CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-434

Medical

CLINICAL REVIEW

Review and Evaluation of Clinical Data

NDA 21,434

Alprazolam Extended Release (XANAX XR) for the Treatment of [redacted] Panic Disorder with or without Agoraphobia

Sponsor:	Pharmacia
Drug:	XANAX XR (alprazolam extended release)
Material Submitted:	NDA 21,434; Volumes 1-150 of 150
Correspondence Date:	December 26, 2001
Date Received:	December 28, 2001
Drug Category:	Benzodiazepine; Anxiolytic
Forms available for proposed study:	0.5 mg, 1 mg, 2 mg, and 3 mg tablets
Related INDs:	[redacted] 23,179

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Executive Summary

I. Recommendations

The sponsor seeks an indication for alprazolam XR (XANAX XR) in the treatment [redacted] of Panic Disorder with or without Agoraphobia. I recommend that the Division take an approvable action for NDA 21,434.

II. Summary of Clinical Findings

A. Brief Overview of Submission

The submission contains data from 13 Phase II and Phase III studies using alprazolam XR. These include 5 placebo-controlled trials, 2 active-controlled trials, and 1 open-label study using alprazolam XR in Panic Disorder. There were [redacted] investigating alprazolam XR [redacted] In addition, safety and PK data have been submitted from 24 Phase I studies of alprazolam XR.

The pivotal trial under review for efficacy is Study M/2000/0369. Efficacy data from the other 4 placebo-controlled trials have been submitted; however, these trials did not demonstrate efficacy of alprazolam in Panic Disorder. The 4 studies had failed on face; thus, they will not be reviewed in detail. The safety analysis has been conducted from review of data from all of the 37 Phase I-III studies of alprazolam XR.

B. Efficacy Findings

The efficacy of alprazolam XR (XANAX XR) in the treatment of Panic Disorder was demonstrated in one 6-week, randomized, double-blind, placebo-controlled, multicenter trial. Treatment with the drug resulted in statistically and clinically significant reductions in the number and severity of panic attacks, phobic avoidance, and global measures of the severity of illness and dysfunction associated with the illness.

Safety Findings

In 5 placebo-controlled trials and 32 other Phase I-III studies, alprazolam XR was demonstrated to be reasonably safe and well tolerated in the treatment of patients with Panic Disorder with or without Agoraphobia and in healthy volunteers, based on the evaluation of treatment-emergent adverse effects, drug discontinuation-emergent adverse events, ECGs, clinical laboratory measures, and vital signs. There were no deaths in any of the alprazolam studies. In comparison with safety data regarding treatment with immediate-release alprazolam and with other benzodiazepines, there were no unexpected adverse events attributed to treatment with alprazolam XR. The types, rates, and severity of treatment-emergent and drug discontinuation-emergent adverse events observed with alprazolam XR were similar to those observed with alprazolam IR and other benzodiazepines. During treatment and drug discontinuation phases of placebo-controlled trials with alprazolam XR, adverse events occurred predominantly in the CNS.

The most commonly reported treatment-emergent adverse events attributed to alprazolam XR treatment were sedation (45%), somnolence (23%), memory impairment (15.4), fatigue (13.9), depression (12.1), dysarthria (11%), impaired coordination (9.4%), cognitive impairment (7.2%), ataxia (7.2%), and decreased libido (6%). The most commonly reported adverse events attributed to discontinuation of alprazolam XR treatment were anxiety (30%), tremor (28%), dizziness (27%), headache (26%), insomnia (24%), depression (11%), decreased appetite (9.5%), hyperventilation (8.5%), and derealization (8%).

During the treatment phase of 5 placebo-controlled trials, a total of 22 serious events were recorded for 531 subjects treated with alprazolam XR. Upon reviewing the narrative summaries of the serious adverse events, the reviewer concludes that 6/22 (27%) of the serious adverse events can be attributed to treatment with alprazolam XR and that 8/22 (36%) possibly can be attributed to treatment with alprazolam XR. During the drug discontinuation phase, a total of 25 serious adverse events were recorded for 422 subjects discontinued from treatment with alprazolam XR. Upon reviewing the narrative summaries of the serious adverse events, the reviewer concludes that 19/25 (76%) of the serious adverse events can be attributed to discontinuation of treatment with alprazolam XR and that 5/25 (20%) possibly can be attributed to discontinuation of alprazolam XR.

Alprazolam XR has the potential for abuse. Its estimated potential for abuse is slightly lower than that of alprazolam IR and is intermediate among the abuse potentials of other benzodiazepines.

Dosing

The sponsor proposes formulations of 0.5, 1, 2, and 3 mg alprazolam XR tablets and states that most patients with Panic Disorder will benefit from total daily doses of --6 mg. The sponsor also proposes the administration of the drug on either a once-daily or — basis. Biopharmaceutic data support such dosing regimens. Dosing twice-daily appears likely to confer benefit to patients, as serum levels of the drug would remain relatively stable compared to those observed with administration of alprazolam IR. Lower frequency of dosing with alprazolam XR (QD or BID), compared to dosing with alprazolam IR (TID-QID), would likely improve compliance for patients

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication, Age Group, Dose, Regimens

Drug Established, Proposed Trade Name, Proposed Indication, Drug Substance
The sponsor seeks approval for alprazolam extended release (XANAX XR) tablets for the treatment [redacted] of Panic Disorder with or without Agoraphobia. Alprazolam is a benzodiazepine compound that has anxiolytic, sedative-hypnotic, muscle relaxant, and anticonvulsant properties. The drug substance used in the manufacturing of XANAX XR Tablets is alprazolam USP [redacted] which is the same drug substance used in the manufacture of immediate-release XANAX Tablets. XANAX XR Tablets will be manufactured using only [redacted] Alprazolam USP. This differs from the original [redacted], which indicated that drug substance from either [redacted] could be used.

Proposed Doses and Dosing Regimens
The dosages proposed include 0.5 mg., 1 mg, 2 mg, and [redacted] mg tablets, taken orally once or [redacted] daily. The sponsor proposes the following labeling regarding dosage and administration: "XANAX XR Tablets may be administered once daily, [redacted] The tablets should be taken intact; they should not be chewed, crushed, or broken. [redacted]

B. State of Armamentarium for Indication(s)
Medications currently approved for the treatment of Panic Disorder include: the benzodiazepines alprazolam (immediate-release) and clonazepam, as well as the SSRIs sertraline, paroxetine, and fluoxetine.

C. Important Milestones in Product Development

Alprazolam (XANAX IR) was the first compound to be approved by FDA for the treatment of Panic Disorder. This triazolobenzodiazepine represents a class of modified benzodiazepines characterized by the incorporation of a triazole ring in the basic benzodiazepine structure. The alprazolam tablet initially approved for the treatment of Panic Disorder is an immediate-release formulation. This formulation must be taken 3 to 4 times daily, a regimen which, the sponsor states, may not be convenient or conducive to compliance for some patients. With the aim of enhancing convenience and compliance, Pharmacia & Upjohn formulated an extended release (XR) alprazolam tablet with a longer duration of action related to slower absorption. The terminal half-life of alprazolam XR is not different than that of alprazolam IR. The extended release formulation may provide a more convenient dosing regimen and is expected by the sponsor to improve patient compliance by allowing less frequent dosing.

Following discussions with the Division on July 19, 2001, Pharmacia now submits a new NDA for XANAX XR Tablets (NDA 21-434).

XANAX XR was first approved in Finland on August 15, 1994. Registration approval has been granted for XANAX XR in 51 countries for indications which vary by location. Indications include: Panic Disorder, anxiety, anxiety associated with depression, mixed anxiety-depression, and depression associated with functional or organ disease. XANAX XR has never been refused approval due to safety reasons, and it has never been removed from marketing. According to the sponsor, the formulation approved in other countries is "very similar to the proposed US formulation, differing primarily in tablet shapes and colors."

On July 19, 2001, a pre-NDA meeting was held between the Division and representatives of Pharmacia & Upjohn. The sponsor requested the meeting in order to reach agreement with the Division regarding information that would be required for submission of a new NDA for XANAX XR Tablets.

XANAX XR

At that time, Division policy required two such studies for review. The following points were discussed in the pre-NDA meeting and were submitted in writing to the sponsor:

1. The Division stated that the sponsor would be required to conduct only a single efficacy study, along with pharmacokinetic characterization of alprazolam XR and relevant safety data, as a basis for seeking approval for the drug. The Division also requested data pertaining to pharmacokinetic-pharmacodynamic relationships of the drug.
2.

3. Based on summary information provided, the new application would likely be filable. However, this would be a matter for review at the time of actual filing.
4. The sponsor would be required to [redacted]
5. It was noted that the clinical efficacy trial was conducted with once daily dosing of alprazolam XR. In order to support twice daily dosing with the extended release formulation, the sponsor would be required to demonstrate that plasma concentrations with twice daily dosing of alprazolam XR fall between those with once daily dosing with alprazolam XR and QID dosing with the immediate release formulation of alprazolam.
6. A literature search and a synopsis of current ADME and drug-drug interaction data with alprazolam must be included in the submission.
7. An *in vitro* assessment of the metabolism of alprazolam and potential drug-drug interaction data with alprazolam must be included in the submission.
8. Development of an in *vitro-in vivo* correlation of the new formulation should be included in the submission if sufficient data are available.
9. Electronic submission of all clinical pharmacology, pharmacokinetic, and clinical trials studies was requested.
10. The proposed XANAX XR formulation must be identical to the formulation submitted in the 1991 NDA.

US Regulatory History of XANAX XR

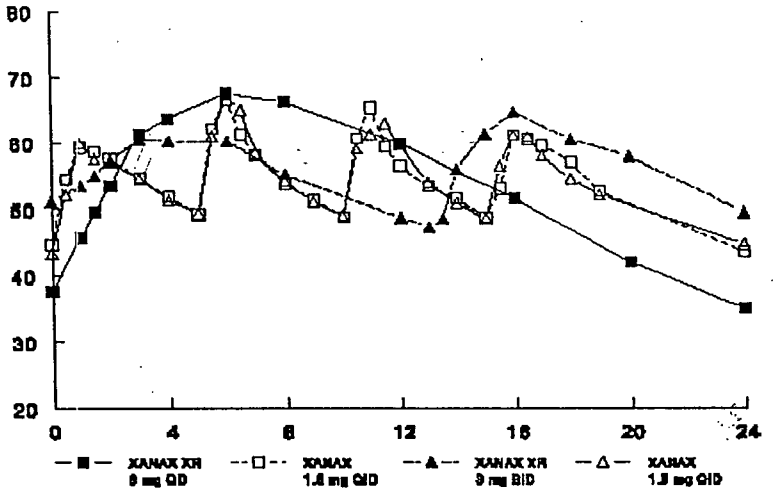
Division of Neuropharmacological Drug Products	
Date	**Summary of Events**
February 14, 1991	Upjohn met with the Division to discuss the proposed NDA for XANAX XR Tablets. The Division suggested a biopharmaceutic approach as an alternative to clinical data as the primary support for the extended release formulation.
April 8, 1991 & May 29, 1991	Upjohn submitted letters to the Division providing a description of the biopharmaceutic studies to be used as primary support of the XANAX XR NDA.
August 27, 1991	Upjohn submitted [redacted] for XANAX XR Tablets extended-release dosage form of alprazolam. The therapeutic indications included [redacted]
February 28, 1995	Upjohn [redacted] the XANAX XR Tablets NDA when it became apparent that the Division [redacted] the application.
May, 1998	FDA issued final "Guidance for Industry, Providing Evidence of Effectiveness for Human Drug and Biological Products."
July 19, 2001	Pharmacia met with the Division to discuss a proposed NDA for XANAX XR Tablets (alprazolam extended-release tablets) based on a single, well-controlled efficacy study. The Division indicated that this approach would be acceptable.
October 1, 2001	Pharmacia submitted a Proposed Pediatric Study Request
October 2, 2001	Pharmacia submitted a request for Deferral of Pediatric Studies for proposed NDA 21-434.

II. Clinically Relevant Findings from Biopharmaceutics and the Division of Scientific Investigations

A. Biopharmaceutic Findings

the sponsor has provided data that appear to demonstrate that plasma concentrations with twice daily dosing of alprazolam XR fall between those with once daily dosing with alprazolam XR and QID dosing with the immediate release formulation of alprazolam. The figure below illustrates the sponsor's findings. However, it should be noted that the final review of the Biopharmaceutics Consultant is not available as of this review.

Figure 1. Plasma alprazolam concentrations following administration of alprazolam XR tablets once daily (study 0002) and twice daily (study 0010) and alprazolam CT tablets four times daily (studies 0002 and 0010) in healthy volunteers



The plot shows that plasma concentration profiles from the IR tablets from the two studies are virtually superimposable, supporting the validity of the correction factor used. The alprazolam concentration-time profile following twice daily administration of the XR tablets is within the C_{max} to C_{min} range for the once daily XR administration and four times daily IR administration. Therefore, twice daily administration of XR tablets may be an acceptable alternative to once daily administration of XR tablets.

B. Findings from the Division of Scientific Investigations (DSI)

A DSI Clinical Inspection Summary, dated June 3, 2002, has been submitted to the Division by Ni Khin, M.D. The inspection assignment was issued on March 19, 2002 for the 3 sites involved in the study: those of Dr. Rickels (Philadelphia, PA), Dr. Patterson (Birmingham, AL), and Dr. Rosenthal (San Diego, CA). These investigators participated in the conduct of the pivotal study (protocol 4452), a phase 3, three-center, randomized, double-blind, flexible-dose, placebo-controlled trial using Xanax XR in patients with

Panic Disorder. Dr. Khin concluded that data from Dr. Rickels' site and Dr. Patterson's site were acceptable. However, it was concluded that data from Dr. Rosenthal's site was not acceptable and should be excluded from the final analysis of the trial. The inspection findings were as follows: "28 of 37 subject records were not available for review, as Dr. Rosenthal had destroyed these records in March 1999. DSI notes that all drug accountability records were also destroyed; therefore, validity of the data reported could not be verified...it is recommended that the Review Division should consider excluding all data generated at this site and reanalyzing efficacy data in support of this NDA."

III. Clinical Pharmacology of Alprazolam Extended Release

A. Pharmacokinetics in Humans

The biopharmaceutic, pharmacokinetic, and pharmacodynamic development program for alprazolam XR tablets was designed in order to: 1) establish the comparable extent of alprazolam absorption between the extended release (XR) formulation and the immediate-release (IR) formulation and document the prolonged absorption from alprazolam XR tablets; 2) demonstrate comparable peak to trough alprazolam concentration ratios for the two formulations; 3) document the biopharmaceutic performance of the XR formulation and the influence of food on its bioavailability; 4) establish an *in vitro-in vivo* correlation for alprazolam XR tablets; and 5) assess whether the slower release rate of alprazolam XR tablets has an effect on the pharmacodynamics of the compound. The development program was initially designed to support once daily dosing of the XR formulation; however, the mean Cmin for this formulation fell below that for the IR formulation. Additional biopharmaceutical studies were conducted to establish that a twice-daily dosing regimen with the XR tablets would result in a Cmin that would fall within an acceptable range. The program consisted of 23 clinical studies, the results of which will be summarized in this section. Full analyses of 21 studies were not included in the submission under review.

1. PHARMACOKINETIC PROFILE SUMMARY TABLE

Mean Clinical Pk Parameters with Alprazolam Extended-Release Tablets

Single Dose (mg)	AUC (ng- h/ mL)	C max (ng/ mL)	t max (h)	t ½ (h)	Vd/ F (L/ kg)	Clearance (mL/ min/ kg)
1 mg	267.3	11.1	5.6	13.8		
6 mg	1166.1	43.3	8.4	11.7	1.24	1.22

1. Dose Proportionality

Results from several clinical studies using 0.5, 2, and 3 mg Xanax XR tablets suggest that there is a proportional relationship between alprazolam serum concentration and dosage of XR tablets.

Mean Dose Corrected Alprazolam AUC and Cmax Resulting from the Oral Administration of Three Different Single Doses of a Sustained Release Formulation of Alprazolam (Protocol M/2000/0253)

Parameter	Treatment		
	B	C	D
Dose	1 mg	3 mg	6 mg
AUC_D (ng x h/mL)*	230 (96.6)	217 (78.2)	264 (65.8)
CmaxD (ng/mL)*	7.82 (1.71)	8.31 (3.13)	8.39 (3.46)

3. In Vitro-In Vivo Correlation

The dissolution profiles for the 4 strengths of Xanax XR tablets differ; however, the various *in vitro* behaviors of the different strengths do not result in differences in the *in vivo* absorption of alprazolam, as illustrated by the bioequivalence of the 0.5, 1, 2, and 3 mg XR tablets.

4. Absorption

Results of clinical studies across various doses of Xanax XR indicate that alprazolam is well absorbed from XR tablets, to the same extent as from the immediate release form of alprazolam. Relative bioavailability in studies ranged from 0.969-0.981. The differences in AUC between the XR and IR formulations were very small.

5. Distribution

The distribution of alprazolam is not influenced by its rate of absorption. Results from clinical studies indicate that there is no difference in the alprazolam volume of distribution (Vd/F) after administration of the XR and IR formulations.

6. Metabolism

Alprazolam is metabolized via oxidation in the liver. Its primary metabolites are the pharmacologically active compounds, 4-hydroxyalprazolam and alpha-hydroxy-alprazolam. It is thought that 4-hydroxyalation is the major metabolite in humans, probably mediated by CYP3A4 activity. Ketaconazole substantially inhibits metabolism of alprazolam. Activity of the following human enzymes do not produce significant quantities of the alprazolam metabolites 4-hydroxyalprazolam and alpha-hydroxy-alprazolam: CYP1A2, CYP2A6, CYP2B6, CYP2D6, and CYP2E1. Cells expressing CYP2C9 and CYP2C19 produced 4-hydroxyalprazolam, but the rate of production by cells expressing CYP3A4 was 84 times greater.

The metabolism of alprazolam following administration of the XR formulation has been assessed by comparing the oral clearance of alprazolam after single and multiple doses of XR and IR tablets. Metabolite PK profiles of the 2 formulations have also been compared. The profiles are extremely similar. Metabolism of alprazolam is not affected by absorption rate.

7. Excretion

The sponsor states that the excretion of alprazolam after administration of XR tablets has not been studied, because metabolism is the major route of elimination. Since metabolism is unchanged by absorption rate, excretion of unchanged alprazolam would also be expected to be unchanged.

8. Factors Affecting Pharmacokinetics

a. Food Effect

The alprazolam AUC for the XR tablet administered with food was 7% below the AUC when alprazolam XR was administered in the fasting state. The alprazolam AUC for the fed and fasting administration of the XR tablet were 2% lower and 5% greater, respectively, than those following the administration of the IR tablet. The Cmax for alprazolam XR treatment in the fed state was 12% greater than that for treatment in the fasting state. The Cmax values were 31% and 39% lower for the respective IR treatments. The Tmax for alprazolam XR was unchanged with feeding. The sponsor concludes that no specific instructions are warranted regarding alprazolam XR tablet dosing in relation to meals.

b. Steady-State Formulation Performance

With once daily dosing of the XR tablet (6 mg QD) and QID dosing with IR tablets (1.5 mg QID), the extent of absorption was equivalent. Steady-state Cmax did not differ between treatments, although Tmax was later for IR tablets, occurring after the second daily dose given 5 hours after the first dose. With the XR treatment, the steady-state Cmin was lower than that for IR administration (34.3 ng/mL versus 41.6 ng/mL), and the XR Cmin to Cmax fluctuation ratio (Fr) was greater than that for the IR treatment (0.739 versus 0.129). The sponsor states that the clinical relevance of the lower Cmin for XR tablets is likely to be minimal, since once daily dosing has demonstrated efficacy relative to placebo, and reduction in panic attacks was associated with mean steady-state serum alprazolam concentrations.

With twice-daily dosing of alprazolam XR, the Cmin and Fr were not different from those observed with treatment with the IR formulation. The values were 48.9 ng/mL versus 49.3 ng/mL and 0.512 versus 0.570, respectively. The sponsor concludes that with dosing of the XR tablets every 12 hours in equivalent daily doses, alprazolam serum concentrations will fall within the same range as that resulting from a QID dosing regimen of alprazolam IR tablets. The sponsor also states that twice-daily administration of alprazolam XR may be an acceptable alternative to once daily administration of XR tablets.

8. Drug Interactions

As described above, in vitro studies indicate that alprazolam is primarily metabolized via the CYP3A4 system. Thus, drugs which are potent inhibitors of CYP3A4 would be expected to increase plasma alprazolam concentrations in vivo. The following drugs have been studied in vivo, and the extent of increases in alprazolam AUC are indicated:

Itraconazole (2.7 fold); nefazodone (1.98 fold); ketoconazole (3.98 fold); erythromycin (1.61 fold); and fluvoxamine (1.96 fold). Fluoxetine resulted in a modest (30%) increase in alprazolam concentrations.

CYP3A4 inducers would be expected to decrease plasma alprazolam concentrations. Following administration of carbamazepine 300 mg/day for 10 days, oral clearance of alprazolam was increased from 0.90 mL/min/kg to 2.13 mL/min/kg.

In the sponsor's proposed labeling, it is stated that alprazolam can 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. In addition, it is stated that drugs which inhibit the cytochrome P450 3A metabolic pathway may have a profound effect on the clearance of alprazolam.

Based on clinical drug interaction studies, caution is recommended for co-administration of alprazolam with the following medications: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from *in vitro* studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. Co-administration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.

Data from *in vitro* studies of benzodiazepines other than alprazolam suggest possible drug interactions with the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during the co-administration of any of these with alprazolam.

B. Pharmacodynamics in Humans

The pharmacodynamics of the extended release formulation of alprazolam were examined in several studies of normal volunteers, using psychomotor and cognitive performance tests, sedation scores, and paradigms of abuse liability. Single doses of XR tablets 6 mg, compared to dosing with alprazolam IR 1.5 mg QID, resulted in significantly greater maximal sedation and decrements in performance in Study R/2002/0002. However, with single doses of alprazolam XR 3 mg and alprazolam IR 1.5 mg BID, the results were comparable. After single doses of XR tablets, acute tolerance developed to these psychomotor effects. Similarly, chronic tolerance to these effects developed. Comparing multiple dose administration of the XR and IR formulations, the pharmacodynamic profiles are similar regarding psychomotor performance and sedation.

On the PCAG sedation scale comparing various benzodiazepines, alprazolam IR and diazepam had the highest scores at one hour. Alprazolam IR and clonazepam scores both

peaked at 2 hours, and the score for alprazolam XR peaked at 4 hours. All active treatments were more sedating than placebo at 3, 4, and 5 hours.

In quantitative EEG studies, both XR and IR administration, compared to placebo, resulted in significant differences in the percentage of beta-wave activity. However, at steady state, there were no significant differences in EEG effects between the two alprazolam formulations.

IV. Description of Clinical Data and Sources

A. Overall Data

Data reviewed included those from 37 (13 Phase II/III & 24 Phase I) studies submitted in NDA 21,434. For the primary analysis of efficacy, the pivotal study **M/2000/0369** was reviewed in detail. Summaries of efficacy analyses were reviewed for 4 other "supportive studies." However, as these 4 studies failed on face, the efficacy data were not reviewed in detail. Furthermore, the Division had required that the sponsor submit data from only one positive well-controlled trial for the purposes of establishing efficacy for this NDA. For the primary safety analysis, safety data from all 37 alprazolalm XR studies were reviewed. In addition, literature searches were performed regarding the safety, efficacy, drug withdrawal and discontinuation phenomenon, and abuse liability of treatment with alprazolam XR. Finally, this review incorporates results of analyses performed by reviewers in the following divisions: Biometrics (statistics), Biopharmaceutics, and the Division of Scientific Investigations (DSI). The table below lists the trials that have been reviewed.

B. Tables Listing the Clinical Trials Reviewed

1. Review of Efficacy: the Pivotal Placebo-Controlled Study of XANAX XR in Panic Disorder (Study M/2000/0369)

Study Number	Study Design	Duration	Treatment Regimen	ITT: # of Patients
M/2000/0369 Reviewed for efficacy & safety	Randomized, D-B, P-C, Flexible Dose	6 weeks of treatment; 5 wk Discontinuation	XANAX XR 1-10 mg QD	104
			Placebo QD	96

2. Review of Safety: 4 Other Placebo-Controlled Studies of XANAX XR in Panic Disorder

Study Number	Study Design	Duration	Treatment Regimen	# of Patients
M/2000/0271 Reviewed for safety & discontinuation AE	Randomized, D-B, P-C, Flexible Dose	6 weeks treatment; 16 weeks Discontinuation	XANAX XR 1-10 mg/d	70
			XANAX IR 1-10 mg/d BID to 5 times daily	70
			Placebo BID to 5 times daily	69
M/2002/0002 Reviewed for safety & discontinuation AE	Randomized, D-B, P-C, Fixed Dose, Parallel Group	10 weeks treatment; 4 wk Discontinuation; 2 wk post-dc	XANAX XR 4 mg/d BID	79
			XANAX XR 4 mg/d BID	75
			Placebo BID	74
M/2002/0003 Reviewed for safety & discontinuation AE	Randomized, D-B, P-C, Fixed Dose, Parallel Group	10 wk treatment; 4 wk Discontinuation; 2 wk post-dc	XANAX XR 4 mg/d QD	88
			XANAX XR 6 mg/d QD	89
			Placebo QD	81
M/2002/0032 Reviewed for safety & discontinuation AE	Randomized, D-B, P-C, multiple ascending dose Cognitive-Behavioral Therapy	8 weeks treatment; 4 weeks Discontinuation	XANAX XR 4mg/d BID	23
			Placebo BID	24

3. Table of the 13 Phase II/III Studies Reviewed for the Safety Analysis

Table 1. Scope of the Clinical Program

Type of Study	No. of Studies	Protocol No. [ref]	No. of Treated Patients				
			ALP XR	ALP IR	Placebo	Other	Total
Placebo-Controlled Studies in Panic Disorder							
Phase 3 Placebo – Controlled	5	M/2000/0369 [25]	104		96		200
		M/2000/0271 [26]	69	70	69		208
		M/2002/0002 [27]	155		76		231
		M/2002/0003 [28]	178		83		261
		M/2002/0032 [29]	25		25		50
Total	5		531	70	349		950
Active-Controlled Studies in Panic Disorder							
Phase 3 Active-Controlled	1	M/2002/0015 [30]	129			128[a]	257
Phase 2 Active-Controlled	1	M/2000/0385 [31]	13	7			20
Total	2		142	7		128	277
Uncontrolled Study in Panic Disorder							
Phase 3 Open-Label	1	M/2002/0021 [32]	29[d]				29
Total	1		29				29
Phase 2/3 Studies in Other Indications							
Generalized Anxiety Disorder	3	M/2002/0014 [33]	59			62[b]	121
		M/2002/0039 [34]	32			34[e]	66
		M/2000/0365 [35]	6			8[b]	14
IR to XR Switch in Anxiety	1	M/2002/0022 [36]	54[d]				54
MADD	1	M/2002/0045 [37]	113			125[c]	238
Total	5		264			229	493
TOTAL All Studies	13		966	77	349	357	1749

a Clomipramine
b Bromazepam
c Fluoxetine
d Also received Alprazolam IR in this IR-to-XR switch study
e Lorazepam

Source: Integrated Safety Database

4. Tables of 24 Phase I Studies Using Alprazolam XR (refer to Appendix C)

C. Postmarketing Experience

There has been considerable post-marketing experience with alprazolam XR in other countries since 1994, when the drug was first approved in Finland. Registration approval has been granted for alprazolam XR in 51 countries for indications which vary by location. Indications include: Panic Disorder, anxiety, anxiety associated with depression, mixed anxiety-depression, or depression associated with functional or organ disease. There are a number of different trade names for the formulation: ALPRA PAN RETARD, TAFIL LIBERACION PRO, TAFIL RETARD, XANAX DEPOT, XANOR DEPOT, XANOR RETARD, TRANKIMAZIN RETARD, and ZOTRAN. Alprazolam XR has never been refused approval due to safety reasons, and it has never been removed from marketing.

D. Literature Reviews

1. Sponsor's Literature Review

The sponsor conducted a literature search regarding treatment with alprazolam XR for Panic Disorder. A Synopsis of ADME & Drug-Drug interactions have been provided and are discussed above in this review. Five online databases were searched (Medline, Derwent Drug File, Embase, Biosis Previews, and Scisearch) from 1989 to August 2001 to retrieve articles that were indexed with alprazolam and its synonyms (alprazolam, alprazolam immediate release, alprazolam extended release, Xanax ® , Xanax ® immediate release, Xanax ® extended release, Xanax ® XR, Xanax ® IR, Xanax ® SR). All review articles were removed, as were company-sponsored articles. One of the 3 articles found was related to panic disorder and is summarized below. Alprazolam sustained-release was administered in an open-label study involving 18 patients with panic disorder or agoraphobia with panic disorder. Patients began taking the medication at a dose of 1 mg/day, and then the dose was individualized. By the end of the 8-week treatment period, the average dose was 3 mg/day. After 8 weeks of treatment, 67% of the patients had zero full panic attacks. Two patients dropped out during the study. The authors concluded that alprazolam sustained-release was an effective and well-tolerated treatment for panic disorder.

2. Reviewer's Literature Review

Search terms, using the PubMed database, included the following: alprazolam extended release, alprazolam XR, Xanax XR, and Xanax extended release. The search generated citations for 8 journal articles, 6 of which are clinically relevant. Generally, the information and findings of the authors are consistent with the data and conclusions presented in the sponsor's submission. The central points of the articles will be summarized:

3. One study demonstrated that sustained-release alprazolam was highly effective in the acute treatment of panic disorder at doses comparable to those used in treatment with the

immediate formulation of alprazolam. The medication was well tolerated, but rebound effects were observed during a rapid drug taper after 6 weeks of treatment.

4. In a study comparing the efficacy of alprazolam IR, alprazolam XR, and placebo in the treatment of anxiety disorders, the active treatments were equally effective throughout a 6-week trial and were significantly more efficacious than placebo. Drowsiness occurred more frequently with alprazolam IR (86% of patients) than with the XR preparation (79%) or placebo (49%).

5. The effects of alprazloam XR treatment on neuropsychological function in Panic Disorder patients was tested in a placebo-controlled study lasting 6 weeks. The mean dosage was 4 mg/day. Compared to baseline testing results, no significant changes were noted in measures of learning, verbal memory, or reaction time, and neither group showed any deterioration from baseline in re-testing for any aspect of neuropsychologic function. The authors concluded that these findings call into question the assumption that long-term benzodiazepine therapy produces significant neuropsychologic deficit in patients with diagnosed anxiety disorders.

6. From a prospective naturalistic study of 68 anxiety patients treated with alprazolam XR for 21 weeks, the investigators concluded that the medication demonstrates good efficacy. There were significant reductions in global anxiety (HAMA, GCI and CGI improvement) throughout the study. There was a reduction in the number of panic attacks and in the severity of Agoraphobia. Global clinical impression (efficacy and tolerability) was good or very good in 75% of the patients, as assessed by the investigator and the patients. Fifty percent (50%) of the patients had an adverse event (mainly sedation); most cases were mild and transient. Sixteen patients who had been treated with alprazolam IR and switched to treatment with Alprazolam XR needed a slightly higher total dose of the extended release formulation. In these cases, the change in medication formulation was not difficult to accomplish for the majority of patients. The dosing regimen was usually 2-3 mg in two daily doses.

7. In a study evaluating the abuse potential of alprazolam XR and IR, subjects with a history of substance use disorders were treated and tested. The amount of money subjects were willing to pay to take the drug was significantly greater than that for placebo and for 2 doses of immediate-release alprazolam but for neither of 2 doses of extended-release alprazolam. The authors concluded that extended-release alprazolam has less potential for abuse than immediate-release alprazolam.

V. Clinical Review Methods

A. How the Review was Conducted

Materials described in **Sections IV.A** and **IV.B.** were reviewed in detail. Original data and summaries of results submitted by the sponsor were reviewed and compared with the results of the reviewer's analyses. Relevant statistical analyses were conducted, and pertinent literature searches were performed.

B. Overview of Materials Consulted in Review

The materials described in **Section IV.A.** were consulted and reviewed.

C. Overview of Methods Used to Evaluate Data Quality and Integrity
The reviewer and consultants examined original data such as Case Report Forms, data sets, and data collected for individual subjects during the conduct of the pivotal trial under review. Results of these examinations, as well as results of statistical analyses, were compared with the results and summaries submitted by the sponsor.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards?
It appears that the trials under review were conducted in accordance with accepted ethical standards. There is no evidence to suggest otherwise.

E. Evaluation of Financial Disclosure
In Volume 1, item 19, the sponsor has provided adequate information regarding financial disclosure for clinical investigators:
"As communicated to FDA in our correspondence regarding XANAX XR Tablets, dated September 27, 2001(IND 23,179, Serial #123), and confirmed in FDA's response dated November 26, 2001, **Study M/2000/0369 [4452]** is the only 'covered' clinical study [as defined in 21CFR 54.2(e)] for purposes of this application. However, we are providing financial disclosure for other supportive studies as well. Pharmacia & Upjohn is providing Form 3454 in accordance with the FDA Guidance Document 'Financial Disclosure by Clinical Investigators,' Part II.A-C, 'Disclosable Financial Arrangements.' Certification is provided that none of the participating investigators entered into any financial arrangements with the sponsor of this trial (the former Upjohn Company) in regards to the following categories of financial interest:

1. Financial arrangements whereby the value of compensation would be influenced by the outcome of the protocol.
2. An equity interest in the sponsor of a covered study, i.e., any ownership interest, stock options, or financial interest whose value can be readily determined through reference to public prices.
3. A proprietary interest in the tested product, including, but not limited to, a patent, trademark, copyright or licensing agreement.

All other requirements for reporting such an interest regarding significant payments of other sorts or significant equity interest in the sponsor of the study (Part II.D-E of the above-mentioned guidance document) do not apply because the covered study (and the supportive studies) were completed prior to 2 February 1998."

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The efficacy of alprazolam XR (XANAX XR) in the treatment of Panic Disorder was demonstrated in one 6-week, randomized, double-blind, placebo-controlled, multicenter trial in which the drug was dosed once-daily. Treatment with the drug resulted in statistically and clinically significant reductions in the number and severity of panic attacks, phobic avoidance, and in global measures of the severity of illness and dysfunction associated with the illness.

B. General Approach to the Review of Efficacy

Study M/2000/0369 was reviewed for efficacy, as it has been designated as the pivotal placebo-controlled efficacy trial. The other 4 placebo-controlled studies, for which data had been submitted, were briefly reviewed for efficacy analyses. These trials failed on face. Furthermore, the Division had previously made the decision that one positive pivotal trial was adequate to establish efficacy.

The study took place at 3 sites. DSI investigated all 3 sites and found that complete data were not available at one of the sites. Thus, the Division performed 2 separate efficacy analyses, one using data from all 3 sites and one using data from the 2 sites in which complete data were available.

C. Detailed Review of the Pivotal Trial, M/2000/0369

C-1 Investigators and Sites

Refer to the Appendix (Section XI.A.)

C-2 Objectives

The primary objective of the study is to compare the efficacy and safety of XANAX XR with that of placebo in the treatment of [redacted] Panic Disorder with or without Agoraphobia.

C-3 Table. Pivotal Trial Reviewed for the Analysis of Efficacy

Placebo-Controlled Study (M/2000/0369) of Alprazolam XR in Panic Disorder

Study Number	Study Design	Duration	Treatment Regimen	ITT: # of Patients
M/2000/0369 Reviewed for efficacy & safety	Randomized, D-B, P-C, Flexible Dose	6 weeks of treatment; 5 wk Discontinuation	XANAX XR 1-10 mg QD	104
			Placebo QD	96

C-4 Study Population

Enrolled subjects were male and female outpatients, between the ages of 18 and 65, who had a diagnosis of Panic Disorder with or without Agoraphobia (as defined by DSM-III), with limited or extensive phobic avoidance. For details regarding subject inclusion and

exclusion criteria, refer to the Appendix (**Section XI.B.**). The inclusion and exclusion criteria are appropriate.

C-5 Baseline Demographics and Severity of Illness

Baseline Demographics for Study 0369 ITT Population

Variable	XANAX XR	Placebo
Age (yrs)	n=104	n=95
Mean	35.0	34.8
p-value	0.855	
Sex, No. (%) pts	n=104	n=95
Male	43 (41)	36 (38)
Female	61 (59)	59 (62)
p-value	0.619	
Race, No. (%) pts	n=104	n=95
White	99 (95)	92 (97)
Black	3 (3)	2 (2)
Hispanic	1 (1)	1 (1)
Oriental	0 (0)	0 (0)
American Indian	0 (0)	0 (0)
Other	1 (1)	0 (0)
p-value	0.789	
Weight (lbs)	n=99	n=94
Mean	162.3	158.8
p-value	0.519	
History of mental illness, No. (%) pts	n=104	n=95
Yes	9 (9)	1 (1)
p-value	0.014	

Baseline Severity of Illness in Intent-to-Treat Population

Primary Efficacy Parameters at Baseline	XANAX XR (N=104)	Placebo (N=95)	P-value
Total Panic Attack Mean (SD)	6.27 (6.14) N=104	5.99 (5.57) N=95	0.82
Overall Phobia State Mean (SD)	6.89 (2.29) N=102	6.95 (1.99) N=93	0.81
Clinician's Global Impression: Severity of Illness Mean (SD)	4.54 (0.83) N=103	4.41(0.94) N=95	0.45

C-6 Study Design

The study was a randomized, double-blind, placebo-controlled, adjustable dose, three-center study. Two-hundred subjects were enrolled. The treatment duration was 6 weeks. Subsequently, there was a 5-week phase for monitoring of drug discontinuation and withdrawal phenomena. Dosing of alprazolam ranged from 1-10 mg once daily. The study included the following phases: (a) a screening visit; (b) a one-week drug-free run-in period; (c) a 6-week double-blind treatment period in which dosing could be adjusted to a maximum of 10 mg per day, based on response and tolerability; (d) a medication tapering period of up to five weeks until no medication was administrated; and (e) a post-discontinuation evaluation period in which subjects returned two weeks after discontinuation of medications. Medication was administered once daily in the morning. Dosing was initiated at 1 mg/day, and doses were not to exceed 10 mg/day for a total of 6 weeks. The mean daily dose after titration was in the range of 4.2- 4.7 mg. In the discontinuation phase, doses were reduced stepwise to zero over no more than 5 weeks. Efficacy and safety assessments were performed at weekly intervals for 6 weeks during the treatment phase for 5 weeks during the discontinuation phase and for 2 weeks during the post-discontinuation phase of the study.

C-7 Endpoints and Analysis of Endpoints

Primary Endpoints

The primary efficacy endpoints were:

1) Total number of panic attacks during the previous week
2) Clinical Global Impressions (CGI)
3) Overall Phobia State

The number of Total Panic Attacks is the sum of situational panic attacks and unexpected panic attacks. For Total Panic Attacks, three sub-measures are used: a) Mean Change from Baseline, b) ≥ 50% Decrease in Number of panic attacks, and c) Achieved Zero panic attacks. Similarly, for the Clinician's Global Impression, three sub-measures were used: a) Severity of Illness, b) Improvement in Condition, and c) Therapeutic Effect. These endpoints were measured at baseline and at weekly intervals during the treatment and discontinuation phases

Secondary Endpoints

Secondary Endpoints included:

1) 3 Panic Attack Scale variables (Situational Panic Attacks, Spontaneous Panic Attacks and Anticipatory Anxiety); 2) Phobia Scale; 3) HAM-A; 4) HAM-D; 5); Sheehan Patient-Rated Anxiety Scale (SPRAS); 6) Patient's Status Scale; 7) Patient's Global Impression; 8) Relative Effectiveness of Study Medications; 9) Sheehan Disability Scale; and 10) Quality of Life Scale.

C-8 Patient Disposition in Study 0369

Variable	Alprazolam XR	Placebo Group
Number of subjects randomized	109	108
Number of subjects treated	104	96
Number of subjects in ITT population	104	95
Number (%)subjects who completed 6-week treatment course	87 (84)	61 (67.4)

Reasons for Study Discontinuation in the ITT Population in Study 0369

Reason	Alprazolam XR	Placebo
Lack of efficacy	1	19
Loss to follow-up	5	3
Adverse event	4	1
Inter-current illness	2	1
Protocol violation	2	1
Subject decided to withdraw	3	9
TOTAL	17	34

C-9 Baseline Demographics and Severity of Illness

Baseline Demographics for Study 0369 ITT Population

Variable	XANAX XR	Placebo
Age (years)	n=104	n=95
Mean	35.0	34.8
p-value	0.855	
Sex, No. (%) subjects	n=104	n=95
Male	43 (41)	36 (38)
Female	61 (59)	59 (62)
p-value	0.619	
Race, No. (%) subjects	n=104	n=95
White	99 (95)	92 (97)
Black	3 (3)	2 (2)
Hispanic	1 (1)	1 (1)
Oriental	0 (0)	0 (0)
American Indian	0 (0)	0 (0)
Other	1 (1)	0 (0)
p-value	0.789	
Weight (lbs)	n=99	n=94
Mean	162.3	158.8
p-value	0.519	
History of mental illness, No. (%) subjects	n=104	n=95
Yes	9 (9)	1 (1)
p-value	0.014	

Baseline Severity of Illness in Intent-to-Treat Population

Primary Efficacy Parameters at Baseline	XANAX XR (N=104)	Placebo (N=95)	P-value
Total Panic Attack Mean (SD)	6.27 (6.14) N=104	5.99 (5.57) N=95	0.82
Overall Phobia State Mean (SD)	6.89 (2.29) N=102	6.95 (1.99) N=93	0.81
Clinician's Global Impression: Status of Mental Illness Mean (SD)	4.54 (0.83) N=103	4.41(0.94) N=95	0.45

C-10 Efficacy Analysis

C-10-a) Sponsor's Analyses of Primary Efficacy Measures in Study 0369

The sponsor conducted two types of analyses for the primary endpoints in the Intent to Treat population. The first was a Last Observation Carried Forward (LOCF) analysis, and the second was an Observed Value (OV) analysis. The OV analysis was based on data gathered at a particular evaluation time point. In the LOCF analysis, the baseline values were carried forward if no other data were available.

Results of statistical comparisons of primary endpoint measures between XANAX XR and placebo groups of the ITT population at the sixth week of treatment are provided in the table below. In the primary efficacy analysis, there are statistically significant differences between treatment groups in favor of XANAX XR with respect to all seven co-primary efficacy parameters at the sixth week endpoint for the LOCF analysis. In the OV analysis, there were significant differences in five of seven co-primary efficacy measures; there were not statistical differences between treatment groups for the 2 endpoints, Total Panic Attacks and Overall Phobia State. As depicted in the table, significantly more patients in the XANAX XR group achieved a 50% reduction in the total number of attacks and had a reduction to zero attacks after six weeks of treatment compared to the placebo group. Treatment with XANAX XR was also associated with significantly greater reductions in the mean scores from baseline in all 3 CGI ratings compared to placebo in both the OV and LOCF analyses.

Table. **Primary Efficacy Analyses at Week 6 for the ITT Population in Study 0369**

Parameter	XANAX XR		Placebo		P-Value	
	OV	LOCF	OV	LOCF	OV	LOCF
Total Panic Attacks						
Mean Change from Baseline (SD)	-5.13(7.09) N=78	-4.65(6.85) N=104	-3.78(6.63) N=51	-1.95(6.62) N=95	0.416	0.026
≥ 50 % Decrease (% pts)	92.3 N=78	84.3 N=102	78.4 N=51	62.1 N=95	0.023	<0.001
Achieved zero (% pts)	79.5 N=78	70.2 N=104	58.8 N=51	45.3 N=95	0.011	<0.001
Overall Phobia State						
Mean Change from Baseline (SD)	-3.97(2.88) N=72	-3.55(2.91) N=102	-3.13(2.91) N=48	-2.18(2.79) N=93	0.160	0.0028
Clinician's Global Impression						
Status of Mental Illness Mean Change from Baseline (SD)	-2.34(1.21) N=77	-2.03(1.35) N=103	-1.53(1.39) N=51	-1.00(1.38) N=95	0.0045	0.0001
Change in Condition Mean (SD)	1.81(0.97) N=77	2.04(1.24) N=103	2.45(1.36) N=51	3.05(1.59) N=95	0.0083	0.0001
Therapeutic Effect Mean (SD)	4.35(0.84) N=77	4.17(1.04) N=103	3.69(1.24) N=51	3.17(1.41) N=95	0.0022	0.0001

C-10-b) Sponsor's Analyses of Secondary Efficacy Measures in Study 0369

The results of statistical comparisons of secondary efficacy endpoints between alprazolam XR and placebo groups for the ITT population at the sixth week of treatment are summarized in the table below. Alprazolam XR-treated subjects demonstrated significant improvement in the mean percent of time spent worrying ($p=0.019$). These subjects also demonstrated significantly greater improvement in the fear score and HAM-A score compared with placebo-treated subjects. Between-group comparisons of outcomes on the mean numbers of situational and spontaneous panic attacks, HAM-D score, and Sheehan Patient-Rated Anxiety Scale did not show a significant improvement for the alprazolam XR group compared the placebo-treated subjects. There was no significant difference between groups in the avoidance scores of the Phobia Scale.

Table. **OV Analyses of Secondary Efficacy Measures at Week 6 for the ITT Population in Study 0369**

Parameters	XANAX XR	Placebo	P-value
Panic Attack Scale Variables			
Situational Panic Attack Mean Number per Week (SD)	-2.04(5.45) N=78	-2.27(3.36) N=51	0.78
Spontaneous Panic Attack Mean Number per Week (SD)	-3.09(4.47) N=78	-1.51(5.33) N=51	0.072
Anticipatory Anxiety Mean % Time Spent Worry (SD)	-24.5(29.77) N=78	-12.6(24.37) N=51	0.019
Phobia Scale Variables			
Total Main Phobia Fear Score	-14.0(9.42) N=72	-10.18(10.15) N=50	0.035
Avoidance Score	-3.93(3.60) N=72	-3.35(3.56) N=49	0.38
Hamilton Anxiety Scale Score	-11.77(7.71) N=77	-8.10(8.64) N=51	0.013
Hamilton Depression Scale Score	-5.83(6.41) N=64	-4.85(5.93) N=47	0.41
Sheehan Patient-Rated Anxiety Scale			
Part I (Problem/complaints)	-40.61(28.46) N=77	-35.02(28.96) N=51	0.212
Part II (How Patient Felt)	-9.49(10.40) N=77	-8.06(12.20) N=51	0.477
Patient's Status Variables			
How Much Time Illness Prevent Activity	-1.53(1.26) N=77	-0.98(1.12) N=51	0.013
Distress due to Personal Events	-0.51(1.59) N=77	-0.94(1.38) N=51	0.12

C-10-c) Statistician's Review and Analyses of Efficacy Data from Study 0369

The reviewer replicated the sponsor's analyses according to the protocol and found the sponsor's results to be accurate. However, the high percentage of dropouts and the imbalance in the number of dropouts between treatment groups raised a theoretical concern about the reliability of results using LOCF data. Such a single imputation method usually reduces the standard deviation estimations.

The Division of Scientific Investigations (DSI) inspected the three clinical sites and found that the source documents for 28 of 37 subjects at Dr. Rosenthal's site were destroyed. DSI recommended excluding all data generated at this site and reanalyzing the efficacy data with data from the 2 other sites. Thus, the data for the 37 subjects at the site of Dr. Rosenthal were excluded, and the remaining data were reanalyzed for the primary endpoints at the sixth week by the reviewer. The results are depicted in the table

below. These results do not change the conclusions reached by the sponsor using the data from all three sites. In fact, many of the p-values were smaller after excluding the data from the single site.

Table. **Primary Efficacy Analyses at Week 6 after Excluding the 37 Subjects from Dr. Rosenthal's Site**

Parameter	XANAX XR		Placebo		P-Value	
	OV	LOCF	OV	LOCF	OV	LOCF
Total Panic Attacks						
Mean Change from Baseline (SD)	-5.45(6.0) N=62	-4.89(6.1) N=85	-3.87(6.64) N=39	-1.76(6.9) N=76	0.28	0.0026
≥ 50 % Decrease (% pts)	95.2 N=62	85.9 N=85	76.9 N=39	61.8 N=76	0.006	0.0005
Achieved zero (% pts)	82.3 N=62	71.8 N=85	53.9 N=39	42.1 N=76	0.002	0.0001
Overall Phobia State						
Mean Change from Baseline (SD)	-4.0(2.57) N=60	-3.58(2.6) N=83	-3.0(2.78) N=36	-2.14(2.67) N=74	0.066	0.0005
Clinician's Global Impression						
Status of Mental Illness Mean Change from Baseline (SD)	-2.34(1.20) N=62	-2.05(1.33) N=84	-1.28(1.28) N=39	-0.83(1.23) N=78	<0.0001	<0.0001
Change in Condition Mean (SD)	1.85(1.04) N=62	2.07(1.25) N=85	2.67(1.42) N=39	3.21(1.55) N=78	0.0022	<0.0001
Therapeutic Effect Mean (SD)	4.31(0.88) N=62	4.14(1.05) N=85	3.49(1.27) N=39	3.04(1.36) N=78	0.0005	<0.0001

Subgroup analyses were performed by the reviewer to determine whether the treatment effects were concentrated in particular subgroups rather than in the general subject population. The study population was separated into subgroups according to gender, race, age, and clinical sites. The proportions of female and male subjects were approximately 60% and 40%, respectively, for whom there are data available for statistical analysis of primary endpoints. The corresponding proportions of white and nonwhite subjects were approximately 95% and 5%, respectively. Subjects < 45 years of age accounted for 90% of the study population. Dr. Rickels' site had 143 subjects, and that of Dr. Patterson had 71 subjects. However, the corresponding number of subjects available for analysis at the sixth week were 100 and 60, respectively, for LOCF analyses and 60 and 50, respectively for OV analyses. Due to the small number of subjects in the nonwhite group and the group ≥ 45 years of age, the subgroup analyses were performed only according to gender and study site.

Subgroup analyses by the reviewer for male and female subgroups indicate that the treatment effects in both subgroups favored treatment with alprazolam XR over placebo; however, in the female group, there was a higher level of statistical significance, especially for the OV analyses. Similarly, the treatment effects in both study sites favored

treatment with alprazolam XR compared to placebo. Although the site of Dr. Patterson had a smaller number of subjects, there was a higher percentage of subjects available for analyses at Week 6, and the treatment effects tended to be higher for most of the primary endpoints.

D. Efficacy Conclusions

For all 7 co-primary efficacy endpoints in the pivotal study, there were statistically significant differences between the group treated with alprazolam XR and the group treated with placebo. The differences suggest that there was a significant treatment effect for alprazolam XR. Moreover, the treatment effect of alprazolam XR, as measured by endpoints relevant for Panic Disorder with or without Agoraphobia, was clinically meaningful and significant. Treatment with the drug resulted in statistically and clinically significant reductions in the number and severity of panic attacks, phobic avoidance, and in global measures of the severity of illness and dysfunction associated with the illness. It is concluded that this study supports the claim that alprazolam XR is effective in the treatment of Panic Disorder with or without Agoraphobia.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Alprazolam XR was reasonably safe and well tolerated in the treatment of subjects with Panic Disorder with or without Agoraphobia, based on the evaluation of treatment-emergent and discontinuation-emergent adverse events, clinical laboratory measures, and vital signs. There were no deaths during the 5 placebo-controlled studies or any of the other 32 studies using alprazolam XR. In comparison with safety data regarding treatment with alprazolam IR and other benzodiazepines, there were no unexpected adverse events attributed to treatment with alprazolam XR. The types, rates, and severity of treatment-emergent and discontinuation-emergent adverse events with alprazolam XR were quite similar to those observed with alprazolam IR treatment. During treatment and drug discontinuation phases of placebo-controlled trials with alprazolam XR, adverse events occurred predominantly in the central nervous system. The most commonly reported treatment-emergent adverse events attributed to alprazolam XR were somnolence, sedation, fatigue, dizziness, and memory impairment. The most commonly reported discontinuation-emergent adverse events attributed to discontinuation of alprazolam XR group were insomnia, headache, nausea, tremor, dizziness, and anxiety. Alprazolam XR has the potential for abuse. Its potential for abuse is slightly lower than that of alprazolam IR and is intermediate among other benzodiazepines.

B. Description of Patient Exposure in Placebo-Controlled Trials of Alprazolam XR In Panic Disorder

- In the 5 placebo-controlled studies, the overall exposure calculated for the alprazolam XR treatment group was 62.4 subject-years. The majority (86.6%) of subjects treated with alprazolam XR received a mean daily dose of between 2 mg and 6 mg. The majority (81.2%) of alprazolam XR-treated subjects received a mean final dose of

between 2 mg and 6 mg. Age, gender, race, and concurrent illness did not affect the distribution of mean daily or mean final dose.

- In the 2 active-controlled studies, the exposure for the alprazolam XR treatment group was 28.7 patient-years. The majority of alprazolam XR patients (88.1%) received a mean daily dose of between 2 mg and 6 mg. Similarly, the majority of alprazolam XR patients (85.9%) received a mean final dose of between 2 mg and 6 mg.
- In the single non-controlled study in Panic Disorder, the exposure for the alprazolam XR treatment group was 3.3 patient-years.
- For the 5 studies in other indications, the exposure for the alprazolam XR treatment groups was 19.3 patient-years. Age, gender, race, and concurrent illness did not affect the distribution of mean daily or mean final dose in the active-controlled studies, uncontrolled study, or studies in other indications.

Type of Study	No. of Studies	Protocol No. [ref]	No. of Treated Patients				
			ALP XR	ALP IR	Placebo	Other	Total
Placebo-Controlled Studies in Panic Disorder							
Phase 3 Placebo – Controlled	5	M/2000/0369 [25]	104		96		200
		M/2000/0271 [26]	69	70	69		208
		M/2002/0002 [27]	155		76		231
		M/2002/0003 [28]	178		83		261
		M/2002/0032 [29]	25		25		50
Total	5		531	70	349		950
Active-Controlled Studies in Panic Disorder							
Phase 3 Active-Controlled	1	M/2002/0015 [30]	129			128[a]	257
Phase 2 Active-Controlled	1	M/2000/0385 [31]	13	7			20
Total	2		142	7		128	277
Uncontrolled Study in Panic Disorder							
Phase 3 Open-Label	1	M/2002/0021 [32]	29[d]				29
Total	1		29				29
Phase 2/3 Studies in Other Indications							
Generalized Anxiety Disorder	3	M/2002/0014 [33]	59			62[b]	121
		M/2002/0039 [34]	32			34[e]	66
		M/2000/0365 [35]	6			8[b]	14
IR to XR Switch in Anxiety	1	M/2002/0022 [36]	54[d]				54
MADD	1	M/2002/0045 [37]	113			125[c]	238
Total	5		264			229	493
TOTAL All Studies	13		966	77	349	357	1749

a Clomipramine
b Bromazepam
c Fluoxetine
d Also received Alprazolam IR in this IR-to-XR switch study
e Lorazepam

C. Overview of Phase II/III Trials

a. Placebo-Controlled Studies in Panic Disorder (M/2000/0369, M/2000/0271, M/2002/0002, M/2002/0003, and M/2002/0032)
The grouping of primary interest consists of 5 Phase 3 placebo-controlled studies in panic disorder. The total number of treated patients in this group is 950; 531 were treated with alprazolam XR, 70 with alprazolam IR, and 349 with placebo.

b. Active-Controlled Studies in Panic Disorder (Studies M/2000/0385 & M/2002/0015)
The second grouping consists of 2 active-controlled studies in panic disorder: a Phase 3 study with clomipramine as the comparator and a Phase 2 study with alprazolam IR as the comparator. The total number of treated patients in this grouping is 277. In the Phase 3 study, 129 patients were treated with alprazolam XR and 128 with clomipramine; in the Phase 2 study, 13 patients were treated with alprazolam XR and 7 with alprazolam IR.

c. Uncontrolled Study in Panic Disorder (Study M/2002/0021)
One Phase 3 uncontrolled study. In this IR-to-XR switch study, 29 patients were treated with both alprazolam XR and alprazolam IR.

d. Studies in Other Indications (Studies M/2002/0014, M/2002/0039, & M/2000/0365 [Generalized Anxiety Disorder]; Study M/2002/0022 [IR to XR switch in anxiety]; and Study M/2002/0045 [Mixed Anxiety-Depressive Disorder]
The fourth and final grouping consists of 5 studies in other anxiety-related indications. The total number of treated patients in this group is 493; 264 were treated with alprazolam XR, 70 with bromazepam, 34 with lorazepam, and 125 with fluoxetine.

2. SAFETY INFORMATION FROM 24 PHASE I CLINICAL PHARMACOLOGY STUDIES

The studies for the biopharmaceutic/pharmacokinetic/pharmacodynamic development program for alprazolam XR tablets were conducted in healthy volunteers, under single- and multiple-dose conditions. Single doses tested in these trials ranged from 0.5 to 10 mg. Multiple doses ranged up to 6 mg/day. In general, these were crossover design trials. (Refer to Tables in Appendix C for details).

In summary, there were no deaths, serious adverse events, or unexpected adverse events observed during the course of these 24 studies involving 598 subjects. Eight (1%) subjects in the pharmacokinetic/bioavailability studies dropped out because of medical events. Alprazolam XR tablets, in single doses ranging from 1 mg to 10 mg and in multiple doses ranging from 1 mg to 6 mg daily for 3 to 7 days, were well tolerated by the healthy subjects who participated in the pharmacokinetic /bioavailability studies. The adverse events that were reported during these studies were consistent with the known pharmacologic profile of alprazolam and with the study conditions that were imposed on the subjects. No serious, unexpected, or life-threatening adverse events occurred, and there were no deaths.

D. Adequacy of Safety Testing & Analysis

The methods of monitoring and analyzing potential safety concerns were adequate and appropriate in the placebo-controlled studies. The types and frequencies of safety assessments were sufficient. ECG studies in the placebo-controlled studies were not performed; however, there was adequate ECG information provided from other studies using alprazolam XR.

The variables used to assess safety included adverse events that emerged during the treatment phase, adverse events that emerged during the discontinuation phase, laboratory findings (chemistry, hematology and urinalysis), vital signs, and electrocardiogram (ECG) results. In addition, demographic information, treatment exposure, comorbid conditions, concomitant medication use, and the reason for termination were summarized. Not all safety information was available for all studies. Adverse events were collected in all trials. In studies M/2000/0271 and M/2000/0385, adverse events were solicited using a checklist. In all other studies, patients were asked to report any adverse events and were not prompted by a checklist. Information about adverse events (eg, severity, relationship to study drug, action taken, and outcome) was not consistently collected in all trials. Relationship to study drug and outcome of the adverse event were not collected in Study M/2000/0385. In addition, the start date of an adverse event was not collected in studies M/2000/0369, M/2000/0385 and M/2000/036 and was assumed to be the date the adverse event was reported. The studies in which demographic, dosing information, reason for discontinuation, concurrent/comorbid illness, and concomitant medications were collected are displayed below.

E. Methods Used for Monitoring Adverse Medical Event

All subjects who received one or more doses of study medication were included in all safety analyses. A record was kept of the daily doses of study medication, as well as of prescription medications taken during the study and within the 2 months before entering the study. For monitoring medical events, a 46-item checklist of medical events (SAFTEE-UP) was administered at each assessment visit. The severity of events (on a scale of 0-3) was recorded, along with any necessary action taken. The 46 items were divided into 7 different body systems: psychological; head, eyes, ears, nose, and throat; neuromuscular; chest; gastrointestinal; genitourinary; and miscellaneous. In addition, vital sign monitoring and chest auscultation were performed at baseline and at each weekly assessment visit.

Clinical Laboratory Monitoring

Hematology, chemistry, and urinalysis testing was performed at screening, baseline, and at the week-6 visit or upon premature study discontinuation.

F. Summary of Critical Safety Findings and Limitations of Data

F-1 Deaths in Alprazolam XR Studies and Trials

Summary
There were no deaths reported among subjects in the alprazolam XR ISS database.

Placebo-Controlled Studies in Panic Disorder
No patients died in any of the placebo-controlled studies in panic disorder in either the treatment or the discontinuation phase.

Active-Controlled Studies in Panic Disorder
No patients died in either the treatment or the discontinuation phase of the 2 active-controlled studies in panic disorder.

Uncontrolled Study in Panic Disorder
No patients died in Study M/2002/0021 [32].

Studies in Other Indications
No patients died in any of the 5 studies conducted in other indications.

Pharmacokinetic Studies
There were no deaths among the subjects who participated in the pharmacokinetic/bioavailability studies.

F-2 Serious Adverse Events and Unexpected Adverse Events

Definition of Serious Adverse Event
Serious adverse events were defined as those that were fatal or life threatening, permanently disabling, required or prolonged hospitalization, or were congenital anomalies, cancer, or medication overdoses. This category also included any other events the investigator judged to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Placebo-Controlled Studies: Treatment Phase	ALP XR	ALP IR	Placebo	Other
Pts with at least 1 adverse event	489 (92.09)	68 (97.14)	290 (83.09)	Not
Pts with at least 1 Related TES	268 (50.47)	6 (8.57)	73 (20.92)	applicable
Pts with TES causing study medication termination	91 (17.14)	6 (8.57)	27 (7.74)	
Pts with Serious TES	19 (3.58)	11 (15.71)	18 (5.16)	
Pts with Any Serious Event leading to discontinuation	12 (2.26)	5 (7.14)	6 (1.72)	
Placebo-Controlled Studies: Discontinuation Phase	**ALP XR**	**ALP IR**	**Placebo**	**Other**
Pts with at least 1 discontinuation event	348 (82.46)	56 (90.32)	180 (68.97)	Not
Pts with at least 1 Related DES	84 (19.91)	4 (6.45)	20 (7.66)	applicable
Pts with DES causing study medication termination	35 (8.29)	5 (8.06)	2 (0.77)	
Pts with Serious DES	18 (4.27)	14 (22.58)	6 (2.30)	
Pts with Any Serious Event leading to discontinuation	3 (0.71)	2 (3.29)	1 (0.38)	
Active-Control Studies: Treatment Phase	**ALP XR**	**ALP IR**	**Placebo**	**Other**
Pts with at least 1 adverse event	89 (62.68)	7 (100.0)	Not	81 (63.28)
Pts with at least 1 Related TES	63 (48.84)	0.00	applicable	74 (57.81)
Pts with TES causing study medication termination	12 (8.45)	1 (14.29)		22 (17.19)
Pts with Serious TES	4 (2.82)	0.00		3 (2.34)
Pts with Any Serious Event leading to discontinuation	2 (1.41)	0.00		3 (2.34)
Active-Control Studies: Discontinuation Phase	**ALP XR**	**ALP IR**	**Placebo**	**Other**
Pts with at least 1 discontinuation event	44 (39.29)	Not	Not	22 (24.72)
Pts with at least 1 Related DES	20 (17.86)	applicable	applicable	9 (10.11)
Pts with DES causing study medication termination	11 (9.82)			1 (1.12)
Pts with Serious DES	1 (0.89)			1 (1.12)
Pts with Any Serious Event leading to discontinuation	0.00			0.00
Studies in Other Indications: Treatment Phase	**ALP XR**	**ALP IR**	**Placebo**	**Other**
Pts with at least 1 adverse event	133 (50.38)	Not	Not	104 (45.41)
Pts with at least 1 Related TES	92 (34.85)	applicable	applicable	74 (32.31)
Pts with TES causing study medication termination	11 (4.17)			13 (5.68)
Pts with Serious TES	4 (1.52)			2 (0.87)
Pts with Any Serious Event leading to discontinuation	3 (1.14)			2 (0.87)
Studies in Other Indications: Discontinuation Phase	**ALP XR**	**ALP IR**	**Placebo**	**Other**
Pts With at Least 1 discontinuation event	30 (16.22)	Not	Not	32 (16.41)
Pts with at least 1 Related DES	10 (5.41)	applicable	applicable	7 (3.59)
Pts with DES causing study medication termination	0.00			2 (1.03)
Pts with Serious DES	1 (0.54)			0.00
Pts with Any Serious Event leading to discontinuation	0.00			0.00

Pts = Patients, TES = treatment-emergent symptom (adverse event), DES =discontinuation-emergent symptom(adverse event)

a. Serious Adverse Events in Placebo-Controlled Trials

1.Treatment Phase

In the alprazolam XR group, 19/531 (3.6%) patients had ≥ 1 serious treatment-emergent adverse event. The corresponding numbers in the alprazolam IR and placebo groups were 11/70 (15.7%) and 18/349 (5.2%), respectively. The rates of serious treatment-emergent adverse events was similar in the alprazolam XR and placebo groups. The rate of serious adverse events was greatest in the CNS (1.3% in the alprazolam XR group and 1.7% in the placebo group). Of note, there were 4 seizures (preferred terms convulsion NOS [n=2], grand mal convulsion [n=1], or partial seizures NOS [n=1]) reported as serious adverse events; 3 in the alprazolam XR group and 1 in the alprazolam IR group. Two in the alprazolam XR group and the 1 in the alprazolam IR group led to discontinuation of study drug. All but 1 (in the alprazolam XR group) were considered drug-related. Six

subjects reported an SAE of sedation or aggravated sedation, (4 in the alprazolam XR group and 2 in the alprazolam IR group). All 6 cases led to discontinuation of study drug. Two subjects took intentional overdoses of alprazolam XR. All 5 subjects recovered from these serious adverse events. In the active treatment and placebo groups, 3.6% and 5.2% of subjects, respectively, discontinued from the study due to serious adverse events.

The 5 most frequent severe adverse events in the alprazolam XR group were sedation (59/489, 12.1%), fatigue (20/489, 4.1%), somnolence (16/489, 3.3%), irritability (14/489, 2.9%), and headache (12/489, 2.5%).

2. Drug Discontinuation Phase
During the drug discontinuation phase, 18/422 (4.3%) of the alprazolam XR subjects had $\geq$ 1 serious discontinuation-emergent adverse event, and 6/261 (2.3%) of the placebo group experienced $\geq$ 1 serious adverse events. The 5 most common severe discontinuation-emergent adverse events were nervousness 39/348 (11.2%), insomnia 35/348 (10.1%), headache 25/348 (7.2%), dizziness 21/348 (6.0%), and tremor 21/348 (6.0%). Serious adverse events led to study discontinuation in 0.7% and 0.4% of alprazolam- and placebo-treated subjects, respectively. Of the alprazolam-treated subjects with a serious discontinuation-emergent adverse event, 2 cases led to discontinuation from the study (1 case of nervousness and 1 case of panic disorder).

b. Active-Controlled Studies in Panic Disorder

1. Treatment Phase
In the alprazolam XR group, 4/142 (2.8%) patients had at least 1 serious treatment-emergent adverse event. The 4 serious treatment-emergent adverse events were a single instance of each of the following: coronary artery disease, thyroid nodule, hemorrhoids, and uterine cervical disorder. The serious adverse events of thyroid nodule and coronary artery disease led to discontinuation of study drug, but neither was considered drug-related.

2. Discontinuation Phase
In the alprazolam XR group, 1/112 (0.9%) patient had at least 1 serious discontinuation-emergent adverse event. The serious discontinuation-emergent adverse events occurring in the same patient were breast cancer and suicidal depression. Neither of these serious adverse events led to discontinuation of study drug. The suicidal depression was considered drug-related.

c. Uncontrolled Study in Panic Disorder
A summary table of serious adverse events leading to discontinuation was not prepared for Study M/2002/002 because the small number of patients (N=29) does not lend itself to a meaningful subgroup analysis. However, no treatment-emergent or discontinuation-emergent serious adverse events were observed in Study M/2002/0021.

d. Studies in Other Indications

1.Treatment Phase
A total of 4/264 (1.5%) patients treated with alprazolam XR had at least 1 serious treatment-emergent adverse event. In the alprazolam XR treatment group, the numbers of patients with each serious treatment-emergent adverse event were decreased platelet count (2), edema (1), hyponatremia (1), benign breast neoplasm (1), and dermatitis (1). Three (3/264, 1.1%) of the 4 alprazolam XR treated patients discontinued from the study. The diagnosis of benign breast neoplasm in 1 patient in the alprazolam XR treatment group did not lead to the patient's discontinuation from the study. None of these serious adverse events was considered drug-related.

2. Discontinuation Phase
1/185 (0.5%) patient treated with alprazolam XR had at least 1 serious discontinuation-emergent adverse event. These events were anxiety, depression, and insomnia. The patient did not discontinue from the study. Anxiety and depression were considered to be unrelated to study drug and relationship was not reported for insomnia.

e. Phase I Studies
There were no serious adverse events reported for any of the 539 subjects in the 24 Phase I studies.

Attributions for Serious Adverse Events During Placebo-Controlled Trials
During the treatment phase, a total of 22 serious events were recorded for the 531 subjects treated with alprazolam XR in double-blind studies of Panic Disorder. Upon reviewing the narrative summaries of the serious adverse events, the reviewer concludes that 6/22 (27%) of the serious adverse events can be attributed to treatment with alprazolam XR and that 8/22 (36%) possibly can be attributed to treatment with alprazolam XR.

During the drug discontinuation phase, a total of 25 serious adverse events for 18/422 (4.3%) subjects were recorded during drug discontinuation from alprazolam XR. Upon reviewing the narrative summaries of the serious adverse events, the reviewer concludes that 20/25 (80%) of the serious adverse events can be attributed to discontinuation of treatment with alprazolam XR and that 4/25 (16%) possibly can be attributed to discontinuation of alprazolam XR. These serious events were: drug withdrawal syndrome (2); aggravated anxiety or panic (5); alprazolam overdose (1); insomnia (1); dizziness (2); confusion (2); disturbance of attention (1); tremor (1); headache (2); psychiatric d/o NOS (1); tearfulness (1); depressed mood (2); nausea & vomiting (2); and paresthesia (1).

Such adverse events were not unexpected in comparison to drug discontinuation adverse events observed with alprazolam IR and other benzodiazepines. None of these serious adverse events are unlabeled.

Unexpected Serious Adverse Events
For all of the Phase I-III studies, there were no unexpected or unlabeled serious adverse events, compared to those observed for treatment and drug discontinuation with alprazolam or other benzodiazepines

F-3 Discontinuations Due to Adverse Events In Placebo-Controlled Trials

Summary
In the 5 placebo-controlled studies of alprazolam XR in Panic Disorder, the treatment-emergent adverse events most commonly leading to subject discontinuation in the alprazolam XR group during the treatment phase were sedation and somnolence. The drug discontinuation-emergent adverse events most commonly leading to study discontinuation in the alprazolam XR group were insomnia and aggravated anxiety. The study discontinuation profiles due to adverse events during the treatment and drug discontinuation phases are similar to the profiles observed with alprazolam IR treatment and discontinuation. In the alprazolam XR group, 17.14 % of subjects discontinued from the study due to adverse events. In the placebo group, 7.74 % of subjects discontinued due to adverse events. In the alprazolam XR and placebo groups, 2.3% and 1.8% of subjects, respectively, discontinued from the treatment phase of the study due to serious adverse events. During the drug discontinuation phase, 0.7% of the alprazolam XR group and 0.4% of the placebo group discontinued from the study due to experiencing serious adverse events.

Treatment Phase of Placebo-Controlled Trials
In the alprazolam XR group, 91/531 (17.1%) subjects had $\geq$ 1 treatment-emergent adverse event that led to discontinuation. In the placebo group, 27/349 (7.7%) had $\geq$ 1 treatment-emergent adverse event that led to discontinuation. Thus, the rate of treatment-emergent adverse events that led to discontinuation in the alprazolam XR group was more than twice that in the placebo group. The rate of adverse events that led to discontinuation was greatest for CNS adverse events (13.8% in the alprazolam XR group and 3.4% in the placebo group). The 5 adverse events most commonly leading to premature termination in the alprazolam XR group were sedation (7.5%), somnolence (3.2%), depression (2.5%), dysarthria (2.1%), and abnormal coordination (1.9%). The rates of premature withdrawals for these adverse events were consistently lower in the placebo group.

Drug Discontinuation Phase
In the alprazolam XR group, 35/422 (8.3%) subjects had at least 1 discontinuation-emergent adverse event that led to study discontinuation. In the placebo group 2/261 (0.8%) subjects experienced treatment-emergent adverse event which led to study discontinuation. The rate of discontinuation-emergent adverse events that led to study discontinuation in the alprazolam XR group was more than twice that in the placebo group. The rates of adverse events that led to discontinuation in the alprazolam XR treatment group were greatest for psychiatric events and CNS events (5.9%, and 3.1%),

respectively. In the placebo group, psychiatric events leading to discontinuation were observed in 0.8% of subjects, and CNS events leading to discontinuation were not observed. The most commonly observed discontinuation-emergent adverse events in the alprazolam XR treatment group were insomnia (1.9%), aggravated anxiety (1.4%), palpitations (1.2%), dizziness (1.2%), vomiting (1.2%), and anxiety (1.2%). Rates <1% were observed in the placebo group for all of these discontinuation-emergent adverse events.

F-4 Adverse Events

Summary of Adverse Event Findings in Placebo-Controlled Studies of Alprazolam XR in Panic Disorder

In the 5 placebo-controlled studies of alprazolam XR in Panic Disorder, the most commonly reported treatment-emergent adverse events attributed to treatment with alprazolam XR group were: sedation (45%), somnolence (23%), memory impairment (15.4), fatigue (13.9), depression (12.1), dysarthria (11%), impaired coordination (9.4%), cognitive impairment (7.2%), ataxia (7.2%), and decreased libido (6%). The most commonly reported drug discontinuation-emergent adverse events attributed to discontinuation of alprazolam XR were anxiety (30%), tremor (28%), dizziness (27%), headache (26%), insomnia (24%), depression (11%), decreased appetite (9.5%), hyperventilation (8.5%), and derealization (8%). The overall rate of drug-related treatment-emergent adverse events in the alprazolam XR treatment group was more than twice that in the placebo group. Details are listed in tables below.

In the alprazolam XR group, 489/531 (92.1%) subjects had $\geq$ 1 treatment-emergent adverse event. In the placebo group, 290/349 (83.1%) subjects had $\geq$ 1 treatment-emergent adverse event. The rate of adverse events was greatest in the CNS (79.7%) in the alprazolam XR group as well as in the placebo group (57.3%). Of the 9 most common treatment-emergent adverse events in the alprazolam XR treatment group, all were CNS events: sedation (45%), somnolence (23%), memory impairment (15.4), fatigue (13.9), depression (12.1), dysarthria (11%), impaired coordination (9.4%), cognitive impairment (7.2%), and ataxia (7.2%).

More than two-thirds of the treatment-emergent and discontinuation-emergent adverse events were mild or moderate. Severe events appeared to be due to a combination of the pharmacologic properties of alprazolam XR (eg, sedation, somnolence) or manifestations of the disease (eg, nervousness, irritability, and headache). The incidence of the most commonly reported treatment-emergent and discontinuation-emergent adverse events in the alprazolam XR group was slightly lower in patients > 45 years old than in patients $\leq$45 years old. Gender had a minimal association with either the treatment-emergent or discontinuation-emergent adverse event profiles. Women tended to report slightly more adverse events than men. Analysis according to race was inconclusive because > 90% of the population was white.

Table. **Treatment-Emergent Adverse Events in All Placebo-Controlled Clinical Trials with XANAX XR (rate > 1%)**

System Organ Class/ Adverse Event	Percentage of Subjects Reporting Adverse Event	
	XANAX XR (n=531)	Placebo (n=349)
Nervous System Disorders		
Sedation	45.2	22.6
Somnolence	23.0	6.0
Memory Impairment	15.4	6.9
Dysarthria	10.9	2.6
Coordination Impairment	9.4	0.9
Mental Impairment	7.2	5.7
Ataxia	7.2	3.2
Attention Disturbance	3.2	0.6
Balance Impairment	3.2	0.6
Paresthesia	2.4	1.7
Dyskinesia	1.7	1.4
Hypoesthesia	1.3	0.3
Hypersomnia	1.3	0
General Disorders		
Fatigue	13.9	9.2
Lethargy	1.7	0.6
Infection		
Influenza	2.4	2.3
Upper Respiratory Tract Infection	1.9	1.7
Psychiatric Disorders	**XANAX XR**	**Placebo**
Depression	12.1	9.2
Libido Decreased	6.0	2.3
Disorientation	1.5	0
Confusion	1.5	0.9
Depressed Mood	1.3	0.3
Anxiety	1.1	0.6
Metabolism and Nutrition Disorders		
Appetite Decreased	7.3	7.2
Appetite Increased	7.0	6.0
Anorexia	1.5	0
Gastrointestinal Disorders		
Dry Mouth	10.2	9.7
Constipation	8.1	4.3
Nausea	6.0	3.2
Pharyngolaryngeal Pain	3.2	2.6
Investigations		
Weight Increased	5.1	4.3
Weight Decreased	4.3	3.7
Injury, Poisoning, and Procedural Complications		
Road Traffic Accidents	1.5	0
Reproductive System and Breast Disorders		
Dysmenorrhea	3.6	2.9
Sexual Dysfunction	2.4	1.1
Premenstrual Syndrome	1.7	0.6
Musculoskeletal and Connective Tissue Disorders		

Arthralgia	2.4	0.6
Myalgia	1.5	1.1
Limb Pain	1.1	0.3
Vascular Disorders		
Hot Flushes	1.5	1.4
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	1.5	0.3
Allergic Rhinitis	1.1	0.6
Skin and Subcutaneous Disorder		
Pruritis	1.1	0.9

Severity of Adverse Events in Placebo-Controlled Studies of Alprazolam XR in Panic Disorder

Treatment Phase

Overall, 489 subjects in the alprazolam XR group and 290 subjects in the placebo group had at least 1 adverse event with a severity rating recorded. The rates of subjects in the respective treatment groups reporting at least 1 adverse event of mild severity were 78.5% and 79.0%; rates with moderate severity were 76.3% and 66.2%; and rates of adverse events with severe intensity were and 30.7%. The 5 most frequent adverse events rated with severe intensity in the alprazolam XR group were sedation (59/489, 12.1%), fatigue (20/489, 4.1%), somnolence (16/489, 3.3%), irritability (14/489, 2.9%), and headache (12/489, 2.5%). However, the majority of these adverse events were rated as either mild or moderate in severity. The rates of these particular adverse events are presented in the table below according to severity.

	Mild		Moderate		Severe	
Preferred Term (N)	n	%	n	%	n	%
Sedation (240)	63	26	118	49	59	25
Fatigue (74)	23	31	31	42	20	27
Somnolence (122)	49	40	57	47	16	13
Irritability (62)	27	44	21	34	14	23
Headache (118)	57	48	49	42	12	10

Drug Discontinuation Phase

The most common adverse events are summarized according to severity in the table below. Overall, 348 subjects in the alprazolam XR group and 178 subjects in the placebo group had at least 1 adverse event with a severity rating recorded. The percentages of subjects in the treatment groups reporting at least 1 adverse event of mild severity were 69.5% and 74.7%, respectively; rates with moderate severity were 77.0%, 87 and 68.5%, respectively; and rates with severe adverse events were 41.1% and 26.4%, respectively. The 5 most frequent severe discontinuation-emergent adverse events were nervousness 39/348 (11.2%), insomnia 35/348 (10.1%), headache 25/348 (7.2%), dizziness 21/348 (6.0%), and tremor 21/348 (6.0%). However, the majority of these adverse events were either mild or moderate in maximum severity.

Preferred Term (N)	Mild n	Mild %	Moderate n	Moderate %	Severe n	Severe %
Nervousness (91)	20	22	32	35	39	43
Insomnia (102)	19	19	48	47	35	34
Headache (111)	27	24	59	53	25	23
Dizziness (114)	38	33	55	48	21	18
Tremor (119)	43	36	55	46	21	18

F-5 Drug Discontinuation and Withdrawal Phenomena

Discontinuation Phase in Placebo-Controlled Studies
Over three-fourths of the subjects who participated in the treatment phase also participated in the discontinuation phase. There were no differences in the demographic characteristics of the subjects in the treatment and discontinuation phases.

In the alprazolam XR group, 348/422 (82.5%) subjects had at least 1 discontinuation-emergent adverse event, compared with 180/261 (69.0%) in the placebo group. As shown in the table below, the incidence of discontinuation-emergent adverse events in the alprazolam XR group was highest for neuropsychiatric (72.8%) and CNS (69.6%) adverse events. For subjects treated with placebo, the incidences of such discontinuation-emergent adverse events were 29.9% and 28.3%, respectively.

The following discontinuation-emergent adverse events occurred at rates which were $\geq$5% and twice that observed in the placebo group: tremor (28.2%), dizziness (27%), headache (26.5%), insomnia (24.2%), nervousness (21.8%), diarrhea (12.1%), depression (10.9%), decreased appetite (9.5%), hyperventilation (8.5%), derealization (8.1%), anxiety (7.8%), hypoesthesia (7.8%), muscle twitching (7.4%), paresthesia (7.1%), depersonalization (5.7%), and hot flushes (5.9%).

Table. Discontinuation-Emergent Adverse Events in Placebo-Controlled Trials with Alprazolam XR (AE rate > 5% and twice the rate in Placebo Group)

System Organ Class/ Adverse Event	Percentage of Subjects Reporting Adverse Event	
	XANAX XR (n=422)	Placebo (n=261)
Nervous System Disorders	Percentages (%)	
Tremor	28.2	10.7
Dizziness	27.0	unspecified
Headache	26.5	12.6
Hypoesthesia	7.8	2.3
Paresthesia	7.1	2.7
Psychiatric Disorders		
Insomnia	24.2	9.6
Nervousness	21.8	8.8
Depression	10.9	5.0
Derealization	8.0	3.8

Anxiety	7.8	2.7
Gastrointestinal Disorders		
Diarrhea	12.1	3.1
Respiratory Disorders		
Hyperventilation	8.5	2.7
Metabolism and Nutrition Disorders		
Appetite Decreased	9.5	3.8
Musculoskeletal Disorders		
Muscle Twitching	7.4	2.7
Vascular Disorders		
Hot Flushes	5.9	2.7

F-6 Abuse Liability of Alprazolam XR

Studies examining abuse liability of alprazolam, in subjects with a history of sedative drug abuse, compared the abuse potential of alprazolam XR with those of alprazolam IR, several benzodiazepines, and placebo. On the euphoria scale, alprazolam XR produced significantly less euphoric effect than alprazolam IR or diazepam. On the Street Value Questionnaire, the XR tablet had a lower estimated average street value than the IR tablet, but had a higher value than diazepam and clonazepam.
On the "use again" question, no drug achieved a mean score higher than 50 on a 100-point scale. Rank ordered, alprazolam IR had the highest score (48), followed by diazepam (45), clonazepam (42), alprazolam XR (41), and placebo (19).
On the Recalled Favorite Drug Estimate Scale, no benzodiazepine was markedly preferred over the others. Generally, the data suggest that alprazolam has a similar abuse liability potential as other benzodiazepines including alprazolam IR, although administration of the XR tablet was associated with lower scores on most measures in the study.

F-7 Clinical Laboratory Testing Results

The following laboratory parameters were tested:

- **Hematologic** (hematocrit, hemoglobin, white blood cells (WBC), lymphocytes, monocytes, neutrophil , basophils, eosinophils, and platelet count)
- **Serum Chemistry:** (SGPT, SGOT, alkaline phosphatase, calcium, cholesterol, creatinine, glucose, LDH, total bilirubin, total protein, and uric acid.
- **Urinalysis:** RBC, specific gravity, glucose, WBC, and pH.

Testing Schedule

The parameters above were assessed at baseline and at the study endpoint or upon premature study discontinuation

a. Analysis of Hematology Testing

For the mean change from baseline to endpoint for the hematology parameters, there were minor fluctuations (not exceeding approximately ±10% in both the alprazolam XR and placebo groups). There were no statistically significant differences in parameters between treatment groups. Only a small number of subjects (≤ 1.1% for any parameter)

who had normal baseline values had either abnormally high or low post-baseline measurements in either the alprazolam XR (9) or placebo (4) groups. Five subjects in the alprazolam XR group had WBC counts that were within normal limits at baseline and exceeded the normal value (>13x10 3 /uL) at the endpoint laboratory evaluation. The high values for 2 of these subjects were only slightly > 13x10 3 /uL. No abnormal value exceed 15.1 x10 3 /uL. In 2 subjects, the elevated WBC values could possibly have been residual effects of upper respiratory tract infections that were reported. One subject with an elevated WBC reported having an ear infection, and another reported having earaches and a sore throat which began approximately 1 month before the endpoint laboratory evaluations. Another subject had a record of an elevated baseline WBC that was higher than the endpoint value.

The sponsor did not attribute any of the abnormal hematologic parameters to treatment with alprazolam XR. Similarly, the reviewer concludes that it is unlikely that any of these laboratory abnormalities can be attributed to treatment with alprazolam XR. No subject failed to enter the drug discontinuation phase due to abnormal hematologic tests.

b. Analysis of Serum Chemistry Testing

For the mean change from baseline to endpoint for serum chemistry parameters, there were minor fluctuations (not exceeding approximately ±10%) in both the alprazolam XR and placebo groups. Relatively few subjects (≤ 6.1% for any parameter) who had normal baseline values had abnormally high or low post-baseline measurements in either the alprazolam XR (n =16) or placebo (n = 13) group. Results of liver function tests indicate that 3 subjects in the alprazolam XR group and 1 subject in the placebo group had mildly elevated LFTs, none of which were judged as being clinically significant.. It is possible that some of the elevations in LFTS resulted from active drug treatment; however, the elevations were mild and were not associated with clinical signs or symptoms suggestive of significant hepatic dysfunction. Elevated total bilirubin was observed in none of the alprazolam group and in one of the placebo-treated subjects. It is unclear whether any of the abnormal serum chemistry results were attributed to treatment with alprazolam. Furthermore, no subject failed to enter the drug discontinuation phase due to abnormal liver function tests.

Abnormally high cholesterol levels were observed in 2 and 3 subjects, respectively, in the alprazolam and placebo group. There were no abnormalities in creatinine levels for either treatment group.

c. Analysis of Urinalysis Testing

Generally, few subjects in either the alprazolam XR or placebo group who had baseline urinalysis values within reference range limits had endpoint values which were outside reference range limits. However, the results of specific gravity testing indicate that 11.7% of subjects in the alprazolam XR group had abnormally high values at endpoint, and 5.1% in this group had abnormally low values. In the placebo group, 11.5% of subjects had abnormally high values at endpoint, and 9.0% had abnormally low values. These results do not suggest that there was a treatment effect of alprazolam XR on

urinalysis parameters or renal function. There were no other significant changes in urinalysis parameters for either treatment group.

F-8 Electrocardiogram Results

ECG monitoring was not performed in any of the placebo-controlled studies of alprazolam XR. From Study M/2002/0015, the sponsor reports that ECG measurements for the majority of patient with baseline ECGs that were within normal limits in either the alprazolam XR or clomipramine groups remained normal at endpoint, (89.3% [92/103] and 93.1% [81/87], respectively). The sponsor reports that alprazolam XR did not appear to have any clinically relevant effects on ECG parameters in this study. Specific information regarding potential effects of the drug on QT intervals is not available. No ECG data has been included in this submission.

F-9 Weights and Vital Signs

Vital signs measured included blood pressure, pulse, and oral body temperature. Alprazolam XR did not appear to have any clinically relevant effects on weight or vital signs by either analysis of central tendency or examination of outliers.

F-10 Safety Conclusions

Alprazolam XR was reasonably safe and well tolerated in the treatment of subjects with Panic Disorder with or without Agoraphobia. The conclusion is based on analyses of treatment-emergent and discontinuation-emergent adverse events, clinical laboratory measures, and vital sign measurements. There were no deaths during any of the alprazolam XR studies. In comparison with safety data regarding treatment with the immediate-release formulation of alprazolam and other benzodiazepines, there were no unexpected adverse events attributed to treatment with alprazolam XR. The types, rates, and severity of treatment-emergent and discontinuation-emergent adverse events observed with alprazolam XR were quite similar to those observed with alprazolam IR treatment and treatment with other benzodiazepines. During treatment, the most commonly occurring adverse events in alprazolam XR-treated patients were sedation, somnolence, memory impairment, dizziness, and other symptoms that are related to the pharmacologic properties of alprazolam XR. During the discontinuation phase, the rates of adverse events was approximately equal for events related to the discontinuation of alprazolam XR and those related to the re-emergence of panic disorder. Tremor, dizziness, headache, insomnia, and nervousness were predominant symptoms.

Patient characteristics such as age, gender, race, and concurrent illness did not affect the distribution of the mean daily or mean final dose of alprazolam XR. A mean daily dose of between 2 and 6 mg of alprazolam XR was shown to be well tolerated in the treatment of panic disorder, based on the evaluation of treatment-emergent and discontinuation-emergent adverse events, the incidence of serious adverse events, the incidence of premature termination, and clinical laboratory and vital signs measurements.

VIII. Labeling Issues

Sponsor's Proposed Labeling Under "CLINICAL EFFICACY TRIALS"
The sponsor proposes the following labeling for XANAX XR: "The efficacy of XANAX XR Tablets in the treatment of panic disorder was established in [redacted] placebo-controlled studies [redacted] However, only one placebo-controlled study demonstrated the efficacy of XANAX XR in the treatment of Panic Disorder. The other three placebo-controlled studies failed to demonstrate efficacy. Therefore, it is recommended that the sponsor change the language in this section of labeling, in order to indicate that a single trial demonstrated efficacy.

IX. Use in Special Populations

A. Pediatric Population

The sponsor notes that the safety and effectiveness of XANAX XR in individuals below 18 years of age have not been established.

The current submission does not include studies of treatment with XANAX XR in pediatric populations. As discussed during the pre-NDA meeting on July 19, 2001, Pharmacia [redacted] The 2 planned pediatric studies are described in the Proposed Pediatric Study Request submitted to FDA on October 1, 2001 (copy included in this submission). The sponsor intends [redacted] of the NDA for XANAX XR Tablets in the adult population.

B. Women

In labeling, the sponsor appropriately provides the following information regarding the use of XANAX XR by women:

1. **Pregnancy**
   a) Teratogenic Effects:
   XANAX XR has been placed in Pregnancy Category D.
   The sponsor directs readers: "(See WARNINGS section)."
   b) Nonteratogenic Effects:
   The sponsor states: "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."

2. **Labor and Delivery:**
   has no established use in labor or delivery.

3. **Nursing Mothers:**
   The sponsor states: "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

C. Geriatric Population

The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. The sponsor states that the smallest effective dose of alprazolam should be used in the elderly to preclude the development of ataxia and oversedation

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X. Conclusions and Recommendations

A. Efficacy of Alprazolam XR

It is concluded that alprazolam XR is effective in the treatment of Panic Disorder with or without Agoraphobia. All 7 co-primary efficacy endpoints in the pivotal study were statistically significantly superior in the group treated with alprazolam XR compared to the group treated with placebo. The differences suggest that there was a significant treatment effect for alprazolam XR. Moreover, the treatment effect of alprazolam XR, as measured by clinically relevant endpoints for Panic Disorder with or without Agoraphobia, was clinically meaningful. Treatment with the drug resulted in statistically and clinically significant reductions in the number and severity of panic attacks, phobic avoidance, and in global measures of the severity of illness and dysfunction associated with the illness

B. Safety of Alprazolam XR

Alprazolam XR was reasonably safe and well tolerated in the treatment of patients with Panic Disorder with or without Agoraphobia, based on the evaluation of treatment-emergent and discontinuation-emergent adverse events, clinical laboratory measures, and vital signs. There were no deaths during the placebo-controlled studies. In comparison with safety data regarding treatment with alprazolam and other benzodiazepines, there were no unexpected adverse events attributed to treatment with alprazolam XR. The types, rates, and severity of treatment-emergent and discontinuation-emergent adverse events with alprazolam XR were quite similar to those observed with alprazolam IR treatment.

C. Labeling

Under the section in labeling, "CLINICAL EFFICACY TRIALS," the sponsor states that the efficacy of XANAX XR in the treatment of panic disorder was established in

[redacted]

D. Recommendations

1. I recommend that the Division take an approvable action for this NDA, in which the sponsor seeks a claim for an indication for alprazolam XR (XANAX XR) in the treatment of [redacted] of Panic Disorder with or without Agoraphobia.
2. [redacted]
3. [redacted]

/S/

Robert L. Levin, M.D., October 15, 2002
Medical Reviewer,
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XI. Appendix

A. Investigators and Clinical Trial Sites

1. Karl Rickels, M.D.
   University of Pennsylvania
   Philadelphia, PA
2. William Patterson, M.D.
   Birmingham Research Group
   Birmingham, AL
3. Murray Rosenthal, M.D.
   2710 Health Circle Drive
   San Diego, CA

B. Subject Inclusion and Exclusion Criteria

Inclusion Criteria

- The Structured Clinical Interview for Diagnosis (SCID-UP) administered at the screening visit was used to elucidate subjects' symptoms and to confirm the diagnosis of Panic Disorder. The following SCID-UP criteria for panic disorder were used:

1. Discrete periods of intense discomfort or fear.
2. At least 4 of the panic attack symptoms were present during the attacks.
3. Most of the symptoms were experienced within 10 minutes of onset.
4. At least some of the attacks were unexpected.
5. Symptoms were not due to a specific organic factor.

- Women had to be surgically sterile, postmenopausal, or using reliable contraceptive methods.
- Subjects were required to discontinue use of psychoactive drugs before enrollment and must have been able to take medication orally.
- Subjects must have been willing to participate voluntarily as described in the informed consent statement.
- Subjects who previously had a favorable clinical response to alprazolam IR tablets were eligible for study participation.
- Nonresponders to alprazolam IR tablets were eligible only if they had originally taken doses of alprazolam IR < 4 mg/day for less than 4 consecutive weeks.

Exclusion Criteria

Exclusion criteria included the following:

1) Acute suicidal ideation; pregnancy, or lactation
2) Hypersensitivity to benzodiazepines
3) Taking medication containing alpha-blockers or beta-blockers
4) Undergoing concurrent psychotherapy or behavioral therapy
5) Distinctly abnormal laboratory values
6) Uncontrolled renal, hepatic, cardiac, pulmonary, endocrine, or collagen disease
7) The first episode of a mixture of panic and depression after the age of 40 years, as determined by clinical judgment

8) History of major depression unless the following were met: 1) Major Depression was not dominant during the occurrence of panic attacks as determined by clinical judgment and 2) major depressive episodes, unassociated with panic attacks, occurred more than 3 years before study enrollment
9) History or diagnosis of: epilepsy or seizures, dementia, bipolar disorder, cyclothymic disorders, major depression with melancholia, obsessive-compulsive disorder, alcoholism or drug abuse with the last 6 months, or psychotic disorder or drug-induced psychosis within the last 6 months; taking chronic concurrent medication that will be maintained during the study.

C. Tables of Phase I Studies Providing Safety Data

Table 2. Table of All Phase 1 Studies in the Integrated Summary of Safety

Study No. [ref] Investigator(s) Study Dates/Sites	Study Design	Regimen, Route and Dose*	Subjects			Report Location In NDA Item/Volume/Page
			Number Treated	Age (y) Range (Mean)	M/F W/B/O	
M/2000/0214 [1] [redacted] 6 April 1985 Single Center, US	Randomized, open-label, crossover, bioavailability study.	Five single doses; 1-week washout between doses Oral alprazolam (IR and XR) dose of 1 mg	30	20-51 (29.9)	15/15 28/2/2	Rep: Item 6/Vol 6/Pg 90
M/2000/0235 [2] [redacted] 9 November 1985 Single Center, US	Randomized, open-label, crossover bioavailability study.	Five single doses; 1-week washout between doses Oral alprazolam (XR) dose of 1 mg IV alprazolam dose of 1 mg	28	22-53 (32.6)	14/14 28/2/0	Rep: Item 6/Vol 8/Pg 1
M/2000/0243 [3] [redacted] 22 February 1987 22 March 1987 Single Center, US	Randomized, open-label, crossover, bioavailability study	Five single doses; 1-week washout between doses Oral alprazolam (IR and XR) dose of 1 and 2 mg	24	20-51 (29.7)	22/2 21/1/2	Rep: Item 6/Vol 9/Pg 1
M/2000/0243 [4] [redacted] 13 February 1987 15 March 1987 Single Center, US	Randomized, open-label, crossover, bioavailability study	Five single doses; 1-week washout between doses Oral alprazolam (IR and XR) dose of 1 and 3 mg	24	24-55 (37.3)	14/10 22/1/1	Rep: Item 6/Vol 10/Pg 1
M/2000/0253 [5] [redacted] 10 April 1988 Single Center, US	Randomized, open-label, parallel group with a single dose phase and multiple dose phase	Single dose IV treatment on day 1 Single dose oral treatments on day 8, and then on days 10 - 12, doses administered as a single daily dose x 3 days Oral alprazolam (XR) dose of 1, 3 and 6 mg. Intravenous alprazolam dose of 1 mg.	42	18-54 (29.1)	42/0 26/16/0	Rep: Item 6/Vol 13/Pg 1

*XR = alprazolam sustained-release; IR = alprazolam compressed tablet (immediate-release)

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Table 2. Table of All Phase 1 Studies in the Integrated Summary of Safety						
Study No. [ref] Investigator(s) Study Dates/Sites	Study Design	Regimen, Route and Dose[a]	Subjects			Report Location In NDA Item/Volume/Page
			Number Treated	Age (y) Range (Mean)	M/F W/B/O	
M/2000/0275 [6] [redacted] 16 March 1988 2 April 1988 Single Center, US	Randomized, open-label, crossover, food effect/bioavailability study	Three single doses; 1-week washout between doses Oral alprazolam (IR and XR) dose of 1 mg	21	21-43 (31)	12/9 20/0/1	Rep: Item 6/Vol 16/Pg 129
M/2000/0305 [7] [redacted] 25 October 1986 8 November 1986 Single Center, US	Randomized, open-label, crossover, bioequivalence study	Four single doses; 1-week washout between doses Oral alprazolam (IR and XR) dose of 1 mg	25	19-55 (32.8)	19/6 23/1/1	Rep: Item 6/Vol 14/Pg 238
M/2000/0348 [8] [redacted] 21 January 1988 17 February 1988 Single Center, US	Randomized, open-label, crossover, bioequivalence study	Three single doses; 1-week washout between doses Oral alprazolam (IR and XR) dose of 1 mg	24	18-39 (26.3)	24/0 23/0/1	Rep: Item 6/Vol 15/Pg 1
[redacted] 16 October 1987 1 November 1987 Single Center, US	Randomized, open-label, crossover, bioequivalence study	Three single doses; 1-week washout between doses Oral alprazolam (XR) dose of 6 mg.	24	22-52 (34.8)	12/12 23/1/0	Rep: Item 6/Vol 35/Pg 1
P/2002/0001 [10] [redacted] 25 September 1989 31 October 1989 Single Center, US	Randomized, open-label, [redacted]er, bioavailability	Five single doses; 1-week washout between doses Oral alprazolam (XR) doses of 1 and 3 mg	27	18-50 (31)	27/0 24/2/1	Rep: Item 6/Vol 36/Pg 1

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Table 2. Table of All Phase 1 Studies in the Integrated Summary of Safety						
Study No. [ref] Investigator(s) Study Dates/Sites	Study Design	Regimen, Route and Dose*	Subjects			Report Location In NDA Item/Volume/Page
			Number Treated	Age (y) Range (Mean)	M/F W/B/O	
P/2002/0001 [11] 20 August 1988 10 September 1988 Single Center, US	Randomized, open-label, crossover, bioavailability study	Four single doses; 1-week washout between doses Oral alprazolam (XR) dose of 0.25, 0.5 and 1 mg	24	21-55 (38.1)	18/6 22/0/2	Rep: Item 6/Vol 11/Pg 45
P/2002/0002 [12] 28 April 1989 21 May 1989 Single Center, US	Randomized, open-label, crossover, single and multiple doses	Single oral dose of 2 x 3-mg XR tablets on Day 1 and then once a day on days 3 through 8. Single oral dose of 1 x 1-mg and 1x 0.5-mg IR tablets on Day 1 and 4 times a day on days 3 through 8.	23	19-54 (32.1)	23/0 21/0/2	Rep: Item 6/Vol 17/Pg 1
P/2002/0003 [13] 11 March 1989 3 April 1989 Single Center, US	Double blind, randomized modified 4-way crossover with placebo administered in the first phase	Four single doses; 1-week washout between doses Oral alprazolam (XR) dose of 2, 4, 8 and 10 mg or placebo	24	19-49 (28)	24/0 24/0/0	Rep: Item 6/Vol 30/Pg 1
P/2002/0007 [14] 17 August 1990 10 September 1990 Single Center, US	Randomized, open-label, crossover study	Four single doses; 1-week washout between doses Oral alprazolam (IR and XR) doses of 1 and 3 mg administered at 7 AM or 10 PM	24	20-55 (37)	24/0 22/0/2	Rep: Item 6/Vol 33/Pg 1
P/2002/0008 [15] 25 June 1991 4 January 1993 Single Center, US	Double-blind, placebo controlled, crossover, bioavailability study	Five single doses Oral alprazolam (IR and XR) doses of 1, 2 and 3 mg or placebo	24	21-45 (31.4)	24/0 12/12/0	Rep: Item 6/Vol 42/Pg 1

Table 2. Table of All Phase 1 Studies in the Integrated Summary of Safety						
Study No. [ref] Investigator(s) Study Dates/SRes	Study Design	Regimen, Route and Dose*	Subjects			Report Location In NDA Item/Volume/Page
			Number Treated	Age (y) Range (Mean)	M/F W/B/O	
P/2002/0010 [16] 24 March 1991 Single Center, US	Randomized, open-label, crossover, single and multiple doses	Single oral doses of 1.5 mg IR tablets Multiple oral doses (QID x 7d) of 1.5 mg IR tablets Single oral doses of 3 mg XR tablets Multiple oral doses (BID x 7d) of 3 mg XR tablets	25	20-47 (31.7)	12/13 19/4/2	Rep: Item 6/Vol 20/Pg 1
P/2002/0013 [17] 1 April 1991 Single Center, US	Randomized, open-label, crossover, food effect bioavailability study	Three single doses; 1-week washout between doses Oral alprazolam (IR and XR) dose of 1 and 3 mg	21	19-47 (31.3)	17/4 18/1/2	Rep: Item 6/Vol 24/Pg 1
P/2002/0014 [18] 23 October 1991 16 November 1991 Single Center, US	Randomized, open-label, crossover, bioavailability study	Five single doses; 1-week washout between doses Oral alprazolam (XR) dose of 0.5 mg	25	19-49 (30.3)	25/0 19/3/3	Rep: Item 6/Vol 37/Pg 1
P/2002/0017 [19] 10 January 1992 16 March 1992 Single Center, US	Randomized, open-label, crossover, bioavailability/ food-affect study	Five single doses; 1-week washout between doses Oral alprazolam (XR) dose of 3 mg	31	19-50 (34.1)	21/10 29/1/1	Rep: Item 6/Vol 25/Pg 141
P/2002/0018 [20] 10 August 1992 20 August 1992 Single Center, US	Open-label, crossover study	Two single doses; 1-week washout between doses Oral alprazolam (XR) dose of 3 mg	24	18-52 (26.7)	24/0 24/0/0	Rep: Item 6/Vol 39/Pg 1

Table 2. Table of All Phase 1 Studies in the Integrated Summary of Safety						
Study No. [ref] Investigator(s) Study Dates/Sites	Study Design	Regimen, Route and Dose*	Subjects			Report Location In NDA Item/Volume/Page
			Number Treated	Age (y) Range (Mean)	M/F W/B/O	
[redacted] 1993 March-May Single Center, US	Double-blind, crossover study	Single and multiple doses Oral alprazolam (IR and XR) doses of 0.5 mg/day and 1 mg/day or placebo	18	22-54 (35.8)	18/0 12/6/0	Rep: Item 6/Vol 39/Pg 217
M/2002/0037 [22] [redacted] 1994 April to May Single Center, US	Randomized, double blind, crossover study	Multiple doses Oral alprazolam (IR and XR) doses of 0.5, 1.0, 1.5 and 2.5 mg	20	19-48 (26)	20/0 17/3/0	Rep: Item 6/Vol 6/Pg 32
M/2002/0044 [23] [redacted] 1995 February to May Single Center, US	Randomized, double blind, crossover study	Single dose Oral alprazolam (XR) dose of 1.5 mg with multiple doses of lorazepam or bromazepam	18	20-45 (29.1)	18/0 14/1/1	Rep: Item 6/Vol 6/Pg 1
[redacted] 1995-1998 Single Center US	Randomized, double blind, placebo controlled crossover	Single dose Oral alprazolam IR 2 mg tablet, alprazolam XR tablet 2 mg, diazepam 20 mg, clonazepam 1 mg, and placebo	30	21-30 (24.0)	18/12 26/1/3	Rep: Item 8/Vol 1/Pg 138

D. Tables of Phase 2/3 Studies of Alprazolam XR

Table 3. Table of All Phase 2/3 Studies in the Integrated Summary of Safety

Protocol No. Report No. Reference Location in NDA (Item/Vol/Pg)	No. of Centers No. of Countries (Country) Start Date Complete Date	Study Design	No. of Subjects/Patients (Randomized / Treated / Completed) Sex Age Race	Diagnosis + Criteria for Inclusion (Population)	Tested Agents (Active/Reference Therapy) Dosage Form / Lot No. Strength Route of Administration Treatment Regimen and Duration
Placebo-Controlled Panic Studies:					
M/2000/0369 9152-91-006 [25] (8/2/13)	3 Centers 1 Country (USA) June 1988 January 1990	Randomized, Double-Blind, Double-Dummy, Placebo Controlled	217 / 200 / 145 Alp XR, Placebo Sex: 59%, 62% female Age: 35, 35 yr Race: 95%, 97% white	Male and female outpatients, between 18 and 65 years old, with panic disorder with limited or extensive phobic avoidance	Alp XR 1.0 mg tablets (35,477) Placebo tablets (35,478) 1-10 mg/day or placebo po for 8 wk
M/2000/0271 9152-91-005 [26] (8/8/1)	3 Centers 2 Countries (USA, Canada) July 1988 March 1989	Randomized, Double-Blind, Double-Dummy, Placebo and Active Controlled	212 / 209 / 170 Alp XR, Alp IR, Placebo Sex: 38%, 42%, 45% female Age: 34, 36, 36 yr Race: 88%, 93%, 85% white	Male and female outpatients, between 18 and 65 years old, with panic disorder with limited or extensive phobic avoidance	Alp XR 1.0 mg tablets (85,317) Alp IR 1.0 mg tablets (24,021) Alp IR 0.5 mg tablets (23,649) Placebo tablets (24,026; 24,027; 21,472; 23,650) 1-10 mg/day or placebo po for 8 wk
M/2002/0002 9158-93-018 [27] (8/14/1)	15 Centers 1 Country (USA) June 1990 October 1991	Randomized, Double-Blind, Double-Dummy, Placebo Controlled	231 / 228 / 153 Alp XR 4 mg, Alp XR 6 mg, Placebo Sex: 52%, 56%, 46% female Age: 36 yr (all groups) Race: 67%, 65%, 68% white	Male and female outpatients, between 18 and 65 years old, with panic disorder with agoraphobia	Alp XR 0.5, 1.0, 2.0, or 3.0 mg tablets (35,674; 35,675, 35,676; 35,677) Placebo (35,678) 4 or 6 mg/day or placebo po for 8 wk
M/2002/0003 9158-95-014 [28] (8/19/1)	15 Centers 1 Country (USA) May 1990 October 1991	Randomized, Double-Blind, Double-Dummy, Placebo Controlled	261 / 258 / 178 Alp XR 4 mg, Alp XR 6 mg, Placebo Sex: 59%, 61%, 66% female Age: 35, 39, 38 yr Race: 93%, 91%, 88% white	Male and female outpatients, between 18 and 65 years old, with panic disorder with agoraphobia	Alp XR 0.5, 1.0, 2.0, or 3.0 mg tablets (35,674; 35,675, 35,676; 35,677) Placebo (35,678) 4 or 6 mg/day or placebo po for 8 wk
M/2002/0032 a0098110 [29] (8/24/1)	1 Center 1 Country (USA) 1994 1995	Randomized, Double-Blind, Double-Dummy, Placebo Controlled	50 / 47 / 38* Alp XR, Placebo Sex: 42% female Age: NA Race: 90% white	Male and female outpatients with panic disorder with or without agoraphobia	Alp XR 0.5 mg tablets (38,781) Placebo tablets (36,776) Alp XR up to 4 mg/day or placebo po for 8 wk

[redacted]

Table 3. Table of All Phase 2/3 Studies in the Integrated Summary of Safety (continued)

Protocol No. Report No. Reference Location in NDA (Item/Vol/Pg)	No. of Centers No. of Countries (Country) Start Date Complete Date	Study Design	No. of Subjects/Patients (Randomized / Treated / Completed) Sex Age Race	Diagnosis + Criteria for Inclusion (Population)	Tested Agents (Active/Reference Therapy) Dosage Form / Lot No. Strength Route of Administration Treatment Regimen and Duration
Active-Controlled Panic Studies					
M/2002/0015 1340-96-001 [30] (8/25/1)	22 Centers 8 Countries (Finland, France, Hungary, Israel, Italy, Portugal, Russia, Spain) April 1993 January 1995	Randomized, Single (Evaluator)-Blind, Active Controlled	283 / 257 / 196 Alp XR, Clomipramine Sex: 66%, 62% female Age: 35, 34 yr Race: 78%, 80% white	Male and female outpatients, between 18 and 65 years old, with panic disorder with or without agoraphobia	Alp XR 0.5 or 1.0 mg tablets Clomipramine 10 or 25 mg encapsulated tablets Packaging Lot Numbers/Country (91614, 91612, 91608, 91775, 91610, 91613, 91609, 91611, respectively) Alp XR 2-6 mg/day or Clomipramine 50-150 mg/day po for 12 wk
M/2000/0385 9159-91-007 [31] (8/24/1)	1 Center 1 Country (USA) June 1989 April 1990	Randomized, Double-Blind, Double-Dummy, Active Controlled	22 / 20 / 16 Alp XR, Alp IR Sex: 70% female Age: 41 yr Race: 95% white	Male and female outpatients, between 18 and 65 years old, with panic disorder with or without agoraphobia	Alp XR 1.0 or 2.0 mg tablets (35,675; 35,676) Alp IR 1.0 mg capsules (35,541) Alp XR or Alp IR 2 or 4 mg/day po for 2 wk (No discontinuation phase)
Uncontrolled Panic Study					
M/2002/0021 a0027679 [32] (8/43/5)	1 Center 1 Country (USA) April 1993 December 1993	Open-Label Switch Study	30 / 30 / 27 Sex: 70% female Age: 38 yr Race: NA	Male and female outpatients, between 18 and 65 years old, with panic disorder with or without agoraphobia	Alp XR tablets (26,689; 26,690) Alp IR tablets (26,687; 26,688) Alp IR 0.75-10 mg/day po for 3 wk followed by Alp XR 0.75-10 mg/day po for 6 wk

Abbreviations: Alp XR=Alprazolam Extended Release; Alp IR=Alprazolam Immediate Release; NA=not available; po=oral; wk=weeks; yr=years

Table 3. Table of All Phase 2/3 Studies in the Integrated Summary of Safety (continued)

Protocol No. Report No. Reference Location in NDA (Item/Vol/Pg)	No. of Centers No. of Countries (Country) Start Date Complete Date	Study Design	No. of Subjects/Patients (Randomized / Treated / Completed) Sex Age Race	Diagnosis + Criteria for Inclusion (Population)	Tested Agents (Active/Reference Therapy) Dosage Form / Lot No. Strength Route of Administration Treatment Regimen and Duration
Studies in Other Indications					
M/2002/0014 1340-94-003 [33] (8/43/261)	7 Centers 3 Countries (Israel, Portugal, Spain) July 1992 April 1994	Randomized, Double-Blind, Double-Dummy, Active-Controlled Study in Generalized Anxiety Disorder	123 / 121 / 115 Alp XR, Bromazepam Sex: 73%, 61% female Age: 38, 39 yr Race: 95%, 98% white	Male and female outpatients, between 18 and 65 years old, with generalized anxiety disorder	Alp XR 1.0 or 2.0 mg tablets Bromazepam 1.5 or 3.0 mg capsules Packaging Lot Numbers/Country (91445, 91446, 91406, respectively) Alp XR 2 mg/day or Bromazepam 9 mg/day po for 3 wk
M/2002/0039* a0065558 [34] (8/49/1)	1 Center 1 Country (USA) June 1994 March 1996	Randomized, Double-Blind, Double-Dummy, Active-Controlled Study in Generalized Anxiety Disorder	70 / 65 / 56 Alp XR, Lorazepam Sex: 53%, 61% female Age: 37, 40 yrs Race: 91%, 84% white	Male and female outpatients, between 18 and 70 years old, with generalized anxiety disorder	Alp XR 0.5 mg capsules (27,068; 27,419; 27,544) Lorazepam 1.0 mg capsules (27,068; 27,419; 27,544)] Alp XR 1-3 mg/day po or Lorazepam 2-6 mg/day po for 4 wk
M/2000/0365** 9173-94-091 [35] (8/43/177)	2 Centers 1 Country (Mexico) February 1989 December 1990	Randomized, Double-Blind, Double-Dummy, Active-Controlled Study in Generalized Anxiety Disorder	14 / 14 / 10 Alp XR, Bromazepam Sex: 50% female Age: 37 yrs Race: 27% white	Male and female outpatients, between 18 and 65 years old, with generalized anxiety disorder	Alp XR 1.0 mg tablets (91,053) Bromazepam 3.0 mg encapsulated tablets Alp XR 1-4 mg/day or Bromazepam 3-12 mg/day po for 8 wk
M/2002/0022 9158-94-009 [36] (8/50/1)	3 Centers 1 Country (USA) January 1993 July 1993	Open-Label Switch Study in Anxiety	54 / 54 / 53 Alp XR, Alp IR Sex: 52% female Age: 41 yr Race: NA	Male and female outpatients with common forms of anxiety excluding obsessive-compulsive disorder	Alp XR and Alp IR 0.5 and 1.0 mg tablets (26,666; 26,227; 26,668; 26,669) Alp IR 0.75-4 mg/day po for 2 wk followed by Alp XR 0.75-4 mg/day po for 2 wk

Table 3. Table of All Phase 2/3 Studies in the Integrated Summary of Safety (continued)

Protocol No. Report No. Reference Location in NDA (Item/Vol/Pg)	No. of Centers No. of Countries (Country) Start Date Complete Date	Study Design	No. of Subjects/Patients (Randomized / Treated / Completed) Sex Age Race	Diagnosis + Criteria for Inclusion (Population)	Tested Agents (Active/Reference Therapy) Dosage Form / Lot No. Strength Route of Administration Treatment Regimen and Duration
Studies in Other Indications					
M/20C2/0045 a0091929 [37] (8/50/172)	28 Centers 12 Countries (Belgium, Czech Republic, Denmark, Finland, France, Hungary, Israel, Italy, Poland, Portugal, Russia, South Africa) March 1995 May 1996	Randomized, Double-Blind, Double-Dummy, Active-Controlled Study in Mixed Anxiety Depressive Disorder	234 / 232 / 192 Alp XR, Fluoxetine Sex: 72%, 66% female Age: 41, 37 yr Race: 79%, 82% white	Male and female outpatients, between 18 and 65 years old, with mixed anxiety depressive disorder	Alp XR tablets 2 mg/day po for 5 wk (92595) then Alp XR tablets 1 mg/day po for 1 wk (92596) or Fluoxetine capsules 20 mg/day po for 6 wk (92599)

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/s/

Robert Levin
10/15/02 04:33:42 PM
MEDICAL OFFICER

Thomas Laughren
10/16/02 12:29:11 PM
MEDICAL OFFICER
I agree that this NDA is approvable; see memo to file for more detailed comments.--TPL