

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***  
**NDA 18-276/S-035**

***Name:*** Xanax Tablets

***Generic Name:*** alprazolam immediate-release

***Sponsor:*** Pharmacia & Upjohn Company

***Approval Date:*** 05/02/2000

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:  
NDA 18-276/S-035**

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RESEARCH**

**APPLICATION NUMBER: 18-276/S-035**

**APPROVAL LETTER**

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**MAY 2 2000**

NDA 18-276/S-035

Pharmacia & Upjohn Company  
Attention: Michael D. Burdick  
7000 Portage Road  
Kalamazoo, Michigan 49001

Dear Mr. Burdick:

Please refer to your supplemental new drug application dated August 20, 1998, received August 24, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XANAX® (alprazolam) tablets.

This supplement was submitted in accordance with the August 27, 1997, FR Notice to provide for an additional 'Geriatric Use' subsection.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted draft labeling. Accordingly, the supplemental application is approved effective on the date of this letter.

Please submit 16 copies of final printed labeling, ten of which are individually mounted on heavy-weight paper. Approval of this submission by FDA is not required before it is used.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you should have any questions regarding these comments, please contact Ms. Anna M. Homonnay-Weikel, R.Ph., Project Manager, at (301) 594-5535.

Sincerely yours,

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

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 18-276/S-035**

**FINAL PRINTED LABELING**



alprazolam tablets, USP



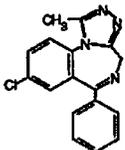
Pharmach  
Alprazolam

#### 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-*a*] [1,4] benzodiazepine.

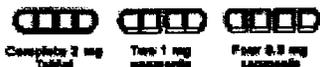
The structural formula is represented to the right:



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:



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 system.

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

Following oral administration, alprazolam is readily absorbed. Peak concentrations in the plasma occur in one to two hours following administration. Plasma levels are proportionate to the dose given; over the dose range of 0.5 to 3.0 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 *o*-hydroxy-alprazolam and a benzophenone derived from alprazolam. The biological activity of *o*-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.

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	Percentage	Body System/Event	Percentage
<b>Neurologic</b>		<b>Gastrointestinal</b>	
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	<b>Metabolic-Nutritional</b>	
Muscular twitching	6.9	Weight loss	13.3
Impaired coordination	6.6	Decreased appetite	12.8
Muscle tone disorders	5.9	<b>Dermatological</b>	
Weakness	5.8	Sweating	14.4
<b>Psychiatric</b>		<b>Cardiovascular</b>	
Anxiety	19.2	Tachycardia	12.2
Fatigue and Tiredness	18.4	<b>Special Senses</b>	
Irritability	10.5	Blurred vision	10.0
Cognitive disorder	10.3		
Memory impairment	5.5		
Depression	5.1		
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 interdose interval. In these situations, it is rec-

ommended that the same total daily dose be given divided as more frequent administrations (see DOSAGE AND ADMINISTRATION).

**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 PRECAU-

TIONS 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 (eg, 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.

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

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

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

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

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

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

**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 generally observed at the beginning of therapy and usually disappear upon continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of alprazolam, eg, drowsiness or 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			
Weight Gain	7.3	9.3	*
Weight Loss	2.7	2.7	*
*None reported	2.3	3.0	*

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

#### PANIC DISORDER

Number of Patients % of Patients Reporting:	Treatment-Emergent Symptom Incidence*	
	XANAX	PLACEBO
<b>Central Nervous System</b>		
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	20.5
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	7.5
Syncope	3.8	4.8
Akathisia	3.0	4.3
Agitation	2.9	2.6
Disinhibition	2.7	1.5
Parasthesia	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
<b>Gastrointestinal</b>		
Decreased Salivation	32.8	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
<b>Cardio-Respiratory</b>		
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
<b>Sensory</b>		
Blurred Vision	21.0	21.4
Tinnitus	6.6	10.4
<b>Musculoskeletal</b>		
Muscular Cramps	2.4	2.4
Muscle Stiffness	2.2	3.3
<b>Cutaneous</b>		
Sweating	15.1	23.5
Rash	10.8	8.1
<b>Other</b>		
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.

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 post-traumatic 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
<b>Hematology</b>				
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	*	*	*	*
<b>Urinalysis</b>				
Albumin	-	*	-	*
Sugar	-	*	-	*
RBC/HPF	-	3.4	-	5.0
WBC/HPF	-	25.7	-	25.9
<b>Blood Chemistry</b>				
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 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 overdose 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<sub>50</sub> 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 overdose.

**General Treatment of Overdose:** Overdose reports with XANAX Tablets are limited. As in all cases of drug overdose, 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 reinstated 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 pro-

portion 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:

<b>0.25 mg (white, oval, scored, imprinted "XANAX 0.25")</b>	
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
<b>0.5 mg (peach, oval, scored, imprinted "XANAX 0.5")</b>	
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
<b>1 mg (blue, oval, scored, imprinted "XANAX 1.0")</b>	
Bottles of 100	NDC 0009-0090-01
Bottles of 500	NDC 0009-0090-04
Bottles of 1000	NDC 0009-0090-13
<b>2 mg (white, oblong, multi-scored, imprinted "XANAX" on one side and "2" on the reverse side)</b>	
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].

**Caution:** Federal law prohibits dispensing without prescription.

#### **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 improvement 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**  
Kalamazoo, Michigan 49001, USA  
RevisedXXXX

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 18-276/S-035**

**MEDICAL REVIEW**

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Review and Evaluation of Clinical Data  
NDA#18-276

APR 25 2000

**Sponsor:** Pharmacia & Upjohn  
**Drug:** Xanax® (alprazolam)  
**Material Submitted:** SLR-035 Geriatric labeling supplement  
**Correspondence Date:** August 20, 1998  
**Date Received:** August 24, 1998

**I. Background**

Xanax® (alprazolam) is a benzodiazepine anxiolytic. This submission from the sponsor is a response to the Federal Register directive that asked for the addition of the "Geriatric Use" subsection in labeling. The sponsor provides draft-labeling changes without any supporting data or journal articles.

**II. Proposed draft changes to labeling**

*Geriatric Use-* The sponsor recommends limiting elderly patients to the lowest effective dose to preclude development of ataxia and over sedation. They state that plasma alprazolam concentrations are higher in elderly due to reduced clearance of the drug when compared to younger patients. This is supported by existing information in the CLINICAL PHARMACOLOGY section. Kaplan, Bertz, and Pomara also report these phenomena in pharmacokinetic and pharmacodynamic studies of alprazolam in elderly and younger subjects (Bertz, Kroboth et al. 1997; Kaplan, Greenblatt et al. 1998; Pomara, Tun et al. 1998).

**III. Conclusions and Recommendations**

The sponsor fulfills the requirement for the geriatric labeling guidelines and submits an attached journal article that is summarized in draft labeling. The draft labeling is approvable from a clinical standpoint.

ISI

Paul J/Andreason, M.D., Date  
Medical Reviewer,  
FDA CDER ODE1 DNDP HFD 120

cc: NDA 18-276  
HFD 120  
HFD 120/  
P Andreason  
AM Homonnay  
T Laughren

4-25-00

ISI

Bertz, R. J., P. D. Kroboth, et al. (1997). "Alprazolam in young and elderly men: sensitivity and tolerance to psychomotor, sedative and memory effects." J Pharmacol Exp Ther 281(3): 1317-29.

Kaplan, G. B., D. J. Greenblatt, et al. (1998). "Single-dose pharmacokinetics and pharmacodynamics of alprazolam in elderly and young subjects." J Clin Pharmacol 38(1): 14-21.

Pomara, N., H. Tun, et al. (1998). "The acute and chronic performance effects of alprazolam and lorazepam in the elderly: relationship to duration of treatment and self-rated sedation." Psychopharmacol Bull 34(2): 139-53.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 18-276/S-035**

**CLINICAL PHARMACOLOGY  
BIOPHARMACEUTICS REVIEW**

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COMPLETED APR 18 2000

APR 18 2000

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

AKW

Submission Dates: 8/20/98  
OCPB Receipt Date: 3/8/2000

NDA: 18-276/S-035  
Name of Drug: Xanax (Alprazolam) Tablets  
Indication of Drug: Anxiety  
Sponsor: Pharmacia & Upjohn  
Type of Submission: Geriatric Labeling Supplement  
Reviewer: Hong Zhao, Ph.D.

**Labeling Change**

This supplement is being submitted in response to the August 27, 1997 Federal Register notice which provided a list of drug classes targeted for priority implementation of Geriatric Use statements. Psychotic drugs, including anxiolytics, are included on the priority list of drug classes. The proposed labeling revision concerns the use of alprazolam in the elderly. A new "Geriatric Use" subsection is being added to the PRECAUTION section of the labeling as follows:

*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).*

**Comment 1**

The information being added to the new "Geriatric Use" subsection of the PRECAUTION section of labeling is based on existing information in the CLINICAL PHARMACOLOGY section of labeling. It is acceptable to add the new subsection on "Geriatric Use" under PRECAUTION section.

**Please convey this Comment to the Medical Officer.**

Hong Zhao, Ph.D. \_\_\_\_\_

SI

100

RD/FT Initialed by Raman Baweja, Ph.D. \_\_\_\_\_

SI

cc: NDA: 18-276/S-035 (Alprazolam Tablets), HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 18-276/S-035**

**ADMINISTRATIVE DOCUMENTS**

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APR 20 2000

Division of Neuropharmacological Drug Products  
REGULATORY PROJECT MANAGER LABELING REVIEW

**Application Number:** 18-276/S-035

**Name of Drug:** Xanax® Tablets, 0.25, 0.5, 1 or 2 mg

**Sponsor:** Pharmacia & Upjohn Co.

**Submission Date(s):** August 20, 1998

**Receipt Date(s):** August 24, 1998

**Background:**

This supplement was submitted in accordance with the August 27, 1997, FR Notice to provide for an additional 'Geriatric Use' subsection under PRECAUTIONS.

**Material Reviewed:**

1. Proposed **marked-up** draft labeling FPL (0811 557 826) submitted as a geriatric labeling supplement SLR-035.
2. Most recently approved FPL (0811 557 826), approved on November 24, 1998, under SLR-034.

**Labeling Review:** (see attached review notes)

**Conclusions:** No additional changes have been effected by the company other than what was submitted in this supplement. Thus, with the concurrence of the Medical Officer and the Biopharmaceutics reviewer, an approval letter may issue if the proposed language for the geriatric subsection is acceptable.

Labeling reviewed by:

SI

\_\_\_\_\_  
Anna M. Homonnay-Weikel, R.Ph.  
Regulatory Project Manager

Supervisory Comment/Concurre:

SI

\_\_\_\_\_  
John Purvis  
Chief, Project Management Staff

cc:

Original 18-276/S-035  
HFD-120/Div. Files  
HFD-120/Homonnay

**Labeling Changes:**

When FPL (811 557 826) was compared to the proposed marked-up draft labeling (811 557 826) included in this supplement, the following labeling changes were noted and are listed below by section:

**PREVIOUS FPL**  
FPL 811 557 826

**PRECAUTIONS:**  
Note #1  
[Addition of geriatric use subsection]

**PROPOSED DRAFT LABELING**  
FPL 811 557 826

**PRECAUTIONS:**  
Note #1  
**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.)



1141

Food and Drug Administration  
Rockville MD 20857

NDA 18-276/S-035

Pharmacia & Upjohn Co.  
7000 Portage Road  
Kalamazoo, MI 49001

SEP 4 1998

Attention: Michael D. Burdick, Senior Regulatory Manager

Dear Mr. Burdick:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Xanax Tablets

NDA Number: 18-276

Supplement Number: S-035

Date of Supplement: August 20, 1998

Date of Receipt: August 24, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 23, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research  
Division of Neuropharmacological Drug Products, HFD-120  
Office of Drug Evaluation I  
Attention: Document Control Room 4008  
5600 Fishers Lane  
Rockville, MD 20857

Sincerely,

151

John S. Purvis  
Chief, Project Management Staff  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

NDA 18-276/035

Page 2

cc:

Original NDA 18-276/035

HFD-120/Div. Files

HFD-120/CSO/A. Homonnay

filename: C:\WPWIN61\TEMPLATE\FDA\18-276.035

SUPPLEMENT ACKNOWLEDGEMENT

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Pharmacia & Upjohn

Office of:  
Michael D. Burdick  
Senior Regulatory Manager  
Regulatory Affairs

Telephone No.: 616-833-8041  
Facsimile No.: 616-833-8009

ORIGINAL

August 20, 1998

Division of Neuropharmacological Drug Products HFD-120  
Center for Drug Evaluation and Research  
Document Control Room, Parklawn Building  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

CENTER FOR DRUG EVALUATION  
AND RESEARCH

AUG 24 1998

RECEIVED HFD-120

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

NDA NO. 18-276 REF. NO. SLR-035  
NDA SUPPL FOR Labeling

Sir/Madam:

We are supplementing our New Drug Application for the above to propose a revision to the package insert. The proposed revision concerns use of alprazolam in the elderly. This supplement is being submitted in response to the August 27, 1997 Federal Register notice which provided a list of drug classes targeted for priority implementation of Geriatric Use statements. Psychotropic drugs, including anxiolytics, are included on the priority list of drug classes.

The proposed text is provided in mock-up form in Attachment 1, using the current insert as a basis. The insert has been changed to add a new "Geriatric Use" subsection to the PRECAUTIONS section.

This proposed revision was developed in consideration of the requirements of 21 CFR §201.57(f)(10). The information contained in the new "Geriatric Use" subsection represents information already stated elsewhere in the current insert.

Pharmacia & Upjohn  
7000 Portage Road  
Kalamazoo, MI 49001-0199  
USA

Telephone (616) 833-4000

We look forward to the approval of this proposed insert change. If you have any questions regarding the contents of this submission, please contact me at (616) 833-8041. Please send correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

A handwritten signature in black ink, appearing to read "Michael Burdick". The signature is fluid and cursive, with the first name "Michael" being larger and more prominent than the last name "Burdick".

Michael D. Burdick  
Senior Regulatory Manager  
Regulatory Affairs

MDB:law

Attachments

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<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b> <b>PUBLIC HEALTH SERVICE</b> <b>FOOD AND DRUG ADMINISTRATION</b> <b>APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE</b> <b>OR AN ANTIBIOTIC DRUG FOR HUMAN USE</b> <i>(Title 21, Code of Federal Regulations, 314)</i>		Form Approved: OMB No. 0910-0001. Expiration Date: 12/31/95 See OMB Statement on Page 3.	
		<b>FOR FDA USE ONLY</b> <b>CENTER FOR DRUG EVALUATION</b> <b>AND RESEARCH</b>	
		DATE RECEIVED AUG 24 1998	DIVISION ASSIGNED DIVISION NO. ASS.
<b>NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314.11).</b>			
NAME OF APPLICANT Pharmacia & Upjohn Company		DATE OF SUBMISSION August 20, 1998	
ADDRESS (Number, Street, City, State and Zip Code) 7000 Portage Road Kalamazoo, Michigan 49001		TELEPHONE NO. (Include Area Code) (616) 833-8542	
		NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (if previously issued) 18-276	
<b>DRUG PRODUCT</b>			
ESTABLISHED NAME (e.g., USP/USAN) Alprazolam		PROPRIETARY NAME (if any) XANAX® Tablets (alprazolam tablets)	
CODE NAME (if any)		CHEMICAL NAME 8-chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3-a][1,4] benzodiazepine	
DOSAGE FORM Oral Tablets		ROUTE OF ADMINISTRATION Oral	STRENGTH(S) 0.25, 0.5 1 and 2 mg
PROPOSED INDICATIONS FOR USE			
LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:			
<b>INFORMATION ON APPLICATION</b>			
<b>TYPE OF APPLICATION (Check one)</b>			
<input type="checkbox"/> THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) <input type="checkbox"/> THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)			
<b>IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION</b>			
NAME OF DRUG		HOLDER OF APPROVED APPLICATION	
<b>TYPE SUBMISSION (Check one)</b>			
<input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> AN AMENDMENT TO A PENDING APPLICATION <input checked="" type="checkbox"/> SUPPLEMENTAL APPLICATION <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> RESUBMISSION			
SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv))			
<b>PROPOSED MARKETING STATUS (Check one)</b>			
<input type="checkbox"/> APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) <input type="checkbox"/> APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)			

**CONTENTS OF APPLICATION**

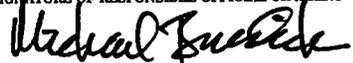
This application contains the following items: *(Check all that apply)*

	1. Index (See letter)
	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling (4 copies)
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER (Specify)

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT Michael D. Burdick, Senior Regulatory Manager	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	DATE August 20, 1998
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ADDRESS (Street, City, State, Zip Code) 7000 Portage Road Kalamazoo, Michigan 49001	TELEPHONE NO. (Include Area Code) (616) 833-8542
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(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)