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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 A6131002

PROTOCOL TITLE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF XANAX XR IN THE TREATMENT OF ADOLESCENTS WITH A PRIMARY DIAGNOSIS OF PANIC DISORDER

Study Center(s): 13 centers in the United States

Study Initiation and Completion Dates: 14 April 2004 – 23 September 2004
Study was terminated prematurely

Phase of Development: 4

Study Objective(s): The primary objective of this study was to assess the efficacy of alprazolam extended release (XR) in adolescents with a primary diagnosis of panic disorder with or without agoraphobia. Secondary objectives were to assess the safety and tolerability of alprazolam XR in adolescents with panic disorder and to assess the pharmacokinetic profile of alprazolam XR in adolescents with panic disorder.

METHODS

Study Design: This was a 6-week, multicenter, randomized, double-blind, placebo-controlled, flexible-dose study of alprazolam XR (1-6 mg/day) for the acute treatment of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) panic disorder, with or without agoraphobia, in adolescents (age range, 13-17 years) in an outpatient setting. The primary diagnosis of panic disorder was based on Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI Kid). The 6 weeks of acute treatment were preceded by a 3- to 14-day washout period with no study drug or placebo. Subjects who completed 6 weeks of treatment and who, in the opinion of the investigator, could have benefited from continued study treatment, were evaluated for entry into an 18-week continuation study (Protocol A6131007). Subjects who were not eligible for entry into the continuation study, or who were eligible but elected not to participate, were tapered off study drug at a rate of 1 mg every 7 days for up to a 6-week taper period. In the current study, eligible subjects were randomized in a 1:1 ratio to 1 of the 2 treatment groups: alprazolam XR or

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placebo. Due to recruitment difficulties in this adolescent population, the clinical program for alprazolam XR was cancelled and this study was terminated. All enrolled subjects at the time of study termination were given the option to complete the study (although some subjects were withdrawn), and no additional subjects were enrolled.

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.

Number of Patients (planned and analyzed): The planned number of evaluable subjects was 228 (114 subjects per treatment group). At the time of study termination, 16 subjects had been randomized and 15 subjects had been treated (8 with alprazolam XR and 7 with placebo).

Diagnosis and Main Criteria for Inclusion: Eligible subjects were male or female outpatients, aged 13-17 years (inclusive) at the time of the screening visit. Subjects were to have a primary DSM-IV-TR diagnosis of panic disorder with or without agoraphobia based on the MINI Kid. Subjects were to have an average of 1) at least one 4-symptom panic attack per week over the last 4 weeks before screening; 2) at least one 4-symptom panic attack per week over the last 4 weeks before baseline; and 3) at least one 4-symptom panic attack in the 7 days prior to baseline.

Study Treatment: Alprazolam XR and matching placebo were supplied as 1-mg tablets. A flexible dosing strategy was used with treatment started at a daily dose of 1 mg (or placebo equivalent) for the first 7 days. Thereafter the daily dosage was titrated at a maximum rate of 1 mg (or placebo equivalent) every 7 days up to a maximum dosage of 6 mg (or placebo equivalent) for lack of response, and in the absence of dose-limiting adverse events. No further increases in daily dose were permitted after Day 36; dosage reductions were permitted if required for tolerability. Subjects who completed 6 weeks of treatment and who, in the opinion of the investigator, could have benefited from continued study treatment, were evaluated for entry into an 18-week continuation study (Protocol A6131007). Subjects who were not eligible for entry into the continuation study, or who were eligible but elected not to participate, were tapered off study drug at a rate of 1 mg (or placebo equivalent) every 7 days for up to a 6-week taper period.

Efficacy Evaluations: *Primary efficacy measures:* Endpoint change in weekly frequency of 4-symptom panic attacks as recorded in a subject diary; endpoint change in Panic Disorder Severity Scale for Adolescents (PDSS-A) total score. *Secondary efficacy measures:* Weekly change in PDSS-A total score; Clinical Global Impression (CGI)-Severity scale; CGI-Improvement scale; PDSS-A item scores; Hamilton anxiety rating scale (HAM-A); Children's Depression Rating Scale (CDRS-R); Pediatric Quality of Life, Enjoyment, and Satisfaction Questionnaire (PQ-LES-Q).

Pharmacokinetic Evaluations: Population pharmacokinetic (PK) analyses were planned based on plasma alprazolam XR samples obtained at 3 time points during the 6 weeks of study treatment.

Safety Evaluations: Safety was assessed through adverse events, laboratory assessments, vital signs, electrocardiograms (ECGs), and physical examinations. Other: Cognitive and memory effects of study drug were evaluated by the Digit Symbol-Coding Test and immediate and

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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: The planned statistical power to detect a mean difference of 3 in the weekly number of panic attacks was based on a planned sample size of 114 subjects per group. Because this study was terminated prematurely, no formal statistical testing was conducted. Summaries of the primary efficacy variables and subject listings of all available efficacy data were provided. Alprazolam XR plasma concentrations were listed by subject. The planned population PK analyses could not be carried out due to the limited number of samples collected in this study. -The full safety analysis based on the original statistical analysis plan was performed. Adverse events (including abnormal physical examination findings) were coded using a Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment-emergent adverse events (regardless of relationship to study medication and also treatment related) were summarized by body system, preferred term, and severity. Subjects 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 by treatment group. Median changes in vital signs and body weight from baseline to final visit were summarized. ECG findings were listed by subject.

RESULTS

Subject Disposition and Demography: 15 subjects were treated with alprazolam XR (n=8) or placebo (n=7). All 15 were included in efficacy and safety summaries.

Subject Evaluation Groups

		Alprazolam XR	Placebo
		n	n
Screened	31		
Assigned to Treatment	16 ^a		
Treated		8	7
Completed		2	3
Discontinued		6	4
Due to termination of the study		2	2
Due to other reasons		4	2

^a One subject was assigned to alprazolam XR and withdrew consent before receiving study medication.

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Discontinuations From the Study

	Alprazolam XR (N=8)	Placebo (N=7)
Discontinuations	n	n
Related to Study Drug	3	1
Adverse event	2	1
Lack of efficacy	1	0
Not Related to Study Drug	1	1
Other	1	0
Subject defaulted	0	1
Other Discontinuations^a	2	2
Total	6	4

^a Two subjects in each of the alprazolam XR and placebo groups were discontinued due to 'study terminated by sponsor' on Days 22, 37, 47, and 49.

All subjects were under 18 years of age, with a mean of 16.5 years (range, 15-17 years) and 15.0 years (range, 13-17 years) in the alprazolam XR and placebo groups, respectively.

Efficacy Results: Because this study was terminated prematurely, no formal statistical testing was conducted; only primary efficacy endpoints were summarized. At baseline, the mean (SD) number of panic attacks since the previous visit was 6.00 (3.38) in the alprazolam XR group and 18.00 (10.89) in the placebo group. At endpoint, the mean (SD) number of panic attacks since the previous visit was 6.63 (8.21) (change of 0.63) in the alprazolam XR group and 11.57 (11.16) (change of -6.43) in the placebo group. At baseline, the mean (SD) PDSS-A total score was 14.00 (3.21) in the alprazolam XR group and 17.14 (3.13) in the placebo group. At endpoint, the mean (SD) PDSS-A total score was 9.38 (5.21) (change of -4.63) in the alprazolam XR group and 12.00 (7.55) (change of -5.14) in the placebo group.

Pharmacokinetic Results: The population PK analyses could not be carried out due to the limited number of samples collected in this study.

Safety Results: No serious adverse events or deaths occurred during this study. Most subjects had at least 1 treatment-emergent adverse event (regardless of causality; 7 of 8 in the alprazolam XR group and 5 of 7 in the placebo group). All but 1 subject (in the placebo group) who reported adverse events had at least 1 adverse event that was considered related to treatment. The most commonly reported adverse events were related to the nervous system or were psychiatric in nature. Adverse events reported by more than 1 subject in either treatment group were dizziness, headache, sedation, and somnolence. Most of these adverse events were judged by the investigators as mild or moderate in severity. In the alprazolam XR group, there was 1 severe case of dizziness and 1 severe case of sedation. In the placebo group, there was 1 severe case of headache.

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Treatment-Emergent Adverse Events Occurring in More than One Subject^a (All Causalities) - Safety Population

System Organ Class / MedDRA preferred term	Alprazolam XR (N=8) n	Placebo (N=7) n
Nervous System		
Dizziness	2	1
Headache	1	2
Sedation	2	0
Somnolence	3	1

^a In either treatment group

Two subjects in the alprazolam XR group (1 of these subjects also had a dosage reduction) and 1 subject in the placebo group discontinued treatment due to adverse events. One additional subject in the placebo group had a dosage reduction or temporary discontinuation of study medication due to adverse events.

A total of 6 and 4 subjects in the alprazolam XR and placebo groups, respectively, had post-baseline clinical laboratory data. One subject (in the alprazolam XR group) had a clinically significant post-baseline laboratory abnormality (blood in the urine during treatment). There were no notable changes in either treatment group in the median changes from baseline to the last measurement in clinical laboratory analyte values. No subjects discontinued treatment due to an adverse event related to a laboratory abnormality. There were no notable changes in blood pressure, pulse, or body weight from baseline to the final visit. There were no clinically significant abnormal ECG findings.

CONCLUSION(S): This 6-week double-blind, placebo-controlled study of alprazolam XR in adolescents with panic disorder was terminated early due to recruitment difficulties in this population, with less than 10% of the planned number of subjects enrolled. 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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