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**PROPRIETARY DRUG NAME/INN:** Xanax XR (alprazolam extended release tablets)

### **THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:**

See USPI

**PROTOCOL NO.:** PROTOCOL A6131004

**PROTOCOL TITLE:** AN OPEN-LABEL STUDY TO ASSESS THE SAFETY AND TOLERABILITY OF XANAX XR IN THE TREATMENT OF ADOLESCENTS WITH PANIC DISORDER OR ANXIETY WITH PANIC ATTACKS

**Study Center(s):** 28 centers in the United States

**Study Initiation and Completion Dates:** 05 May 2004 – 11 October 2004  
This study was terminated prematurely

**Phase of Development:** Phase 4

**Study Objective(s):** The primary objectives of this study were to assess the long-term (6-month) safety and tolerability of alprazolam extended release (XR) in adolescents with panic disorder, with or without agoraphobia, or in anxiety disorder with panic attacks. The secondary objectives were to assess the efficacy of alprazolam XR during long-term (6-month) treatment and assess the population pharmacokinetics (PK) of alprazolam XR, and the relationship between alprazolam XR plasma concentrations and efficacy outcomes.

### **METHODS**

**Study Design:** This was a 6-month, open-label, flexible-dose study of alprazolam XR (1-6 mg/day) for the treatment of DSM-IV-TR panic disorder (with or without agoraphobia), or anxiety disorder (generalized anxiety disorder, social anxiety disorder, posttraumatic stress disorder, separation anxiety, anxiety-NOS) with panic attacks, in adolescent outpatients aged 13 to 17 years. The 6 months of study treatment were preceded by a 7-day washout period with no drug or placebo, and were followed by a 1- to 6-week taper off study drug. This study was terminated early due to recruitment difficulties in this population. No additional subjects were enrolled after the time of study termination and no subjects completed the study.

Notification that the alprazolam XR pediatric program was cancelled before enrollment for this study could be completed was sent to the United States Food and Drug Administration on 1 September 2004.

## CLINICAL STUDY SYNOPSIS

**Number of Patients (planned and analyzed):** The planned number of enrolled subjects was 300. At the time of study termination, 46 subjects had been enrolled and 45 subjects had been treated with alprazolam XR.

**Diagnosis and Main Criteria for Inclusion:** Eligible subjects were male and female outpatients, aged 13 to 17 years at the time of the screening visit. Subjects were to have met 1 of the following DSM-IV-TR diagnoses: 1) A current diagnosis of panic disorder with or without agoraphobia, 2) generalized anxiety disorder with a history of at least 1 panic attack in the course of their illness, 3) social anxiety disorder (social phobia) with a history of at least 1 panic attack in the course of their illness, 4) separation anxiety with a history of at least 1 panic attack in the course of their illness, 5) posttraumatic stress disorder with a history of at least 1 panic attack in the course of their illness, 6) anxiety-NOS with a history of at least 1 panic attack in the course of their illness.

**Study Treatment:** Alprazolam XR was supplied as 1-mg tablets. Subjects were to take alprazolam XR 1 mg/day for 7 days. All upward dose titrations during the course of study treatment were made based on the clinical judgment of the investigators, and were not to exceed 1-mg increases every 7 days, up to a maximum of 6 mg/day. Dosage reductions were allowed, based on clinical judgment of the investigators. Subjects who were unable to tolerate a 1-mg daily dose of alprazolam XR were withdrawn from the study. Subjects who discontinued early or were withdrawn due to termination of the study were to be tapered off medication as described in protocol.

**Efficacy Evaluations:** No primary efficacy measures were defined for this study. Secondary efficacy measures included the Panic Disorder Severity Scale-Adolescent version (PDSS-A) total and item scores; CGI-Severity (CGI-S) scale; CGI-Improvement (CGI-I) scale; Pediatric Quality of Life, Enjoyment, Satisfaction Questionnaire (PQ-LES-Q); Hamilton Anxiety Rating Scale (HAM-A); and Childhood Depression Rating Scale, Revised (CDRS-R).

**Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations:** Blood samples for determinations of plasma alprazolam XR concentrations were obtained at Weeks 12 and 24 of study treatment.

**Safety Evaluations:** Safety: Safety was the primary objective of this study and was assessed through adverse events, laboratory assessments, vital signs, electrocardiograms (ECGs), and physical examinations. Other: Effects of study drug on cognitive and memory were evaluated by the Digit Symbol-Coding Test and immediate and delayed free recall of a word list. Adverse events due to study drug discontinuation during the taper period were evaluated using the Rickels Physician Withdrawal Checklist (PWC).

**Statistical Methods:** *Efficacy:* No statistical power calculation was made to determine the planned enrollment of 300 subjects for this study. Because the clinical pediatric program was cancelled and at the time of study termination 46 subjects had been assigned to treatment, no statistical analyses or summaries of efficacy data were produced.

*Safety:* Treatment-emergent adverse events (regardless of relationship to study medication and also treatment related) were summarized by body system, preferred term, and severity. Subjects

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who discontinued due to adverse events were listed. Serious adverse events were reported from the project database. The incidence of clinically significant laboratory abnormalities and the median changes in clinical laboratory test results from baseline to final visit were summarized. Median changes in vital signs and body weight from baseline to final visit were summarized. ECG findings were listed by subject. Changes from baseline to endpoint for the free verbal recall test, the Digit Symbol-Coding test, and the PWC were summarized.

### **RESULTS**

**Subject Disposition and Demography:** At total of 75 subjects were screened, 46 were assigned to treatment, and 45 were treated (1 subject was dispensed study medication but was subsequently lost to follow-up). All 45 treated subjects were evaluated for adverse events. Thirty-one subjects were evaluated for clinical laboratory data. No subjects completed the study; 30 of the 45 treated subjects discontinued due to termination of the study. Reasons for the remaining 15 discontinuations are shown in the table below.

#### **Discontinuations From the Study – Safety Population**

Discontinuations	Alprazolam XR (N=45)
<b>Related to Study Drug</b>	<b>8</b>
Adverse event	7
Lack of efficacy	1
<b>Not Related to Study Drug</b>	<b>7</b>
Adverse event	1
Other <sup>a</sup>	3
Subject defaulted <sup>b</sup>	3
<b>Other discontinuations<sup>c</sup></b>	<b>30</b>
<b>Total</b>	<b>45</b>

<sup>a</sup> Other=protocol violation.

<sup>b</sup> Subject withdrew consent.

<sup>c</sup> Thirty subjects discontinued due to 'Study terminated by sponsor'.

All subjects were less than 18 years of age (range, 13-17). There were more females than males (28 vs. 17) and most subjects were white. The most common primary diagnoses of were generalized anxiety disorder (n=14), panic disorder without agoraphobia (n=10), social phobia (n=10), and panic disorder with agoraphobia (n=7). Other primary diagnoses were anxiety (n=2), anxiety disorder (n=2), and post-traumatic stress disorder (n=1).

**Efficacy Results:** Not applicable. This study was terminated early due to recruitment difficulties in this population and there were not enough subjects to perform a meaningful efficacy analysis.

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**Pharmacokinetic, Pharmacodynamic, and/or Other Results:** No population PK or pharmacodynamic analyses were carried out due to the limited number of samples collected in this study.

**Safety Results:** No deaths occurred during this study. Two subjects had serious adverse events during treatment (therapeutic agent toxicity [investigator term: benzodiazepine intoxication], anxiety disorder, depression, and disinhibition; and overdose). One of these subjects had serious adverse events that were considered related to study medication (therapeutic agent toxicity, anxiety disorder, depression, and disinhibition); both subjects recovered. An additional subject experienced a serious adverse event post-therapy (factitious disorder) and recovered.

Eight subjects discontinued due to adverse events, 7 of whom had at least 1 adverse event that was considered related to treatment.

Of the 45 subjects in the safety population, 37 had adverse events regardless of causality and 28 had adverse events considered related to treatment. A summary of all treatment-emergent adverse events (all causalities) reported by more than 1 subject is shown below. Most adverse events were mild or moderate in severity.

### The Most Common<sup>a</sup> Treatment-Emergent Adverse Events (All Causalities)

System Organ Class / MedDRA Preferred Term	Alprazolam XR (N=45) n
<b>Gastrointestinal Disorders</b>	
Nausea	4
<b>General Disorders and Administration Site Conditions</b>	
Fatigue	5
Pyrexia	2
<b>Nervous System</b>	
Dizziness	4
Headache	8
Lethargy	3
Sedation	4
Sinus headache	2
Somnolence	11
Syncope	2
<b>Psychiatric</b>	
Anxiety	2
Depression	3
Insomnia	3
Irritability	2
<b>Respiratory, Thoracic and Mediastinal</b>	
Nasal Congestion	2
Pharyngolaryngeal Pain	3

<sup>a</sup> Occurring in more than 1 subject.

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Treatment-related adverse events occurring in more than 1 subject were somnolence (n=11), fatigue (n=5), sedation (n=4), lethargy (n=3), dizziness (n=3), and depression (n=2).

Clinically significant abnormal laboratory values were reported in 1 subject with elevated monocytes (>1.2 times the ULN), 2 subjects with ketones in the urine, 1 subject with protein in the urine, and 4 subjects with blood in the urine. There were no notable changes in median clinical laboratory test values from baseline to last observation. No subjects discontinued treatment due to an adverse event related to a laboratory abnormality.

There were no notable median changes from baseline to last observation in blood pressure, pulse, or body weight. There were no clinically significant abnormal ECG findings.

The mean change from baseline to endpoint in the number of words recalled from a hundred-word list was 2.58 words for the immediate recall test and 0.36 words for the delayed recall test. The mean change from baseline in the Digit Symbol-Coding test score was -6.16, indicating that fewer items were completed correctly at endpoint. The mean change from baseline in the PWC total score was -5.46, indicating that withdrawal symptoms did not increase at endpoint.

**CONCLUSION(S):** This 6-month open-label study of alprazolam XR in adolescent subjects with panic disorder was terminated early due to recruitment difficulties in this population, with 15% of the planned number of subjects enrolled and no subjects completing the study. Therefore, no efficacy conclusions can be drawn from these data. The adverse events observed in this limited sample of adolescent subjects were similar to those observed in adult trials of alprazolam XR in panic disorder.

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