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PROPRIETARY DRUG NAME[®]/GENERIC DRUG NAME: Xanax[®]/Alprazolam

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI).

NATIONAL CLINICAL TRIAL NO.: NCT00810316

PROTOCOL NO.: A6131015

PROTOCOL TITLE: Evaluate the Pharmacokinetics of Two Alprazolam Formulations (Immediate Release and Extended Release Tablets) and a Clonazepam Tablet in a Healthy Mexican Population.

Study Center: The study was conducted at 1 center in Mexico.

Study Initiation Date and Primary Completion or Completion Dates: 24 October 2008 to 18 November 2008

Phase of Development: Phase 1

Study Objective: To estimate the pharmacokinetics (PK) of single doses of alprazolam XR (an extended release formulation of alprazolam), alprazolam (immediate release [IR] tablet) and clonazepam tablet in adult healthy Mexican volunteers.

METHODS

Study Design: This was a randomized, open-label, single-dose, parallel study in 2 cohorts of 12 healthy Mexican volunteers, each from both genders. Every volunteer was randomized to receive 1 of the following 3 feasible treatments:

- Alprazolam TAFIL[®] 1 mg IR tablets (Treatment A),
- Alprazolam TAFIL[®] AP extended release (XR) tablets (Treatment B), or
- Clonazepam RIVOTRIL[®] tablets equivalent to 1 mg (Treatment C).

Subjects were split into 2 cohorts. The study design for Cohort 1 (alprazolam, ie, Treatments A and B) is presented in Table S1.

Table S1. Study Design for Cohort 1 (Alprazolam)

Sequence	n	Period 1	Washout Period	Period 2
1	6	Reference Treatment (IR)	14 days	Test Treatment (XR)
2	6	Test Treatment (XR)		Reference Treatment (IR)

n = Number of subjects in the sequence; IR = Immediate release; XR = Extended release

Cohort 2 was comprised of 12 subjects who received a single dose of clonazepam (ie, Treatment C).

Number of Subjects (Planned and Analyzed): A sample size of 12 subjects for each of Cohorts 1 and 2 was planned. Twenty-four subjects (12 in each cohort) were randomized, treated, and completed the study. All 24 were included in the PK and safety analyses.

Diagnosis and Main Criteria for Inclusion: Overall, male and female subjects aged 18 to 40 with a Quetelet index mass from 19 to 30 kg/m² and in good health as determined by the outcomes of a complete medical history registered by the site investigator and laboratory tests performed in certified clinical laboratories, and with normal sitting systolic blood pressure (BP) (90 to 130 mmHg) and sitting diastolic BP (60 to 90 mmHg), heart rate (between 55 and 100 beats per minute) and respiratory rate (between 14 and 20 breaths per minute) were eligible for study entry.

Study Treatment: Subjects were randomized to a treatment sequence according to a computer-generated randomization schedule.

At approximately 08:00 AM of the first day, randomized subjects received the following treatments in a single oral daily dose:

- Cohort 1: Alprazolam IR (1 mg tablet) and Alprazolam XR (1 mg), or
- Cohort 2: Clonazepam (two 0.5 mg tablets for a total of 1 mg).

Each dose of study medication was administered with 240 mL of water. Subjects were required to fast for 8 hours before administration of study medication.

Subjects in Cohort 1 received single doses of alprazolam IR or XR after 14 days of a washout period in a crossover fashion.

Efficacy Evaluations: No efficacy evaluations were performed for this study.

Pharmacokinetic Evaluations: The PK sampling time was decided by taking into consideration the alprazolam and clonazepam elimination half-life, ie, following 4 half-lives plus the elimination of 90% of the administered dose. Sampling times were defined as follows:

- Cohort 1: 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 18, 24, 36, 48, and 60 hours after drug administration.

- Cohort 2: 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 24, 48, 72, and 96 hours after drug administration.

Safety Evaluations: Safety evaluations included the following:

- An electrocardiogram (ECG) was performed at screening.
- Vital signs measurements (including BP, heart rate, and respiratory rate) were performed on Days 1 to 7 and at end of study.
- Clinical laboratory tests (ie, hematology, chemistry, urinalysis, Hepatitis B and C markers, and Human Immunodeficiency Virus) performed at Day 1 and at the end of the study. A urine pregnancy test was performed on Day 0.
- A physical examination was performed at end of study.
- Adverse events (AEs) were monitored throughout the study.

Statistical Methods:

Pharmacokinetics: The PK concentration population was defined as all subjects randomized and treated who had at least 1 concentration in at least 1 treatment period. The PK parameter analysis population was defined as all subjects randomized and treated who had at least 1 of the PK parameters of primary interest in at least 1 treatment period.

PK parameters following single dose administration were derived from the concentration-time profiles presented in Table S2. Actual PK sampling times were used in the derivation of PK parameters.

Table S2. Pharmacokinetic Parameters

Parameter	Definition	Method of Determination
AUC _{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C _{last}).	Log-linear trapezoidal method
AUC _{inf}	Area under the plasma concentration-time profile from time zero extrapolated to infinite time.	AUC _{last} + (C _{last} */k _{el}), where C _{last} * was the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis and k _{el} was the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline were used in the regression.
C _{max}	Maximum plasma concentration	Observed directly from data
T _{max}	Time for C _{max}	Observed directly from data as time of first occurrence
t _½	Terminal elimination half-life	Log _e (2)/k _{el} .
MRT	Mean residence time	

For Cohort 1, natural log transformed area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUC_{inf}), area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (AUC_{last}), and

maximum plasma concentration (C_{max}) of alprazolam were analyzed using a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (CIs) were obtained from the model. The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. Alprazolam IR was the Reference treatment and alprazolam XR was the Test treatment.

Relative bioavailability was estimated as the ratio of adjusted geometric means for alprazolam XR and alprazolam IR for AUC_{inf} .

For all analytes, the PK parameters AUC_{inf} , C_{max} , AUC_{last} , time for C_{max} (T_{max}), terminal elimination half-life ($t_{1/2}$), and mean residence time (MRT) were summarized descriptively by treatment. For AUC_{inf} , AUC_{last} and C_{max} , individual subject parameters were plotted by treatment. Concentrations were listed and summarized descriptively using by PK sampling time and treatment. Individual subject and median profiles of the concentration-time data were plotted by treatment. For summary statistics and median plots by sampling time, the nominal PK sampling time was used, and for individual subject plots by time, the actual PK sampling time was used.

Safety: All subjects who received at least 1 dose of study medication were included in the safety analyses and listings.

AEs, ECGs, BP, heart rate, respiratory rate, and safety laboratory data were reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory test, ECG, BP, heart rate, and respiratory rate abnormality of potential clinical concern were to be described. Safety data were presented in tabular and/or graphical format and summarized descriptively, where appropriate. Any untoward findings identified on physical exams conducted after the administration of the first dose of study medication were to be captured as an AE, if those findings met the definition of an AE.

RESULTS:

Subject Disposition and Demography: At baseline, none of the subjects had presenting conditions or medical history that the investigators considered sufficient to affect the conduct of the study or to present a potential risk to the subject during study participation. All 24 subjects screened for entry into the study were randomized to open-label treatment, completed the study, and were included in the PK and safety analyses.

During the study, no prior or concomitant treatments were reported. Demographic summaries for Cohorts 1 (alprazolam) and 2 (clonazepam) are presented in Table S3 and Table S4, respectively.

Table S3. Demographic Characteristics of Subjects in Cohort 1 (Alprazolam)

Men (N=6)							
Age (years)		Weight (kg)		Height (cm)		Body Mass Index (kg/m ²)	
Mean	26.67	Mean	72.65	Mean	172.5	Mean	24.335
SD	7.25	SD	9.54	SD	4.80	SD	2.035
Range	18-35	Range	63-89	Range	169-182	Range	21.8-26.87
Women (N=6)							
Age (years)		Weight (kg)		Height (cm)		Body Mass Index (kg/m ²)	
Mean	25.167	Mean	59.15	Mean	159.5	Mean	23.354
SD	2.927	SD	3.139	SD	8.432	SD	2.08
Range	21-28	Range	54.3-62.4	Range	149-172	Range	20.45-26.12

N = Number of subjects; SD = Standard deviation

Table S4. Demographic Characteristics of Subjects in Cohort 2 (Clonazepam)

Men (N=6)							
Age (years)		Weight (kg)		Height (cm)		Body Mass Index (kg/m ²)	
Mean	26.167	Mean	72.75	Mean	170.167	Mean	25.075
SD	3.545	SD	6.766	SD	5.345	SD	1.212
Range	23-32	Range	62.0-81.0	Range	161-176	Range	23.92-27.38
Women (N=6)							
Age (years)		Weight (kg)		Height (cm)		Body Mass Index (kg/m ²)	
Mean	22.667	Mean	59.533	Mean	158.833	Mean	23.704
SD	3.445	SD	2.722	SD	7.468	SD	2.198
Range	18-27	Range	56.0-63.0	Range	150-171	Range	21.2-26.53

N = Number of subjects; SD = Standard deviation

Efficacy Results: No efficacy evaluations were performed in this study.

Pharmacokinetic Results: A summary of PK parameters for Cohort 1 (alprazolam) is presented in Table S5, a statistical analysis of PK parameters for Cohort 1 is presented in Table S6, and a summary of PK parameters for Cohort 2 (clonazepam) is presented in Table S7.

Table S5. Pharmacokinetic Parameters for Cohort 1 (Alprazolam) (N=12)

	C _{max} (ng/mL)		T _{max} (h)		AUC _{last} (ng.h/mL)		AUC _{inf} (ng.h/mL)		t _{1/2} (h)		MRT (h)	
	Treatment		Treatment		Treatment		Treatment		Treatment		Treatment	
	IR	XR	IR	XR	IR	XR	IR	XR	IR	XR	IR	XR
Mean	19.33	8.595	0.917	8.62	242.27	247.78	266.07	282.72	15.93	17.02	22.64	28.52
SD	5.873	2.125	0.733	4.24	58.919	60.382	72.394	87.702	3.876	6.839	5.258	7.585
CV%	30.4	24.7	80.0	49.3	24.3	24.4	27.2	31.0	24.3	40.2	23.2	26.6

N = number of subjects; C_{max} = Maximum plasma concentration; T_{max} = Time for C_{max}; AUC_{last} = Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}); AUC_{inf} = Area under the plasma concentration-time profile from time zero extrapolated to infinite time; t_{1/2} = Terminal elimination half-life; MRT = Mean residence time; IR = Immediate release; XR = Extended release; SD = Standard deviation; CV = Coefficient of variation

Table S6. Statistical Analysis – Pharmacokinetic Parameters for Cohort 1 (Alprazolam)

Parameter	IR	XR	Ratio*	90% CI
C_{max} (ng/mL)	19.33	8.59	44.44	38.56 – 52.84
AUC_{last} (ng.h/mL)	242.27	247.78	102.27	90.14 – 113.86
AUC_{inf} (ng.h//mL)	266.07	282.72	106.26	92.24 – 117.23
MRT (h)	22.75	27.99	123.00	113.90 – 134.72
t_{1/2} (h)	15.93	17.02	106.84	89.18 – 120.44

* Ratio of geometric means.

IR = Immediate release; XR = Extended release; CI = Confidence interval; C_{max} = Maximum plasma concentration; AUC_{last} = Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}); AUC_{inf} = Area under the plasma concentration-time profile from time zero extrapolated to infinite time; MRT = Mean residence time; t_{1/2} = Terminal elimination half-life

Table S7. Pharmacokinetic Parameters for Cohort 2 (Clonazepam) (N=12)

	C _{max} (ng/mL)	T _{max} (h)	AUC _{last} (ng.h/mL)	AUC _{inf} (ng.h/mL)	t _{1/2} (h)	MRT (h)
Mean	7.032	1.771	191.607	251.506	45.627	64.478
SD	1.542	0.962	48.686	74.365	8.010	10.658
SE	0.445	0.278	14.054	21.467	2.312	3.077
CV%	21.9	54.3	25.4	29.6	17.6	16.5

N = number of subjects; C_{max} = Maximum plasma concentration; T_{max} = Time for C_{max}; AUC_{last} = Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}); AUC_{inf} = Area under the plasma concentration-time profile from time zero extrapolated to infinite time; t_{1/2} = Terminal elimination half-life; MRT = Mean residence time; SD = Standard deviation; SE = Standard error; CV = coefficient of variation

Safety Results: There were no deaths, serious AEs, or discontinuations due to AEs reported in this study.

There were a total of 47 mild treatment-emergent AEs reported by 23 subjects (11 reported by 10 subjects receiving alprazolam IR, 14 reported by 10 subjects receiving alprazolam XR, and 22 reported by 12 subjects receiving clonazepam). Somnolence was reported in 10 subjects who received alprazolam IR, in 9 subjects who received alprazolam XR, and in 12 subjects who received clonazepam. Headache was reported in 5 subjects who received alprazolam XR and in 3 subjects who received clonazepam. Hiccup was reported in 1 subject who received alprazolam IR. Dizziness was reported in 6 subjects who received clonazepam. One subject who received clonazepam reported nausea.

There were no laboratory test abnormalities or clinically significant changes in vital signs.

CONCLUSION: The results obtained suggest that in the Mexican population, there are no differences in the quantity of drug absorbed and half-life between alprazolam IR and XR; only absorption was slower with the XR formulation, and the residency half-life was longer. The PK results obtained in this study are similar with those reported in other populations.