfenadine (60 mg twice daily) alone and with paroxetine at steady state (20 mg once daily) in 11 healthy subjects.

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 (SD)	36.4 (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

Subject	Terfenadine C_{ss} (ng/mL)		Terfenadine AUCτ (ng·hr/mL)		Carboxyterfenadine C_{ss} (ng/mL)		Carboxyterfenadine AUCτ (ng·hr/mL)	
	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	1,307
4	5.06	3.94	22.8	34.5	304	145	1,837	1,135
5	4.35	2.85	20.7	11.0	322	252	1,871	1,325
6	5.03	3.32	34.0	23.1	353	206	1,562	1,289
7	5.87	4.46	38.3	30.9	287	245	1,936	1,610
8	2.29	3.84	15.4	23.4	299	245	1,833	1,533
9	4.78	4.55	33.1	36.7	278	246	2,081	1,803
10	40.3	27.3	409	287	209	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 (111–353)	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, 1.06)		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 18-276/S-038

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 18-276/S-038

CORRESPONDENCE

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (269) 833-4000

April 2, 2003

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

RE: NDA 18-276
XANAX® Tablets
(alprazolam tablets)

Prior Approval
Electronic Labeling Supplement

Dear Sir / Madam:

As indicated in the submission to NDA 21-434 XANAX XR® Tablets, dated March 11, 2003, Pharmacia & Upjohn[1] also wishes to submit a labeling supplement for **XANAX Tablets, NDA 18-276.** The purpose of this supplement is to add to the **PRECAUTIONS** section of the package insert under **Drug Interactions** further guidance to the physician regarding potential drug interactions of alprazolam with sertraline and paroxetine.

Labeling

The current **Drug Interactions** section for **XANAX Tablets** 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 – N18276

- Cover Letter (cover.pdf)
- 356h Form (356h.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

- Current PI (copy code: 811 557 929) (pi.pdf)
- Mock up PI of proposed revision (proposed_pi.pdf)
- Labeling Table of Contents (labeltoc.pdf)

Subdirectory – Other

- Userfee Form (userfee.pdf)

The enclosed CD-ROM has been scanned with Trend Micro OfficeScan Corporate Edition for Windows NT version 5.00 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 0200-298-142.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Roma Thomas

Roma J. Thomas
Regulatory Manager
Global Regulatory Affairs

RJT:SEH
Attachments

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