CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 018276/S033

Trade Name : XANAX TABLETS

Generic Name: Alprazolam

Sponsor : Pharmacia and Upjohn

Approval Date: December 20, 1996

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-276/S-033

Pharmacia & Upjohn Company
Attention: Terry L. Reinstein, R.Ph.
7000 Portage Road
Kalamazoo, Michigan 49001-0199

DEC 20 1996

Dear Mr. Reinstein:

Please refer to your December 29, 1995 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xanax (alprazolam) Tablets, 0.25, 0.5, 1, and 2 mg.

We also refer to an Agency approval letter for supplemental application S-017 dated November 6, 1990.

Supplemental application S-033 provides changes to the WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, DRUG ABUSE AND DEPENDENCE, and DOSAGE AND ADMINISTRATION sections of labeling. These proposed labeling changes are supported by the results of two post-marketing studies (Protocols M/200/0474 and M/2000/0473). These studies address all of the Phase IV commitments, i.e., acute dose-response, chronic dose-response, and withdrawal effects (relation to dose and duration at the time of withdrawal and to method of tapering), requested as a condition of approval of the panic disorder indication under supplement S-017.

We have completed the review of supplemental application S-033, including the submitted draft labeling, 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 enclosed marked-up draft labeling dated December 29, 1995. Accordingly, supplemental application S-033 is approved effective on the date of this letter.

Furthermore, we note that you have adequately responded to the Phase IV commitments made as a condition of approval of S-017.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 18-276/S-033. Approval of this submission by FDA is not required before the labeling 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.

Should you have any questions concerning this NDA, please contact Mr. Merril Mille, Senior Regulatory Management Officer at (301) 594-5528.

Sincerely yours,

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

ENCLOSURE

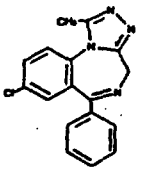
Enclosure

Xanax®

brand of alprazolam tablets, USP

C IV

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.

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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 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 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. The co-administration of oral contraceptives to healthy women increased the half-life of alprazolam as compared to that in healthy control women (mean: 12.4 hours, n=11 versus 9.6 hours, n=9). There was a prolongation in the mean half-life of alprazolam from

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12.4 hours (range: 7.2-18.4 hours, n=9) to 16.6 hours (range: 10.0-24.3 hours, n=9) by the co-administration of cimetidine to the same healthy adults. In patients with alcoholic liver disease the half-life of alprazolam ranged between 5.6 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 lightheadedness; nausea, diarrhea, or other abdominal distress; flushes or chills; frequent urination; trouble swallowing or 'lump in throat'); *Vigilance and Scanning* (feeling keyed up or on edge; exaggerated startle response; difficulty concentrating or 'mind going blank' because of anxiety; trouble falling or staying asleep; irritability). These symptoms must not be secondary to another psychiatric disorder or caused by some organic factor.

Anxiety associated with depression is responsive to 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.

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. Post-marketing surveillance data suggest that the risk of dependence and its severity appear to be greater in patients treated with relatively high doses (above 4 mg per day) and for long periods (more than 8-12 weeks)

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 post-marketing 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

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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			
Neurologic		**Gastrointestinal**	
Insomnia	29.5	Nausea/Vomiting	16.5
Lightheadedness	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. The ability of patients to completely discontinue therapy with XANAX after long-term therapy has not been reliably determined.

In a controlled post-marketing 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 ~~XANAX doses of greater than 4 mg daily~~ 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).

doses of XANAX greater than 4 mg/day

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

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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.

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 ~~higher doses~~ are typically prescribed, should be advised about the risks associated with the use of higher doses.

doses greater than 4 mg/day

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:

doses greater than 4 mg/day,

The use of XANAX at ~~the high doses (above 4 mg per day),~~ often necessary to treat panic disorder, is accompanied by risks that you need to carefully consider. When used at ~~high doses for long intervals,~~ 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 ~~XANAX-treated~~ patients did not completely taper off therapy. ~~The ability of patients to completely discontinue therapy with XANAX after long-term therapy has not been reliably determined.~~ In all cases, it is important that your physician

treated with XANAX

In a controlled post-marketing 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.

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help you discontinue this medication in a careful and safe manner to avoid overly extended use of XANAX.

In addition, the extended use at ~~high dosee~~ 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.

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

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

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

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

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

Pregnancy: Teratogenic Effects: Pregnancy Category D: (See WARNINGS Section)

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

Labor and Delivery: 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 in children below the age of 18 years have not been established.

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 lightheadedness.

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.

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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
Lightheadedness	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, 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

	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
Lightheadedness/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
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

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PANIC DISORDER (continued)

	Treatment-Emergent Symptom Incidence*	
	XANAX	PLACEBO
Number of Patients	1388	1231
% of Patients Reporting:		
Gastrointestinal		
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
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.

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 require an even slower dosage reduction.~~

Some patients may benefit from an even slower dosage reduction. In a controlled post-marketing 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 ~~the higher doses of XANAX~~ 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.

doses of XANAX greater than 4 mg/day

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	–	•	–	•

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(continued)	XANAX		PLACEBO	
	Low	High	Low	High
Urinalysis				
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, 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 ~~higher doses~~ 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,

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pulse rate, and blood pressure should be monitored. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. If hypotension occurs, it may be combated by the use of vasopressors. Dialysis is of limited value. As with the management of intentional overdosing with any drug, it should be borne in mind that multiple agents may have been ingested.

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

DOSAGE AND ADMINISTRATION

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

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 ~~maximum XANAX~~ 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.

~~However, in the absence of systematic studies evaluating the dose response relationship, the dosing regimen for the administration of XANAX to patients with panic disorder must be based on generic principles.~~ 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. Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided. (See WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE)

For patients receiving doses greater 4 mg/day, periodic reassessment and consideration of dosage reduction is advised. In a controlled post-marketing 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.

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 higher dose levels~~ 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. dose levels greater than 4 mg/day

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,

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only after stabilization, should a less rapid schedule of discontinuation be attempted. Although no experimental studies have been conducted to assess the comparative benefits of various discontinuation regimens, a possible approach is to reduce the dose by no more than 0.5 mg every three days, with the understanding that some patients may require an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens.

In a controlled post-marketing 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.

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

(continued below)

(0.5 mg continued)

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
Reverse Numbered Unit Dose (100)	NDC 0009-0090-46
Bottles of 500	NDC 0009-0090-04
Bottles of 1000	NDC 0009-0090-13
2 mg (white, oblong, multi-scored, imprinted XANAX 2)	
Bottles of 100	NDC 0009-0094-01
Bottles of 500	NDC 0009-0094-03

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

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 lose of benefit.

US Patent No. 3,987,052

The Upjohn Company
Kalamazoo, Michigan 49001, USA
Revised ~~June 1993~~

~~811-557-783~~
691157

NOV 22 1996

Review and Evaluation of Clinical Data
sNDA # 18-276

Sponsor:	Upjohn Company
Drug:	Xanax Tablets
Material Submitted:	Supplement to NDA 18-276, two studies reviewing long-term efficacy and tapering regimens, to provide a proposed revision to package insert.
Correspondence Date:	December 29, 1995
Date Received:	January 5, 1996
Related NDAs	

I. Background

Xanax (alprazolam) is a triazolo-benzodiazepine that is marketed worldwide for the treatment of anxiety, mixed anxiety and depression, and panic disorders is currently approved for "management of anxiety disorder" (most closely resembling DSM-III-R generalized anxiety disorder), panic disorder, and anxiety associated with depression in the United States. As part of the approval letter, the FDA requested clinical studies that would address 1)issues related to dose, duration of treatment and discontinuation of alprazolam in patients with panic disorder, specifically, the relationship of maintenance dose and duration of treatment to the incidence and severity of discontinuation effects and to the ability to withdraw from therapy successfully, and 2) whether tapering regimens would have different effects during discontinuation after long-term use of alprazolam at high doses.

The sponsor presents the results of two studies in this supplement that address the above Phase IV study requests.

II. Data Reviewed

Two post-marketing studies in patients with panic disorder with and without agoraphobia treated with alprazolam and draft labeling changes based on the results of those studies were submitted. The studies were titled:

- Short and long-term discontinuation of alprazolam in patients with panic disorder with and without agoraphobia (TR 9158-95-001)

- Short and long-term response study of alprazolam in the treatment of panic disorder with agoraphobia (TR 9158-95-017).

III. "Short and long-term discontinuation of alprazolam in patients with panic disorder with and without agoraphobia." (TR 9158-95-001)

A. Objectives

The primary objectives of the study were 1) to examine the relationship of maintenance dose and duration to the incidence and severity of discontinuation effects and to the ability of patients to successfully withdraw from alprazolam therapy, and 2) to evaluate two different discontinuation regimens for alprazolam after long-term use at high (greater than 4 mg/day) doses.

B. Experimental Design

This was a 4 phase study that consisted of the following:

- Phase 1- a one week placebo washout phase followed by randomization into one of four treatment groups:

  1-Short term, 8-week (ST), single-blind maintenance phase followed by double-blind "standard taper discontinuation" (STD) regimen of a 0.5 mg reduction in dose every 3-4 days as described in the currently approved labeling.

  2-ST single blind maintenance phase followed by a double blind slow taper discontinuation regimen (SLW) consisting of no more than 1 mg/week reduction in dose for 6 weeks then 0.5 mg/week reduction in dose for the next four weeks then 0.25 mg/week reduction in dose for the next seven weeks.

  3-Long term, 22-week (LT), single-blind maintenance phase followed by double-blind STD taper discontinuation phase.

  4-LT single-blind maintenance phase followed by double-blind SLW taper discontinuation phase.

- Phase 2- a single blind flexible dose treatment phase where an effective treatment dose of alprazolam reached, medical adverse events prevented further dose increases, or a maximum dose of 10 mg/day was attained. Patients who reached the

maximum dose of 10 mg/day were to have reached this dose by the sixth week of treatment.

- Phase 3- a single blind ST or LT maintenance phase as described above.

- Phase 4- a double blind STD or SLW taper discontinuation phase as described above.

Patients who dropped out of the study during the maintenance or discontinuation phase had the option of continuing on the blinded taper medication or being referred to a unblinded physician to be treated at his/her discretion.

C. Description of study

This was a multi center study that systematically examined the success of tapering patients to no medication, the rate at which discontinuation effects occurred and the severity of those effects between two taper-discontinuation regimens. The study was open to male and non-pregnant, non-lactating, female patients between the ages of 18-65 inclusive with panic disorder with and without agoraphobia. The treatment dose titration schedule is listed in table 1 in the appendix.

The schedule of assessments for both the titration/maintenance and taper phases are listed in the appendix in tabes 2 and 3 respectively.

The primary efficacy variables were taper-to-zero dose success rate, tolerance-reduction percentage, and remission/rebound/relapse. These efficacy measures and their results will be discussed in detail by Hillary Lee, Ph.D. in her discussion of efficacy of the two studies submitted with this supplement.

Criteria measured to assess the safety of alprazolam during the course the study included the number of treatment-emergent signs and symptoms (TESS), DESS, and post-discontinuation-emergent signs and symptoms (P-DESS), as determined from the CRFs; withdrawal syndrome; vital signs; and laboratory results.

a. <u>Treatment-Emergent Signs and Symptoms</u>

TESS were defined as signs and symptoms that occurred for the first during the treatment phase or those that occurred during the treatment phase with a severity greater than at baseline (Week 1).

b. Discontinuation-Emergent Signs and Symptoms

DESS were defined as any sign or symptom that occurred for the first time during the taper-discontinuation phase (including two weeks post-taper) or that occurred during the taper-discontinuation phase with a severity greater than at baseline (last maintenance) or any prior treatment week (including Week 1).

C. Post-Discontinuation-Emergent Signs and Symptoms

P-DESS were defined as any sign or symptom that occurred more than two weeks after the post-taper-continuation phase for the first time or those that occurred with a greater severity than at any previous time in the study, including baseline (Week 1), maintenance phase, and taper-discontinuation phase plus two weeks post-taper.

d. Withdrawal Syndrome

Withdrawal syndrome was to be determined by the ratio of the symptom frequency of DESS versus the symptom frequency at baseline. The ratio was used to rank order the CRF items. Those items that had a higher ratio became "Indicator Symptoms" (the numerical value for the ratio that identified an Indicator Symptom was determined at the end of the study in an effort to improve sensitivity and specificity). A cluster of three or more Indicator Symptoms in any week was used to identify patients with withdrawal syndrome.

e. Vital Signs

Vital signs, including height, weight, blood pressure, and pulse, were measured at the screening visit. Weight, blood pressure, and pulse were also measured at the Week 1 visit, at Week 13 for the S-T and L-T maintenance phase patients, at Week 27 for the L-T maintenance phase patients, and at the Week T20 visit for all patients (or at the point at which they dropped out of the study).

f. Laboratory Evaluations

Laboratory evaluations included the following tests:

Hematology	**Clinical Chemistry**	**Urine Analysis**
Hemoglobin	Glucose	Albumin
Hematocrit	Creatinine	Sugar
White Cell Count	Uric Acid	Microscopic
Differential	Total Bilirubin	White blood cell (WBC)
Seg Neutrophils	Serum Glutamic OxaloaceticTransaminase (SGOT, AST)	Red blood cell (RBC)
Bands	Serum Glutamic Pyruvic Transaminase (SGPT; ALT)	Casts
Lymphocytes	Alkaline Phosphatase	
Monocytes		
Eosinophils		
Basophils Other (specify) Platelet Estimate		

These evaluations were conducted for all patients at the screening visit; at the initial medication visit for patients with abnormal values at the screening visit; the Week 13 visit for all (S-T and L-T) patients in the maintenance phase; and at the last visit for all patients.

D. Results

1. Patient Disposition

A total of 312 patients were enrolled in the study and 236 (75.6%) completed the single-blind treatment phase. 122 (39.1%) completed the taper-discontinuation phase. Of the 312 patients enrolled, 196 received doses up to and including 4 mg/day and 116 received doses over 4 mg/day.

Patient disposition study 001		
Reason for termination	**Maintenance n=312 n (%)**	**Taper n=312 n %**
Lack of Efficacy	3 (1)	0
Death	0	0
Adverse events (serious & non-serious)	20 (6)	29 (9)
Intercurrent Illness	6 (2)	4 (1)
Other	48 (15)	80 (26)
Total Discontinued during phase	77 (25)	113 (36)
Completed Phase	235 (75)	122 (39)

2. Efficacy Results

a. Taper to Zero:

The only factor which reached significance in the success rate at tapering to zero was the final maintenance dose. Significantly fewer patients taking greater than 4 mg/day of alprazolam were able to taper to zero than those taking 4 mg/day or less (55% vs 81% respectively; $p<0.001$). Duration of maintenance and taper-discontinuation regimen had no effect of whether patients were able to taper to zero.

b. Tolerance to reduction (Tolerance reduction potential [TRP])

Low dose patients were generally more successful at reducing their dose as opposed to patients needing higher doses; however, there were no discernable differences in the survival curves of patients in the four treatment groups. Low versus high dose patients were self-selecting based on the severity of their illness and their tolerance to adverse events associated with taking alprazolam.

c. Remission/relapse/rebound

Patients in the LT group remained in remission statistically more often in the taper-discontinuation phase than the ST group. There was no effect on remission/relapse/rebound with regard to slow

versus standard taper-discontinuation regimen or the mg amount of the final maintenance dose.

3. Safety Results
There were no deaths in this study.

There were 15 adverse events that met FDA criteria as serious. The patients' summaries were reviewed individually. None of these events were likely to be related to alprazolam.

Case summaries of dropouts were reviewed individually. Reasons for discontinuation were either currently in labeling or judged likely not to be related to alprazolam treatment.

Potentially clinically significant laboratory abnormalities were reviewed on a case by case basis. No labeling changes are necessary based on these uncontrolled cases.

The most pertinent safety finding was that more patients in the STD group experienced withdrawal syndrome than in the SLW group (6.1% vs 0% respectively).

IV. Short and long-term response study of alprazolam in the treatment of panic disorder with agoraphobia (TR 9158-95-017).

A. Objectives

The objectives of this study were to compare doses of alprazolam of 4 mg/day versus doses greater than 4 mg/day in the treatment of panic disorder with and without agoraphobia and to determine if the initial maintenance dose can be reduced by 50% for long-term maintenance without loss of therapeutic effect.

B. Experimental Design

This was a multi center, randomized double-blind, fixed versus flexible dose, parallel-group, study. The design comprises three periods.

- Phase 1-prerandomization single-blind placebo washout followed by 3-6 week titration up to a dose of 4 mg/day of alprazolam.
- Phase 2-double-blind postrandomization maintenance period which includes first, a final titration phase to doses greater than 4 mg/day versus doses held at 4 mg/day; second, a short term maintenance phase (9 weeks duration) where the alprazolam doses will remain stable; third, a long-term maintenance phase

where the higher dose group will have their maintenance dose decreased by 50% (11 weeks duration).

- Phase 3-a double-blind taper-discontinuation period of 13 weeks.

The study was open to male and non-pregnant, non-lactating, female patients between the ages of 18-65 inclusive with panic disorder with and without agoraphobia.

C. Description of study

Eligible patients were withdrawn from current psychoactive medications and entered into the single-blind Prerandomization Period during which they were initially treated with placebo to achieve a drug-free period of 1 week. Patients who remained eligible for the study at the end of placebo treatment began taking alprazolam daily in a single-blind fashion. The initial daily dose of 0.5 mg of alprazolam was increased until a beneficial clinical effect (defined by zero panic attacks for a 1-week period or a rating of "very much improved" or "much improved" on the Clinical Global Impressions (CGI assessment completed by the investigator) was observed, a maximum-tolerated dose was achieved, or a maximum daily dose of 4 mg was achieved and maintained for a minimum of 10 to 14 days. Responders to alprazolam treatment at daily doses of $\leq$ 4 mg were discontinued from the study and treated at the investigator's discretion.

Non-responders to $\leq$ 4 mg/day of alprazolam were randomized to one of three groups:

1) Held at 4 mg: The alprazolam dosage was held constant at 4 mg/day for the 23-Week Maintenance Period (25% of patients).

2) Titrated to > 4 mg and Maintained Dose(Maintained Dose Group): The alprazolam dosage was titrated upward until a beneficial clinical effect was achieved, or the maximum daily dose of 10 mg was reached, or the maximum-tolerated dose was reached; patients were maintained at that dose until the end of the Maintenance Period (37.5% of the patients).

3) Titrated to > 4 mg and 50% Dose Reduction (50% Dose Reduction Group):The alprazolam dosage was titrated upward until a beneficial clinical effect was achieved, the maximum daily dose of 10 mg was reached, or the maximum, tolerated dose was reached. After 12 weeks of treatment at this dose, the dose was reduced by 50% and then maintained for an additional 11 weeks (37.5% of the patients).

Patients who discontinued treatment for any reason after randomization and all patients who completed 23 weeks of double-blind, maintenance treatment entered the double-blind, Taper-Discontinuation Period, during which their dose of alprazolam was tapered to zero at a rate of 0.5 mg every 3 to 4 days. Patients who could not tolerate this rate of taper were removed from the taper-&discontinuation portion of the study and referred to a non-blinded referral physician to be treated at his/her discretion. Three months after referral, the non-blinded referral physician was contacted by study site personnel to determine if the patient had tapered off alprazolam and if any medical events had occurred.

Table C in the appendix contains a schedule of assessments for the study 017.

Efficacy Measures

a. Primary Efficacy Outcome Measures

Primary efficacy outcome measures were response rate to alprazolam, total number of panic attacks, and CGI Severity of Illness and Global Improvement.

b. Secondary- Efficacy Outcome Measures

Secondary efficacy outcome measures were the Phobic Anxiety and Depression Dimensions of the SCL-90, the Phobia Scale, the HAM-A total score, and the MOSCT-36 health status questionnaire.

Safety Measures

a. Adverse Events

Patients were observed and interviewed by the investigator for adverse events at each office visit. An adverse event (the sponsor uses the term "medical event") was defined as any experience that affected a person's health regardless of their relationship to the study drug. Medical events spontaneously reported by the patients and medical events elicited from the patients through open-ended questioning by the investigator were recorded from the time of the first dose of placebo to the end of treatment with blinded study medication, and at the 3-month follow-up visit for dropouts sent to a non-blinded referral physician. Additionally, at each study visit, except for the 3-month follow-up visit, patients were asked if they experienced any one of 34 specific symptoms that are

expected in this patient population or during alprazolam treatment. Investigators recorded all medical events in the CRF.

Investigators were provided with specific medical event reporting instructions which required them to do each of the following: 1) classify the event by seriousness (serious or non-serious); 2) record the time of onset and cessation of the event; 3) record the nature of the event (episodic, constant/single event, or chronic); 4) record the maximum intensity of the event (mild, moderate, or severe); 5) record the outcome of the event (recovered/no residual effects, recovered/residual effects, continues, or death); 6) judge whether the event was related to the study medication (yes/no); and 7) record the actions taken with the study medication because of the event (none, discontinued, reduced dose, interrupted therapy, or increased dose).

Investigators were provided with a dictionary of selected medical events, each of which was classified according to a primary, secondary, or tertiary term. If possible, investigators were to record certain medical events using this dictionary. In the event that a primary, secondary or tertiary term for a medical event did not best describe a symptom spontaneously reported by the patient, the exact symptom reported by the patient was recorded. Medical events were reported according to each investigator's verbatim description of the event.

Adverse events considered serious were defined as fatal or life-threatening (resulted in an immediate risk of death), was permanently or substantially disabling, required or prolonged hospitalization, or was a congenital anomaly, cancer, or medication overdose. All medical events were to he followed until the events resolved or until the patient's participation in the study ended, or until the investigator could classify them as "chronic" or "stable." A Post-Study Follow-Up Report form was used to document the resolution of such events.

b. Laboratory Evaluations

Hematology, chemistry, and urinalysis measurements were obtained at Screen and at the end of the Short-term Maintenance Period (Week M12) or at the time the patient was discontinued from the study. The end of the Short-term Maintenance Period was chosen as the final laboratory point because patients would be receiving the highest dose of study medication at this time point; laboratory values were evaluated for changes that occurred during drug treatment. The investigator also evaluated laboratory values for any clinical significance related to the patient's medical history and health status.

D. Results

1. Patient disposition

A total of 336 patients were enrolled in the study. 292 completed the 1-week placebo washout period and entered the initial titration phase. Of the 292 patients who received alprazolam, 175 completed the initial up-titration period to a dose of 4 mg/day without reaching a therapeutic response as defined above. These 175 patients were randomized into the three treatment groups.

Patient disposition study 017: Taper-discontinuation period			
Study Status	Held at 4mg N=29(100)	M.D. N=39(100)	50% R.D. N=46(100)
Discontinuation			
Adverse Events	8 (28)	8 (21)	7 (15)
Other	7 (24)	13 (33)	19 (41)
Comleted Taper Protocol	14 (48)	18 (26)	20 (44)

2. Efficacy Results

Efficacy results will be discussed in the review by Hillary Lee, Ph.D.

3. Safety Results

There were no deaths in the study.

There were 13 patients who had serious adverse events. The patients' summaries were reviewed individually. None were judged as likely to be related to alprazolam treatment by this reviewer.

Line listings of patients who discontinued the study due to adverse events were reviewed along with selected case summaries if the adverse event was not listed in labeling. Reasons for discontinuation were either mentioned in current labeling or were judged unlikely to be related to alprazolam treatment.

Patients' summaries were reviewed when these patients had laboratory values judged to be potentially clinically significant.

All of the abnormalities were either currently listed in labeling or judged unlikely to be related to alprazolam therapy.

The frequency of treatment emergent adverse events that occurred more than 5% of the time and were significantly different between groups is as follow:

Treatment emergent adverse events that occurred more than 5% of the time and were significantly different between groups.

Body System Medical Event	Treatment Group		p-value
	Held at 4 mg n=46 %	Titrated to >4 mg n=129 %	
Rash	7	1	0.03
Incoordination	4	14	0.08
Sedation	26	42	0.06
Difficulty Concentrating	7	19	0.05
Depression	11	26	0.03
Irritability	9	26	0.02

There were no differences in treatment emergent adverse event occurrence rates between the maintained dose group versus 50% dose reduction group that reached a level of >5% and statistically significant.

Depression, irritability, and myalgia were more common in the maintained dose treatment group as opposed to the 50% reduction dose group .

Discontinuation emergent adverse events that occurred more than 5% of the time and were significantly different between groups.			
Body System Medical Event	Treatment Group		p-value
	Maintained Dose n=39 %	50% Dose Reduction n=46 %	
Myalgia	8	0	0.05
Depression	13	2	0.06
Irritability	8	0	0.05

Conclusions and Recommendations

The sponsors draft labeling recommendations are supported by the phase 4 studies that are provided. There are no other additions or deletions to labeling that are necessary at this point.

4/15/96

Paul J. Andreason, M.D.

11-22-96

I agree that labeling can be modified as proposed. See memo to file for more detailed comments.

T. Laughren

cc:
NDA# 18-276
HFD-120
HFD-120/PAndreason
GDubitsky
TLaughren
PDavid
T Parks

December 29, 1995

Internal Use Only
DESTROY UPON DISPOSAL

TR No.: 9158-95-001

Table 1. Titration Schedule

Study Visit When Bottle Dispensed	Bottle Label	Number of Tablets					
		Days of Week	7 AM	12 PM	6 PM	11 PM	Total Daily Dose (mg)
End of Week 1 (0.5-mg tablets)	Week 2	1	0	0	0	1	0.5
		2-4	1	1/2	1/2	1	1.5
		5-7	1	1	1	1	2
End of Week 2 (0.5-mg tablets)	Week 3	1-4	1 1/2	1 1/2	1 1/2	1 1/2	3
		5-7	2	2	2	2	4
End of Week 3 (start 1-mg tablets)	Week 4	1-4	1	1	1	2	5
		5-7	2	1	1	2	6
End of Week 4 (1-mg tablets)	Week 5	1-4	2	2	1	2	7
		5-7	2	2	2	2	8
End of Week 5 (1-mg tablets)	Week 6	1-4	2	2	2	3	9
		5-7	3	2	2	3	10

Table 2. Schedule of Activities: Titration through Short- (S-T) & Long- (L-T) Term Maintenance Phases TR 9158-95-001

Activities	Pre-Screen	Screen	Initial Medicine Visit	End of Week														
				Titration to ≤ 10-mg					S-T Maintenance				L-T Maintenance					
				1	2	3	4	5	7	9	11	13*	15	17	19	21	23	25	27*
SCID-UP-R Score Sheet	X																		
Informed Consent	X																		
History, Physical, Vital Signs		X																	
Medication History		X																	
Laboratory Report		X	(X)									X**							
Panic Diagnostic Checklist				X															
Admission Checklist				X															
Panic Attack and Anticipatory Anxiety				X	X	X	X	X	X	X	X	X**	X	X	X	X	X	X	X**
Clinical Global Impressions (CGI)				X	X	X	X	X	X	X	X	X**	X	X	X	X	X	X	X**
Symptoms Checklist-90 (SCL-90)				X								X**							X**
Phobia Scale				X								X**							X**
Hamilton Anxiety Scale (HAM-A)				X								X**							X**
Non-Investigational Medications (NIM)/Vital Signs				X								X**							X**
Medical Outcomes Studies Questionnaire Revised for Clinical Trials (MOSCT-36)				X								X**							X**
NIM			X		X	X	X	X	X	X	X		X	X	X	X	X	X	
Medication Record				X	X	X	X	X	X	X	X	X**	X	X	X	X	X	X	X**
Patient Diary			X	X	X	X	X	X	X	X	X	X**	X	X	X	X	X	X	X**
Medical Event Form (MEF)				X	X	X	X	X	X	X	X	X**	X	X	X	X	X	X	X**
Medical Event Form—Supplemental Information (MEFSI)	If and When Needed																		
Treatment Termination Record†												X**							X**
Final Termination Record/ Discontinuation Compliance‡	Upon Leaving Study																		
Post-Study Follow-up Report§	As Required																		
Dropout Taper Termination Record#	When Needed																		
Three-Month, Post-Dropout Termination Record©	End of Follow-Up																		

*S-T maintenance phase patients after Week 13 went directly to Taper (T1); L-T maintenance phase patients stayed on maintenance dose to end of Week 27, then Taper (T1).

†Treatment Termination Record was completed at Week 13 for all S-T and L-T maintenance phase patients, again at Week 27 for L-T maintenance phase patients, and at the time of dropout for any patient who left the study early.

‡All patients had a Final Termination Record/Discontinuation Compliance completed at last visit.

§Used to report course of unresolved medical event presumed to be drug-related or serious.

#Used for dropouts at the last week investigator saw the patient.

©Used at end of three months or whenever patient finished unblinded follow-up phase.

(X)Any abnormal labs were repeated.

**These forms were required at Weeks 13 (for S-T patients tapering, Week 27 and T20).

December 29, 1995

Table 3. Schedule of Activities: Taper Phase

TR 9158-95-001

Activities	End of Week																			
	Taper Discontinuation																			
	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20
SCID-UP R Score Sheet																				
Informed Consent																				
History, Physical, Vital Signs																				
Medication History																				
Laboratory Report																				
Panic Diagnostic Checklist																				X**
Admission Checklist																				
Panic Attack and Anticipatory Anxiety	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X**
Clinical Global Impressions (CGI)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X**
Symptoms Checklist-90 (SCL-90)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X**
Phobia Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X**
Hamilton Anxiety Scale (HAM-A)																				X**
Non-investigation Medications (NIM)/Vital Signs																				X**
Medical Outcomes Studies Questionnaire Revised for Clinical Trials (MOSCT-36)																				X**
NIM	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X**
Medication Record	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X**
Patient Diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X**
Medical Event Form (MEF)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X**
Medical Event Form—Supplemental Information (MEFSI)	If and When Needed																			
Treatment Termination Record*																				
Final Termination Record/Taper Discontinuation Compliance†	Upon Leaving Study																			
Post-Study Follow-up Report‡	As Required																			
Drop Out Taper Termination Record§	When Needed																			
Three-Month Post-Drop Out Termination Record#	End of Follow-Up																			

*All patients had a Treatment Termination Record completed at Week 13; all L-T maintenance phase patients at Week 27; and all patients (both S-T and L-T) had the Treatment Termination Record completed at time of dropout if they left the study early.

†All patients had a Final Termination Record/Discontinuation Compliance completed at last visit.

‡Used to report course of unresolved medical event presumed to be drug-related or serious.

§Used for dropouts at the last week investigator saw the patient.

#Used at end of three months or whenever patient finished unblinded follow-up phase.

**These forms were required at Week T20.

December 29, 1995

TR 9158-95-C

Table C. Schedule of Activities

Procedure/Activity	End of Week														
				Prerandomi-zation		Randomi-zation	Final Titration		Short-term Maintenance		Dose-Reduction	Long-term Maintenance		Taper D/C[c]	
	Pre-Screen	Screen	IMV[a]	PR1	PR2-3	PR4-7[b]	M1-2	M3	M4, 6, 8, 10	M12	M13-14	M15, 17, 19, 21	M23	T1-12	T13
Informed Consent, SCID-UP-R	X														
History, Physical, Medication History		X													
Laboratory tests[d]		X	X[f]							X					
Vital Signs[e,c]		X		X						X			X		X
Panic Disorder Diagnostic Checklist, Admission Checklist				X											
Panic Attack & Anticipatory Anxiety				X	X	X	X	X	X	X	X	X	X	X	X
CGI				X	X	X	X	X	X	X	X	X	X	X	X
SCL-90, Phobia Scale[d,e]				X		X		X	X	X	X	X	X	X	X
HAM-A, MOSCT-36[d,e]				X						X			X		X
Medical Events[d,e]				X	X	X	X	X	X	X	X	X	X	X	X
Patient Diary, Concomitant Medications			X	X	X	X	X	X	X	X	X	X	X	X	X

[a]Initial Medication Visit.
[b]Randomization occurred at Week PR4 to Week PR7 depending on the length of time required to maintain the patient on a daily alprazolam dose of 4 mg for 10 days.
[c]Taper Discontinuation.
[d]Obtained at end of Week M12 or earlier if patient dropped out.
[e]Obtained at the end of Week M23 or earlier if patient dropped out after Week M12.
[f]Abnormal laboratory results repeated at Initial Medication Visit.

1991

M E M O R A N D U M

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

DATE: November 22, 1996

Thomas P. Laughren

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Phase 4 Commitments for Xanax/Panic Disorder Approval

TO: File, NDA 18-276 (Xanax)
[**Note:** This memo should be filed with the 12-29-95 submission.]

1.0 Background

As part of the approval of Xanax for panic disorder, we asked and obtained Upjohn's agreement to conduct phase 4 studies to explore several questions:

-Acute dose/response for efficacy beyond 4-6 mg/day
-Dose/response for maintenance efficacy
-Relationship of maintenance dose and duration to withdrawal effects and difficulty in discontinuing treatment
-Relationship of withdrawal schedule to withdrawal effects

Upjohn subsequently conducted studies 473 and 474 to address these questions, and these studies were reported in this 12-29-95 submission. In addition, this submission includes labeling changes on the basis of the results from these 2 studies.

This submission has been reviewed by Drs. Hillary Lee and Paul Andreason, independently, and I refer to their reveiws for more detailed results on these studies.

2.0 Study 473

Study 473 produced data pertinent to the first 3 of the questions posed under Background.

Run-In Phase

-This study began with 292 panic disorder patients who were treated with Xanax at doses up to 4 mg/day during a 3-6 week run-in phase to find a sample of patients who were not fully responsive to a 4 mg/day dose. 67 of this original sample were declared responders, leaving 175 less than fully responsive patients for entry into the first double-blind phase of the study. Data on the clinical status of patients at the time of randomization following this run-in were not provided. Patients original baseline scores at the beginning of the run-in phase were used as baselines for this study.

Upward Titration/Maintenance Phase

-The 175 less than fully responsive patients were randomized to: (1) continuation on 4 mg/day (23 weeks); (2) titration to an optimal dose above 4 mg/day (up to a maximum of 10 mg/day) and maintenance at this dose for 23 weeks; and (3) titration to an optimal dose above 4 mg/day (up to a maximum of 10 mg/day) for 12 weeks, and then a 50% dose reduction for the remaining 11 weeks of this phase.

-Several findings were noteworthy from this phase:

> -The patients titrated beyond 4 mg/day to an optimal dose showed no more improvement than those maintained at 4 mg/day, either at M3 (presumably immediately after titration to optimal dose), or at M12 (after 9 weeks of maintenance at either optimal dose or 4 mg/day). For both groups there was a decrease in mean number of panic attacks per week from about 21/wk at the original baseline to about 9/wk at M3. There was a further reduction to about 6/wk at M12. Thus, there appeared to be no advantage to increasing the dose above 4 mg/day in less than fully responsive patients. However, the extent of the reduction in panic attack frequency in the 4 mg/day patients is also notable, and one has to wonder what it means to say that these 175 patients were non-responders. In fact, that finding raises doubt about the value of this experiment in producing any useful information pertinent to the question of acute dose response, since these patients appeared to be responders to doses of $\leq$ 4 mg/day, despite their characterization as nonresponders by the sponsor.
>
> -Although the results for the dose reduction maintenance phase were more mixed, I still think it is fair to say that there were no consistent differences in reduction in panic attack frequency between the three randomized groups. Thus, reducing the dose by 50% after stabilization did not appear to compromise the clinical effects of Xanax maintenance. Of course, without a placebo control arm during the maintenance phase, it is difficult to interpret this finding of no difference across treatment groups. Patients may have achieved this level of response without any treatment.

Withdrawal Phase

-This phase was described as a double-blind taper-discontinuation phase during which patients were presumably tapered to zero dose with a 0.5 mg/day reduction q 3-4 days. However, it appears that all patients were tapered on the same schedule, so, while the study may have been double-blind regarding the maintenance dose, investigators and patients clearly knew that all patients were being withdrawn and on the same schedule.

-Overall, there were no differences in discontinuation emergent signs and symptoms between the group maintained at their higher optimal dose and those patients whose doses were reduced by 50% during maintenance.

3.0 Study 474

Study 474 produced data pertinent to the last 2 questions posed under Background.

Titration Phase

This study began with 312 panic disorder patients who were treated with Xanax at doses up to 10 mg/day during a 6-week titration phase.

Maintenance/Withdrawal Phase

Once patients were stabilized on Xanax, they were randomized into 4 groups:
-8 week maintenance/standard taper
-8 week maintenance/slow taper
-22 week maintenance/standard taper
-22 week maintenance/slow taper

The standard taper regimen was a 0.5 mg reduction in dose q 3-4 days. Slow taper was a reduction of up to 1 mg/week for 6 weeks, then 0.5 mg/week for 4 weeks, and then 0.25 mg/week for 7 weeks.

The following variables were examined to assess the effects of dose, duration, and taper schedule:
-Success rate in tapering to zero dose
-Tolerance to dose reduction
-Remission/relapse/rebound
-Emergence of withdrawal syndrome

-Several findings were noteworthy from this study:

-Only dose affected the outcome of success in tapering dose to zero, with 55% of > 4 mg/day patients achieving this outcome compared to 81% of ≤ 4 mg/day patients ($p< 0.001$). Duration of treatment and taper regimen did not affect this outcome.

-Neither dose, duration, nor taper regimen affected the variable "tolerance to dose reduction."

-Neither dose nor taper regimen affected the variable remission/relapse/rebound, however, the longer-term maintenance patients remained in remission longer than the ST group.

-Taper regimen did appear to be a factor in emergence of a withdrawal syndrome, with 6% of standard taper patients having such a syndrome, compared to none of the slow taper patients.

4.0 Labeling Changes

The sponsor has proposed changes in several sections of labeling with reference to these 2 studies, including changes in Warnings, Precautions, Adverse Reactions, Drug Abuse and Dependence, and Dosage and Administration. There is some redundancy in these additions, and the overall impact on labeling, which already strongly focuses on dependency and withdrawal difficulties, will be minimal. In summary, the following points are made:

-The finding from study 474 that doses greater than 4 mg/day, but not duration of use, decreases the chances of tapering to zero dose.

-The finding from study 474 that a slower taper schedule than currently recommended did not improve the chances of tapering the dose to zero, however, it was associated with a lower incidence of a withdrawal syndrome.

-The finding from study 473 that a 50% reduction in dose in patients stabilized on doses greater than 4 mg/day were able to reduce the dose by 50% without a loss of clinical benefit.

5.0 Conclusions/Recommendations

In my view, the sponsor has adequately responded to the phase 4 commitment for additional studies, and I have no objection to the proposed labeling changes. An approval letter can be drafted.

104.1

NOV 22 1996

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	18-276, Supplements 015 and 017
Sponsor:	The Upjohn Company
Drug:	Xanax (alprazolam)
Indication:	Panic Disorder
Date of Submission:	December 29, 1995
Materials Reviewed:	Two studies submitted to fulfill Phase IV commitments associated with the approval of Xanax in Panic Disorder

In the 9/12/90 approvable letter from the FDA to the sponsor for Xanax in Panic Disorder, three Phase IV commitments were described. These commitments are given below. The first two questions are efficacy issues and will be addressed in this review. The withdrawal effects and other safety issues as well as the labeling changes associated with the studies are being addressed in the M.O.'s review (P.Andreason, M.D.).

Phase IV Commitments

1. Acute dose-response

You have evidence that 6 mg per day is more effective than 2 mg and it is clear that patients have been titrated, with the impression of an improved response, to 10 mg and more. It is not clear, however, from rigorous studies, whether there is a real enhancement of effect with dose increases beyond 4-6 mg. This is an important question because there is at least some evidence that it is the highest doses that pose the greatest withdrawal problems. The studies carried out should also explore further the adverse reaction rates seen with various doses.

2. Chronic dose-response

After an acute response is attained, even if large doses are needed initially, it may be possible after some period to drop back to 2-4 mg for maintenance without loss of effect. The doses needed for maintenance should be systematically explored and the usefulness and risks of prolonged high dose use should be documented

3. Withdrawal Effects: relation to dose and duration at the time of withdrawal and to method of tapering

Further examination of the relation of maintenance dose and duration to the incidence and severity of withdrawal effects and the ability to withdraw therapy successfully is needed. Ion addition, you should carry out a systematic evaluation of regimens for withdrawal of patients from alprazolam after chronic use at high doses. The current proposal, dropping the dose by 0.5 mg every three days, is reasonably cautious but very prolong and may not be optimal. The initial recommendation of a 1 mg taper every three days was too rapid for many patients. It is not yet clear whether the dose or duration of alprazolam use should influence the tapering regimen.

Protocol M/2000/0473

The short- and long-term response to Xanax in Panic Disorder, with particular emphasis on the effect of doses above 4 mg daily in acute use and of lowering doses in chronic maintenance use, was evaluated in Protocol M/2000/0473. The study consisted of three phases. The first was a single-blind, pre-randomization segment of 3 to 6 weeks with dose-titration up to 4 mg (4 mg for 10 days was the dose/time criterion before declaring responder status). The second was a double-blind maintenance period of 23 weeks (short-term maintenance,12 weeks, and long-term, 11 weeks). The third was a double-blind taper-discontinuation period of 13 weeks which will not be discussed further in this review.

At total of 336 patients were enrolled and 292 received alprazolam. Patients who responded in the first phase at 4 mg or less were dropped from the study (N=67). Patients who did not respond (a total of 175 patients) were randomized to one of three groups: 1. held at 4 mg during the 23 weeks of the double-blind maintenance phase (N=46); 2. titrated to greater than 4 mg daily and maintained above 4 mg for the 23 weeks of maintenance (N=66); 3; titrated to greater than 4 mg daily for 12 weeks followed by a dose reduction of 50% for 11 weeks (23 weeks of maintenance) (N=63).

The subject selection was the same as in the NDA supplement (i.e., DSM-III-R criteria for panic disorder (PD) with or without agoraphobia, 1 panic attack a week for the 4 weeks prior to the study etc). The efficacy assessments were also similar to those used in the Supplement (SCID-UP-R, panic attack and anticipatory anxiety scale, CGI, SCL-90, Phobia Scale and HAM-A). The primary efficacy outcome measures were number of panic attacks, CGI severity and global improvement variables, and "response rate" to alprazolam.

Tables 1 and 1-A show the means and change scores from baseline for the primary variables at key time points throughout the study. The non-responders at the end of the single-blind run-in were randomized to the two groups described above (i.e., held at 4 mg or increased to a maximum of 10 mg). The group who were held at 4 mg were given placebo tablets for dosage increases to maintain the blind for this phase of the study. The results, with respect to the questions under study, indicated that there

was no difference between the two groups in the amount of improvement at the end of the short-term maintenance (i.e., 12 weeks). This finding held for the number of panic attacks, the CGI severity and the CGI improvement scores. The sponsor stated that this finding of no difference was not interpretable because of the potential placebo response.

The second efficacy question addressed in this study was whether the dose could be decreased without losing efficacy after the patient was stabilized, i.e., during long-term maintenance. There was a significant difference between the full dose maintenance and the 50% dose maintenance groups in the mean change from baseline in number of weekly panic attacks from Week 17 to Week 23 inclusive where the maintained group had a larger decrease (improvement) than the reduced dose group. However, at the last maintenance/dose reduction evaluation time point (a LOCF analysis), there was no difference between the two regimens. There was also no difference at the final endpoint between the two regimens on the CGI variables.

Protocol M/2000/0474

This study was primarily a discontinuation-taper trial. There is no information relevant to efficacy and hence, it will not be reviewed here.

Conclusions:

The data indicates that the Xanax dose may be reduced, without a loss in efficacy, after the patient has responded. The sponsor has added a statement in the labeling to this effect.

It also appears that there is no efficacy advantage when the dose is increased above 4 mg during acute treatment. When a patient fails to respond in 3 to 6 weeks, continuation of 4 mg results in the same effect (i.e., improvement) seven weeks later as increasing the dose above 4 (up to 10 mg). There is nothing in the labeling concerning this strategy and it would be helpful to include it.

The FDA office which follows Phase IV requirements should be informed that Upjohn has met their Phase IV commitments for Xanax in PD if the other reviewer agrees.

Hillary Lee

J. Hillary Lee, Ph.D.

cc:
NDA 18-276
HFD-120 Div. File
HFD-120/TLaughren/PAndreason/HLee/MMille/JPurvis
November 13, 1996
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11-22-96

I agree with the substance of a statement to Labeling about no loss of benefit with dose reduction. See memo & talk for more detailed comments.

T. Laughren

Overview of Study Design

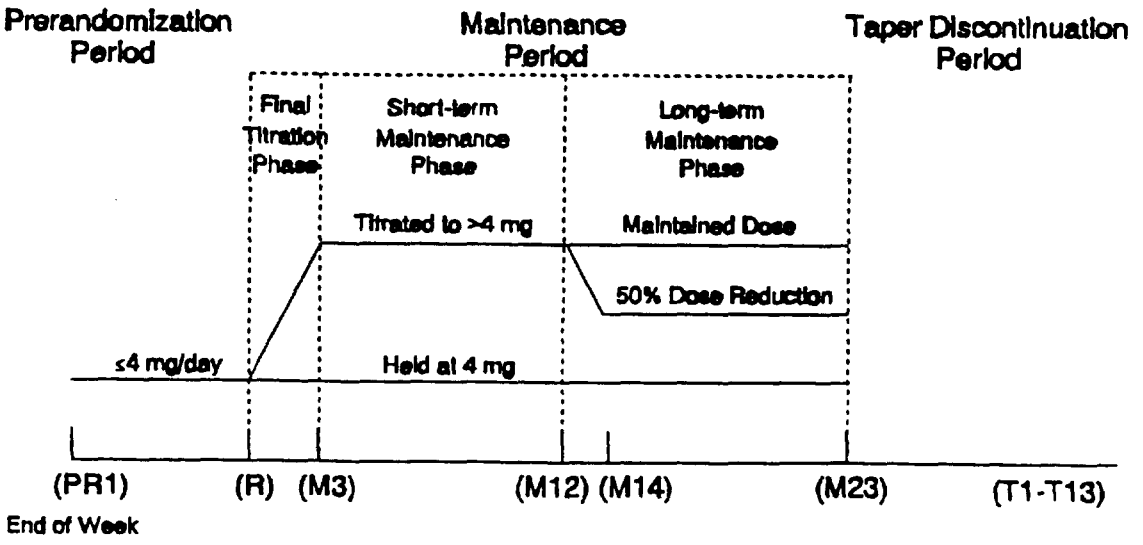

Table 1
Means or Change Scores* of Key Efficacy Variables
for the Segments of the Trial through the Short-Term Maintenance Phase

Efficacy Variables	Study Segments					
	Baseline Means (PR1)		Last Titration LOCF at M3		End of Short-term Maintenance (M12)	
	≤ 4 mg	>4 mg	≤ 4 mg	> 4 mg	≤ 4 mg	> 4 mg
Response Rate**					61.4%	52.8%
No. of Panic Attacks	20.8	21.9	-12	-12.7	-16.4	-14.7
CGI Severity	4.8	4.9	-1.5	-1.4	-2.0	-1.7
CGI Improvement	-	-	2.4	2.6	2.1	2.4

* Negative numbers indicate change scores
** Response rate = No. with zero panic attacks or with CGI much improved or very much improved

Table 1-A
Change Scores of Key Efficacy Variables for the Long-term Maintenance Segment

Number of Panic Attacks and Change from Baseline			
Study Segment	**Held at 4 mg**	**Maintained Dose**	**50% dose reduction**
PR1 (Initial baseline)	18.8	23.8	18.2
Last S-T Maintenance	3.6 (-15.2)	6.3 (-17.5)	4.0 (-14.3)
Last Maint./Dose Reduction	2.7 (-16.1)	6.8 (-17.0)	4.5 (-13.7)

CGI Severity and Change from Baseline			
Study Segment	**Held at 4 mg**	**Maintained Dose**	**50% dose reduction**
PR1 (initial baseline)	4.9	4.8	4.9
Last S-T Maintenance	2.7 (- 2.2)	3.1 (- 1.7)	2.9 (- 1.9)
Last Maint./Dose Reduction	2.6 (- 2.3)	2.8 (- 2.0)	2.9 (- 2.0)

CGI Mean Improvement Scores			
Study Segment	**Held at 4 mg**	**Maintained Dose**	**50% dose reduction**
PR1 (Initial baseline)	-	-	-
Last S-T Maintenance	1.9	2.2	2.2
Last Maint./Dose Reduction	1.9	2.0	2.1

Response Rates		
Study Segment	**Maintained Dose**	**50% dose reduction**
Last Maint./Dose Reduction	75.6%	68.6%

ORIGINAL

NDA NO. 18-276 REF. NO SLR-033

NDA SUPPL FOR labeling

THE UPJOHN COMPANY

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Office of:
Graham H. Burton, M.D.,
Director, Worldwide Regulatory Liaison

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December 29, 1995

Division of Neuropharmacological
Drug Products, HFD-120
Food and Drug Administration
Document Control Room, Parklawn Bldg.
5600 Fishers Lane
Rockville MD 20857

Re: NDA# 18-276
XANAX® Tablets (alprazolam)

Sir/Madam:

We are supplementing our New Drug Application for XANAX Tablets to provide a proposed revised package insert. The proposed changes, provided in draft form, concern information on discontinuation of therapy with XANAX and affect several sections of the insert. In addition, we propose a modification of the Dosage and Administration section to include a recommendation for periodic reassessment and consideration of dosage reduction for patients receiving doses greater than 4mg/day.

The proposed changes are based on the results of two post-marketing studies in patients with panic disorder with agoraphobia. Final reports for these studies are provided with this supplement. The reports are:

1. TR 9158-95-001 - "Short- and long-term discontinuation of alprazolam in patients with panic disorder with agoraphobia (Protocol M/2000/0474)"

2. TR 9158-95-017 - "Short- and long-term response study of alprazolam in the treatment of panic disorder with agoraphobia (Protocol M/2000/0473)"

These two studies were requested by FDA as a condition of approval of the indication for panic disorder. The protocols were submitted to this NDA (Supplement 017) in our communication of March 3, 1992. In addition, we provided notification of a protocol amendment concerning medical event reporting for each study on June 26, 1992.

The proposed insert changes are provided in Attachment 1. Two formats presenting the same content are provided: 1) a mock-up showing the changes to the current printed insert and 2) the same revised text in manuscript form. A one page abstract for both study reports is provided in Attachment 2.

A complete copy of each of the study reports is also provided. Please refer to the submission Table of Contents on the following page for location of documentation contained in the 16 volumes comprising this Supplement.

Following your approval, these changes will be incorporated in the insert current at the time of approval.

A completed User Fee Cover Sheet is also provided. Section 5 of the form is completed to indicate that this application does not contain clinical data. It is our understanding, based on review of the user fee "Interim Guidance" document dated July 12, 1993, that the data summarized in the two study reports supporting this proposed insert revision does not meet the user fee definition of "clinical data".

Please contact Karolee J. Bruzewski at (616) 329-5672 if you have any questions on this labeling supplement

Very truly yours,

THE UPJOHN COMPANY

Karolee J. Bruzewski

Graham H. Burton, M.D.
Director, Worldwide Regulatory Liaison

GHB:kjb