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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-434

**Clinical Pharmacology and Biopharmaceutics
Review**

A total of 23 studies (single dose, repeated dose studies) in healthy volunteers were submitted in Clinical Pharmacology and Biopharmaceutics section. Of these, nineteen were reviewed. In addition, the *in vitro* dissolution methods and specifications were evaluated.

Overall, from the Clinical Pharmacology and Biopharmaceutics perspective, the sponsor had submitted sufficient information to support the approval. The proposed *in vitro* dissolution method and the specifications are also found to be acceptable.

From the Clinical Pharmacology and Biopharmaceutics perspective, the pharmacokinetic parameters (the overall AUC, C_{max}, and C_{min}) following the twice daily (bid) dosing are bracketed by those from XR (qd) and IR (qid) regimens when same daily dose was administered. However, these data analyses have some limitations, i.e., the time-course of the effect was not taken into consideration. If the time-course after the dosing is considered, the steady-state alprazolam plasma concentrations following XR dosing are consistently the highest among three treatments (XR bid, XR qd, and IR qid) between the hours of 14 -24 over a 24-hour time span. However, the potential impact on the safety from these sustained higher alprazolam levels is unknown and needs to be further evaluated by the Clinical Division.

The OCPB also proposes revisions to the proposed labeling text.

1.1 Recommendation

Overall, the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the Clinical Pharmacology & Biopharmaceutics sections of NDA 21-434 acceptable. Issues regarding sponsor's proposed had been discussed with the Medical Officers (Drs. Thomas Laughren and Robert Levin).

The OCPB finds the proposed *in vitro* dissolution method and specifications acceptable.

The OCPB recommends revisions to the proposed labeling text, the revisions are described in section 5.1, (page 38) of the main review.

1.2 Labeling Comments to the Sponsor

1. The Office of Clinical Pharmacology and Biopharmaceutics recommends revisions to the proposed labeling text, the revisions are described in Section 5 LABELING (page 38) of the main review. Similar labeling language revisions, as appropriate, should be adopted for the Xanax IR tablets as well.
2. The sponsor should further explore the ethnic-effect on the pharmacokinetics and safety/efficacy from the available sources (such as literature & post-marketing experience from over the 50 countries outside of U.S. that XR formulation has been marketed) and incorporate relevant information into the label. Following are the bases: (a) Ethnic differences in the alprazolam PK parameters (C_{max}, AUC, Cl, t_{1/2}) had been reported in the literature (Lin KM et al, 1988); (b) Ethnic differences in CYP3A4 enzyme activity have been reported in the literature and CYP3A4 pathway is the major route of elimination for alprazolam.

2 Table of Contents

1	EXECUTIVE SUMMARY	1
1.1	RECOMMENDATION	2
1.2	LABELING COMMENTS TO THE SPONSOR	2
2	TABLE OF CONTENTS	3
3	SUMMARY OF CPB FINDINGS	5
3.1	BACKGROUND	5
3.2	CURRENT SUBMISSION	7
4	QUESTION BASED REVIEW	11
4.1	BACKGROUND	11
4.1.1	What are some of the historical aspects of this submission?	11
4.1.2	From the Agency's and sponsor's perspective, what are the changes the sponsor made since the sponsor submitted in current NDA since last agency's review of Xanax XR?	12
4.1.3	What is the focus of the current review?	13
4.1.4	Are the to-be-marketed XR formulations identical to the formulations submitted under	14
4.2	GENERAL ATTRIBUTES	14
4.2.1	What are the molecular formula and chemical properties of alprazolam?	14
4.2.2	What are the pharmacological properties of alprazolam?	14
4.3	CURRENTLY APPROVED FORMULATION AND INDICATION	14
4.3.1.1	Which Xanax formulation and indication are approved?	14
4.3.1.2	What oral dosing regimens of Xanax are recommended for the treatment of panic disorder?	15
4.3.2	Extended release tablet formulation	15
4.3.2.1	Why has the sponsor developed a new extended release tablet formulation for oral use?	15
4.3.2.2	How is the new extended release tablet formulated and manufactured?	15
4.3.2.3	Was the final-to be marketed alprazolam XR formulation used in all in vivo human studies? Did the sponsor submit sufficient information to support change, if any, made during the drug development? Would the changes affect the conclusions drawn from the bioavailability, bioequivalence and efficacy studies?	16
4.4	GENERAL CLINICAL PHARMACOLOGY	17
4.4.1	Which types of clinical studies were performed to assess the new alprazolam XR formulation?	17
4.4.2	Exposure – response relationships	18
4.4.2.1	How were the exposure-response relationships of efficacy and safety evaluated for XR or IR tablet, and was there a correlation? (Hossain's & Chou's review)	18
4.4.3	Tolerance	19
4.4.3.1	Has tolerance developed from alprazolam treatment? (Hossain's review: M/2000/0253, R/2002/003, P/2002/0010; R/2002/0002)	19
4.4.4	Pharmacodynamics (Safety/efficacy) of XR tablet	19
4.4.4.1	Does the slow release rate of XR tablet have an effect on the pharmacodynamics (Safety/efficacy) of the compound? (Hossain's review; Pharmacometrics review: Mishina)	19
4.4.5	General pharmacokinetics	20
4.4.5.1	What are the PK characteristics of alprazolam following the administration of XR tablet and how do they compare to the administration of IR tablet? (Source: Hossain's review)	20
4.4.6	Dose-proportionality	22

4.4.6.1	Has dose proportionality been established for the XR formulations of alprazolam within the therapeutic dose range (0.5-10mg) ? (Hossain's review: M/2000/0253; R/2002/003)	22
4.4.7	Strength equivalency	22
4.4.7.1	Has the strength equivalency been demonstrated for the 4 strengths of XR tablets (0.5, 1, 2 and 3 mg) proposed for marketing? (Hossain's review: M/2000/0352; R/2002/0001)	22
4.4.8	Sponsor proposed dosing regimen	22
4.4.8.1	What is the sponsor's proposed dosing regimen for the Xanax XR formulation?	22
4.4.8.2	Are plasma profiles of XR given bid completely bracketed by XR (qd) and IR (approved dosing regimen)? From the Clinical Pharmacology and Biopharmaceutics perspective, are the proposed dosing regimen adequate (once daily) [R/2002/0002& P/2002/0010 (Hossain's review); Pharmacometrics review (Mishina); Antal EJ et al & Greenblatt DJ et al (Chou's review)]	22
4.5	INTRINSIC FACTORS	26
4.5.1	Chronopharmacokinetics	26
4.5.1.1	Is PK of alprazolam influenced by circadian variation? If yes, is the effect similar between IR and XR formulations? (Protocol P/2002/007, Hossain's review)	26
4.5.2	Special populations (elderly, pediatrics, hepatic or renal impairment, obesity) (Hossain's review: M/2000/0253; R/2002/0002; P/2002/0010; P/2002/0013):	28
4.5.2.1	Do the PK and safety/efficacy of alprazolam XR in special populations (elderly, pediatrics, hepatic or renal impairment, obesity) differ from those of alprazolam IR?	28
4.5.3	Gender	28
4.5.3.1	Does gender affect the PK or safety/efficacy of alprazolam? (Hossain et al, Chou's review)	28
4.5.4	Pediatrics	29
4.5.4.1	Did the sponsor investigate the PK and safety/efficacy of Xanax in pediatrics?	29
4.5.5	Race (Chou's review & Lin KM et al (1988)	29
4.5.5.1	Did the sponsor investigate the potential race-effect on the PK and safety/efficacy?	29
4.6	EXTRINSIC FACTORS	30
4.6.1	Food-effect [M/2000/0275 (reviewed by Hossain), P/2002/0013 (reviewed by Hossain), M/2002/0017(reviewed by Chou)]	30
4.6.1.1	Does food affect the bioavailability of the Xanax XR?	30
4.6.1.2	Is sponsor's proposed Xanax XR dose administration relative to the food intake adequate? If not, what would be the Agency's recommendation on XR tablet dosing in relation to meals?	32
4.6.2	Cigarette smoking	32
4.6.2.1	Does cigarette smoking affect the disposition of alprazolam after Xanax XR? (Hossain et al 1997; Chou's review)	32
4.6.3	Drug-drug interactions (DDI) (Chou's review)	32
4.6.3.1	Is the proposed labeling text regarding drug-drug interaction current? How does it compare to Xanax IR label language? Is there any important information that is missing?	33
4.7	GENERAL BIOPHARMACEUTICS	33
4.7.1	In vitro release methods and specifications	33
4.7.1.1	Are the proposed drug release methods and dissolution specifications adequate to determine the in-vitro release and provide discriminatory ability to screen out sub-optimal batches?	33
4.7.2	In vitro and in vivo drug release comparisons	35
4.7.2.1	Has the sponsor evaluated the relation between in vitro release and the in vivo performance of Xanax XR? Was the IVIVC properly developed and does it demonstrate satisfactory predictability?	35
4.7.3	Manufacturing site changes (P/2002/0018)	35
4.7.3.1	Did the sponsor submit sufficient information to support manufacturing site change?	36
4.7.4	Debossing issues	37
4.7.4.1	Are the dissolution profiles similar between debossed and non-debossed tablets using the selected dissolution method for all strengths (0.5, 1, 2, and 3 mg) of Xanax XR?	37
4.8	ANALYTICAL SECTION	38
4.8.1	Which analytical methods were used in the plasma analyses? Are the methods acceptable? [Hossain's review; protocol P/2002/0017 (Chou's review)]	38

5	LABELING	38
5.1	WHAT CHANGES HAVE BEEN MADE TO THE APPROVED XANAX IR LABEL THAT ARE UNIQUE FOR THIS XR TABLET? ARE THESE CHANGES ACCEPTABLE?	38
6	SIGNATURES	43
7	APPENDIX	44
7.1	TABLE OF ALL PK AND BIOEQUIVALENCE STUDIES (DIRECT EXCERPTION FROM THE SUBMISSION)	44
7.2	REVIEW OF NEW INDIVIDUAL STUDY AND NEW INFORMATION SUBMITTED IN CURRENT NDA	49
7.2.1	P/2002/0017: The influence of meal timing on the PK and PD of Xanax XR tablets	49
7.2.1.1	Reviewer's comment on P/2002/0017	52
7.2.2	Literature-based Drug-drug interaction studies	55
7.2.3	In vitro release methods and specifications	57
7.2.3.1	Comments from current reviewer	58
7.2.4	Dissolution profiles to support the debossing issues	65
7.2.4.1	Reviewer's Comments for debossing issues	66
7.3	BIOANALYTICAL ASSAY	68
7.4	PHARMACOMETRICS REVIEW	70
7.5	THE SPONSOR PROPOSED LABEL (DIRECT EXCERPTION FROM THE SUBMISSION)	76
7.6	FILING MEMO	101

3 SUMMARY OF CPB FINDINGS

3.1 Background

Alprazolam (Xanax[®]) is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds. CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereo specific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Xanax was first approved by the Agency on October 16, 1981 [NDA 18,276: 0.25, 0.5, and 1mg Immediate-release (IR) tablets], and subsequently, on March 26, 1985 (2 mg IR tablets). Xanax IR tablet is indicated for two indications: (a) the treatment of anxiety disorders and transient symptoms of anxiety: daily dose of 0.25-4mg given in three divided doses, and (b) panic disorders: The efficacy of alprazolam (doses in the range of 1-10 mg) was established for panic disorders with an average daily dose of 5-6mg given in divided doses.

The initial step in alprazolam metabolism is hydroxylation catalyzed by CYP3A4. The predominant metabolites are α -hydroxyalprazolam, 4-hydroxyalprazolam, and a benzophenone derived from alprazolam. 4-hydroxyalprazolam and α -hydroxyalprazolam have relative receptor binding potency of 0.20 and 0.66 relative to alprazolam in the benzodiazepine receptor binding experiments and animal models of induced seizure inhibition. The benzophenone metabolite is essentially inactive. The t_{1/2} of these metabolites appear to be similar to that of alprazolam.

Pharmacokinetic characteristics of alprazolam after oral doses of Xanax IR tablet (source: web-based PDR 2002 for Xanax IR: _____ for Xanax XR, Hossain's review of Xanax and Chou's review of new literature information submitted in current NDA):

- Rapid and complete drug absorption (t_{max} 1-2 h after dose intake)
- Absolute bioavailability of alprazolam: 0.92 (0.58-1.60)
- Plasma protein binding: 80% at drug concentrations ranging from 30 to 1000ng/ml. Serum albumin accounts for the majority of the binding.
- Mainly metabolized via CYP3A4 (new literature-based information submitted under current NDA):
(a) in-vitro metabolism of alprazolam was screened using human liver microsomes: 4-hydroxyalprazolam and α -hydroxyalprazolam are the major metabolites. (b) B-lymphoblastoid cells expressing CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP2E1: no significant quantities of 4-hydroxyalprazolam and α -hydroxyalprazolam were produced. (c) In a study from human microsomes, the formation of 4-hydroxyalprazolam and α -hydroxyalprazolam correlated well with CYP3A4 content and activity.
- Major active metabolites: Alprazolam is extensively metabolized in humans, monkey, mouse and rat. There were some species specific metabolites found in animals. Twenty-nine metabolites were found in humans. The in-vivo and in-vitro data indicated that 4-hydroxyalprazolam and α -hydroxyalprazolam are the major metabolites in human plasma. The in-vivo and in-vitro data indicated that 4-hydroxyalprazolam is primarily metabolized by CYP3A4 (CYP2C9 & CYP2C19 minor) and α -hydroxyalprazolam is primarily metabolized by CYP3A4. The plasma concentrations of 4-hydroxyalprazolam and α -hydroxyalprazolam are always less than 10% and 4%, respectively, of the unchanged alprazolam. The mean molar ratio of the plasma alprazolam to 4-hydroxyalprazolam and α -hydroxyalprazolam after multiple doses (1.5mg qid of alprazolam IR for 6 days) is 39.4-46.5 and 45.8-54.8, respectively (R/2002/0002; P/2002/0010).
- In-vitro screening of alprazolam inhibitory/induction effect on P450s: Not determined.
- Total radioactivity (2 weeks following a single dose of 2mg): excretion occurred predominantly in urine (79%) and 7% was excreted in the feces
- Terminal $t_{1/2}$: 11 hours
- Linear PK over the dose range of 0.25 mg – 3.0 mg
- Food-effect: no information (this reviewer also performed a Medline search).
- Disease states: Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function and impaired renal function. Changes have also been demonstrated in geriatric patients. A mean half-life of alprazolam of 16.3 hours has been observed in healthy elderly subjects (range: 9.0-26.9 hours, n=16) compared to 11.0 hours (range: 6.3-15.8 hours, n=16) in healthy adult subjects. In patients with alcoholic liver disease the half-life of alprazolam ranged between 5.8 and 65.3 hours (mean: 19.7 hours, n=17) as compared to between 6.3 and 26.9 hours (mean=11.4 hours, n=17) in healthy subjects. In an obese group of subjects the half-life of alprazolam ranged between 9.9 and 40.4 hours (mean=21.8 hours, n=12) as compared to between 6.3 and 15.8 hours (mean=10.6 hours, n=12) in healthy subjects.
- Clinically significant or possible clinically significant drug-drug interactions:
 - The benzodiazepines, including alprazolam, produce additive CNS depressant effects when co-administered with other psychotropic medications, anticonvulsants, antihistamines, 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.

- Caution is recommended during coadministration of alprazolam with drugs demonstrated to be CYP3A4 inhibitors
- Fluoxetine--Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased half-life by 17%, and decreased measured psychomotor performance.
- Propoxyphene--Coadministration of propoxyphene decreased the maximum plasma concentration of alprazolam by 6%, decreased clearance by 38%, and increased half-life by 58%.
- Oral Contraceptives--Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.
- Drugs and other substances demonstrated to be CYP 3A inhibitors on the basis of clinical studies involving other benzodiazepines metabolized similarly to alprazolam or on the basis of in vitro studies with alprazolam or other benzodiazepines (caution is recommended during coadministration):
 - Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: 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.
 - Data from in vitro studies of benzodiazepines other than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during the coadministration of any of these with alprazolam.

3.2 Current Submission

The sponsor has developed an extended release tablet (XR) intended for the treatment of panic disorder with or without agoraphobia in adult patients (>18 years of age). The sponsor is seeking approval of XR product based on the BA/BE studies, one positive clinical trial of XR product, and PK/PD relationship established with IR product. The sponsor proposed once-(qd) or _____) regimens for the XR tablet for the treatment of panic disorder. At the pre-NDA meeting, the Clinical Division informed the sponsor, _____ dosing regimen for XR will be acceptable if plasma profiles of XR _____ are completely bracketed by XR (qd) and IR (approved dosing regimen) since the pivotal efficacy trial for Alprazolam XR tablet was carried out with a once daily regimen. The sponsor also requests a deferral of pediatric studies in adolescent panic disorder patients.

According to the sponsor, the biopharmaceutic/pharmacokinetic/pharmacodynamic development program for alprazolam XR tablets was designed to accomplish the following objectives: (1) establish the comparable extent of alprazolam absorption between the XR tablets and the IR tablets 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 from alprazolam XR tablets had an effect on the pharmacodynamics of the compound.

While 23 studies were conducted in this Clinical Pharmacology and Biopharmaceutics program, full analyses of 21 studies are submitted. The analysis of pharmacokinetic/pharmacodynamic data from two studies (M/2002/0044 & M/2002/0037) were not included in this application. Only safety data from these 2 studies were summarized since the sponsor felt that due to the design of this study (sequential shift from immediate release to XR tablets) and its relatively short duration (4 days on each formulation), little additional knowledge would be derived from analyses of these data.

A total of 8 phase II/III clinical studies were conducted with alprazolam XR formulations in patients with panic disorders. The sponsor has indicated that study M/2000/0369 is the pivotal efficacy trial. Plasma samples for drug analysis were collected in clinical trials M/2002/0369(#4452) & M/200/0271(#4438). The sponsor indicated that blood samples from studies 4438 and 4452 were collected to assess compliance, and sufficient dosing and sample collection time information was available to support population pharmacokinetic analyses. However, these analyses were not performed for the following reasons: (1) analytical data for alprazolam at the assay labs used for these analyses were not of the quality contained in the balance of the application, (2) the population pharmacokinetics of alprazolam have previously been published, (3) the population pharmacodynamics of alprazolam have been described, and (4) population analysis of pharmacokinetic data from Phase I studies with alprazolam XR tablets have been described (Hossain et al). Consequently, the evaluation of exposure-response with clinical endpoints for XR tablet was not feasible.

The sponsor requested a deferral of pediatric studies. At the pre-NDA meeting for Xanax XR under IND23:179 dated July 19, 2001,

Eighteen of the 23 studies submitted to the Clinical Pharmacology and Biopharmaceutics were previously submitted in 1991 and reviewed by Dr. Mohammad Hossain. A briefing was held on July 2, 1993. Comments from OCPB were sent to the sponsor before the sponsor

Summarized below are the studies reviewed by Hossain:

- Pharmacokinetics after single doses & repeated doses of alprazolam XR
- Relative bioavailability (0.5, 1, 2, 3mg)
- Dose proportionality (1-10mg)
- Dose strength equivalency (0.5, 1, 2, 3mg)
- Food study
- Manufacturing site change: BE study of highest strength
- in vitro dissolution methods and specifications
- Bioanalytical assay validation

Following are the 5 new studies with XR product submitted in current submission: PK of XR product relative to meal timing (P/2002/0017), abuse liability (P/2002/0008), PK/PD in healthy volunteers [(M/2002/0020 (proof of concept), M/2002/037, M/2002/0044)]. PK data from the latter two studies were neither provided nor analyzed by the sponsor.

Based on the new data submitted and the clinical relevance of the PD measures, following studies/topics were reviewed by current reviewer:

- PK of XR tablet relative to meal timing
- Literature-based drug-drug interaction information
- Literature-based population PK in healthy volunteers.

- PK data to support the proposed dosing: pivotal efficacy trial was carried out with once daily dosing.
- *in vitro* dissolution methods and specifications were reviewed since the sponsor provided some justification for choosing the proposed dissolution specifications and method over the one that was agreed upon between the Agency and the sponsor in this regard.
- Dissolution profile comparisons for three lower strengths between batches manufactured at old and new sites: All the batches used in clinical and biopharmaceutical studies were manufactured at the old site without debossing. Batches from the new site were one-sided debossed. BE was demonstrated in the highest strength (3mg) made from both sites.
- Dissolution profile comparisons regarding debossing issues for the final-to-be marketed formulation: neither clinical nor biopharmaceutical studies were conducted using to-be-marketed 2-sided debossed tablet.

In summary, following information were not reviewed:

- Proposed pediatric development plan: These protocols will be reviewed when the Clinical Division makes a decision whether or not to grant the deferral of pediatrics studies
- IVIVC: The sponsor had indicated during the teleconference (03/22/2002) that since the IVIVC development was not successful, they are not using IVIVC to help set dissolution specifications and has . Therefore, requested individual data were not provided by the sponsor.
- Abuse liability (P/2002/0008), PK/PD in healthy volunteers [(M/2002/0020 (proof of concept), M/2002/037, M/2002/0044)]. Data from the latter two studies were neither provided nor analyzed by the sponsor. PK/PD proof of concept study was not reviewed since it can not be interpreted meaningfully for the following reasons: (1) Studies did not include control group. (2) Only healthy volunteers were enrolled in the studies to evaluate the relationship between alprazolam plasma concentrations and side effects (psychomotor performance and sedation). (3) Psychomotor performance was evaluated with the digital symbol substitution test (DSST) and card sorting tasks after single and multiple doses. The psychomotor performance was neither measured in clinical studies nor correlated with the clinical efficacy or safety measures.

Overall, following conclusions regarding the BA/BE, exposure-response relationships, pharmacokinetics, and biopharmaceutics have been made regarding the alprazolam XR formulation:

- The sponsor did not properly investigate the PK/PD relationship in the target patient population using clinically relevant endpoint(s) for XR tablet. Overall, neither alprazolam plasma concentration after administering IR tablet was related to control of panic attacks nor the alprazolam dose can be used to predict the treatment for an individual patient.
- Tolerance (both acute and chronic) to the sedative effects has been observed from alprazolam treatment. This phenomena is independent of route of administration or formulation (iv, IR, XR) or dose (IR 1.5 mg ; XR, 1, 3, 4, 6, 8 or 10mg).
- The conclusion of the same efficacy and safety of both formulations (IR and XR) may be controversial even though the PK profiles as well as the calculated PD effects for alprazolam obtained after the administration of IR (1.5mg qid) and XR (3mg bid, 6mg qd) formulation are similar. The results from the data analysis of undesired effect such as adverse events were inconsistent when comparing across the IR (qid) and XR(qd) tablet treatment groups in clinical trials.
- The PK of alprazolam and two of its minor active metabolites (4-hydroxyalprazolam and α -hydroxyalprazolam) are linear and concentrations are proportional to dose up to the maximum recommended dose of 10mg a day. In addition, XR tablet follows linear kinetics with multiple doses up to 6mg a day.

- Studies comparing single dose and steady-state kinetics of alprazolam after administration of both IR and XR tablets indicated that there is a reduction in absorption rate (lower C_{max} and longer t_{max}) which is to be expected from the extended release formulation. Other PK parameters remained comparable: extent of absorption (AUC), distribution (V_d/F), metabolism (AUC ratio of parent:metabolite), or elimination (t_{1/2} & Cl/F) of alprazolam.
- The strength equivalency between the 0.5mg XR tablet given as a 1mg dose and the 1.0mg XR tablet has been demonstrated. The strength equivalency between the 1.0, 2.0, and 3.0mg XR tablet given as a single oral dose of 6mg of alprazolam has been demonstrated.
- From the Clinical Pharmacology and Biopharmaceutics perspective, the pharmacokinetic parameters (the overall AUC, C_{max}, and C_{min}) following the twice daily (bid) dosing are bracketed by those from XR (qd) and IR (qid) regimens when same daily dose is administered. However, these data analyses have some limitations, i.e., the time-course of the effect was not taken into consideration. Specifically, from the steady-state alprazolam plasma concentration profiles, plasma concentrations followed XR (bid) dosing are consistently the highest among three treatments (XR bid, XR qd, and IR qid) between the hours of 14 -24 over a 24-hour time span if the time-course after the dosing is considered. However, the potential impact on the safety from these sustained higher alprazolam levels is unknown and needs to be further evaluated by the Clinical Division.
- The PK of alprazolam were influenced by the circadian variation, but the result of this influence was a function of the oral formulation. The IR formulation exhibit a delayed and reduced mean peak concentration after nighttime administration while the XR formulation exhibit an earlier and higher mean peak concentration.
- From Clinical Data Summary section: The sponsor did not formally explore the gender-effect on the safety/efficacy measures for XR tablet and there is no information in this regard in the IR tablet (label). However, the by-sex analysis of 4 clinical trials showed that both males and females treated with Xanax XR tablet had significant greater improvement in their overall clinical condition than males and females treated with placebo. Gender has minimal effect on either the treatment-emergent or discontinuation emergent adverse event.
- Gender has no effect on the PK of alprazolam (IR and XR).
- No PK or safety/efficacy study was performed in special populations with XR tablet. However, this reviewer agrees with Hossain's conclusion that the factors (such as age, hepatic or renal impairment, drug-drug interaction) that may affect the PK of alprazolam after the administration of IR tablets would not be expected to change with the administration of XR tablets since the metabolism of alprazolam is not affected by the absorption rate (IR versus XR) and alprazolam is extensively metabolized with minimal unchanged drug found in the urine.
- No drug-drug interaction study was performed with the XR tablet to evaluate the PK or safety/efficacy. New literature-based drug-drug interaction information between alprazolam IR and CYP3A4 inhibitors (ketoconazole, itraconazole, and erythromycin), and CYP3A4 inducer (carbamazepine) were submitted and incorporated in the label.
- No meaningful comparison of PK or safety/efficacy response by race can be made since the majority of patients that participated in the 4 placebo-controlled efficacy trials including pivotal study (#369) were white (≥85%). Similarly, the majority of subjects that participated in BA/BE studies were White.
- Results from food-effect studies indicated that food taken immediately before the dosing of 3mg XR tablet significantly affects the bioavailability of alprazolam by increasing C_{max} (an average of 21-26% with 90% CI of 116-135 which fell outside of goal post) and shortening t_{max} (an average of a 21-34% earlier t_{max}). The food effect is prolonged even when the food was taken 2 hours before the dosing. In addition, in some individuals, the magnitude of % change in C_{max} may be quite significant (range: -34~+84%). The food-effect may be dose-dependent. These results indicate that separating XR tablet dosing from food intake maybe warranted. Ideally, XR tablet should be taken with an empty stomach or preferably at least 1 hour before or 2 hours after a meal. However, the

pivotal efficacy trial was conducted with 1-10mg once daily administered at nighttime with no regard of food intake.

- From a population PK analysis in literature, cigarette smoking showed a potential effect on alprazolam pharmacokinetics. Cigarette smoking was associated with a 100% increase in clearance of alprazolam as compared to non-smokers.
- The information submitted to date are sufficient to support the level 3 manufacturing site change for all 4 strengths XR tablets (0.5, 1, 2, and 3 mg).
- Formulations are unchanged from those submitted in 1991 in the original. All the to-be-marketed Xanax XR tablet formulations (0.5, 1, 2 and 3 mg) are compositionally (both qualitatively and quantitatively) similar with only minor changes (in some case absence of color).
- Same final to-be-marketed Xanax XR formulations were used in all in vivo human studies (including PK, BE and efficacy) except changes including in color, a level 3 manufacturing site change, 2-sided debossing. These changes have been shown to have no effect on the conclusions drawn from the bioavailability, bioequivalence and efficacy studies.
- Overall, the bioanalytical method validation was found to be acceptable in terms of reproducibility, specificity, sensitivity, linearity, precision and accuracy.
- Previously, DSI inspection was requested for 3 studies [BE of XR 3mg bid and IR (P/2002/0010); food study (P/2002/0013), BE of 1, 2, and 3mg XR(M/2000/0352)]. The results were found satisfactory.

This reviewer agrees with sponsor's proposed individual specification for 4 different strengths and pH 6.0 phosphate buffer as medium. Ideally, one common specification should be used for all 4 different strengths. However, in this specific case, where a strength-dependent drug release phenomenon exists, dissolution specs has to be widened to accommodate all 4 strengths. To justify this widening, an established in-vitro and in-vivo correlation (IVIVC) is required*. Since IVIVC was unsuccessful for XR tablet (4.7.2.1, page 33), the dissolution specifications will be used as QC measures and different specifications for each strength are considered to be acceptable.

The OCPB recommends revisions to the proposed labeling.

Overall, OCPB finds the Clinical Pharmacology & Biopharmaceutics sections of NDA 21-434 acceptable.

4 QUESTION BASED REVIEW

4.1 Background

4.1.1 What are some of the historical aspects of this submission?

Xanax (alprazolam) is marketed as an immediate release (IR) oral dosage form indicated for the treatment of anxiety and panic disorders with or without agoraphobia. In 1991, the sponsor (Upjohn Co) submitted an application for Xanax XR (extended-release) tablets for [redacted] based on bio-studies and one positive clinical study. At that time, sponsors were required to have two controlled clinical trials that evaluated the efficacy of a new formulation of the marketed drug substance. The sponsor, [redacted]. However, the recent FDA Guidance document published in 1998 entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" indicates that the effectiveness of a new dosage form may be extrapolated from efficacy data from another dosage form when well-defined pharmacokinetic/pharmacodynamic relationships exist. In addition, if the relationship between blood concentration and response is not well understood, a single additional efficacy study can be sufficient to provide evidence of effectiveness.

Dr. Mohammad Hossain reviewed this NDA and recommended that the NDA is approvable from OCPB's perspective (11/29/1993, 8/5/1993). Briefly, CPB comments regarding following issues were sent to the sponsor: modify dissolution method and specifications, update labeling regarding DDIs by performing literature search, in-vitro metabolism study, explore PK/PD relationship in target population and include covariates analysis, single versus bid dosing in assessing PK/PD relationship. Furthermore, an agreement was reached for setting a common dissolution specification using water as medium for all strengths of Xanax XR. DSI inspection was satisfactory for 3 studies [BE of XR 3mg bid and IR(P/2002/0010); food study (P/2002/0013), BE of 1, 2, and 3mg XR(M/2000/0352)].

In a pre-NDA meeting (6/15/2001) for Xanax XR under IND#23,179, the sponsor was requested to submit one positive efficacy clinical trial along with PK characterization of Xanax XR, and its safety data, as a basis for approval. In addition, CPB comments from Dr. Gerald Fetterly regarding following issues were conveyed to the sponsor: full data analysis of PK/PD studies; relative alprazolam concentrations from bid of XR relative to those from qd of XR and qid of IR products; update labeling from literature regarding ADME, DDIs, in-vitro metabolism, electronic submission, development of IVIVC.

The sponsor is resubmitting Xanax XR under current NDA with one pivotal clinical trial based on the effectiveness guidance of 1998. A total of 23 studies are submitted. Eighteen of them were previously reviewed by Dr. Hossain. The sponsor is seeking approval of XR product based on the BA/BE studies, one positive clinical trial of XR product, and PK/PD relationship established with IR product (report #4432, under NDA18,276/S017 dated 8/5/1987, which was previously reviewed by clinical and statistical division).

Following are the 5 new studies with XR product: PK of XR product relative to meal timing, (N=1), abuse liability (N=1), PK/PD in healthy volunteers [N=3: proof of concept (N=1), data from other 2 studies were neither provided nor analyzed by the sponsor]. Note: blood levels were measured in 2 efficacy trials (M/2002/0369 & M/200/0271). However, the sponsor did not provide PK data or PK & PK/PD analysis for the following reasons: (1) the concerns in quality of lab measures, (2) Pop PD of IR had been evaluated, (3) Pop PK of XR had been described (literature).

4.1.2 From the Agency's and sponsor's perspective, what are the changes the sponsor made since the sponsor submitted in current NDA since last agency's review of Xanax XR (dated 08/05/1993, 03/06/1995)?

Following are the changes and new information the sponsor submitted under current NDA:

- **Indication:** The sponsor initially proposed _____ Current submission is intended only for panic disorder.
- **Drug substance:** Xanax XR tablets will be manufactured using _____; alprazolam USP. This differs from the original NDA, which indicated that drug substance from _____ could be used.
- **Dissolution method and specification:** The sponsor submitted (under the CMC section) the requested justification and the full report of choosing the proposed dissolution specifications and method over the one that was agreed upon between the Agency and the sponsor in this regard under _____
- **Food-effect:** The sponsor submitted an additional study (P/2002/0017) regarding the PK characteristics of the Xanax XR relative to meal timing.
- **In Vitro-In vivo correlation (IVIVC):** The sponsor submitted IVIVC section without submitting full report. During the 45-day filing meeting, the sponsor was requested to submit full report on the IVIVC development with at least two release rates and demonstration of IVIVC predictability.

However, the sponsor had indicated during the teleconference (03/22/2002) that they are not using

- Literature-based information on population PK of XR formulation, metabolism and drug-interactions of alprazolam.
- Justification of proposed dosing regimen: Once daily dosing.
- **Planned Debossing of the final to-be-marketed formulation:** The sponsor indicated in NDA 21-434 Item 4. Chemistry, Vol.1/Pg.1 that it is proposed that XANAX XR Tablets will be debossed with a stylized "X" on one side and tablet strength on the other. This represents a change from the debossing associated with stability lots. Most of the stability lots reported in NDA 21-434 were compressed with no debossing and all of the confirmatory stability lots will be compressed with no debossing. It should be noted that neither clinical nor biopharmaceutical studies were conducted using to-be-marketed debossed tablet.
 - **Sponsor:** The sponsor requested a teleconference (dated 05/10/2002) to seek FDA agreement on the amount and type of stability data that is proposed for this pending NDA in order to obtain a expiration date for this product. In addition, they were seeking FDA agreement on the acceptability of adding a debossed marking on the tablet. A meeting package was submitted on April 26, 2002, with details about their proposals and the teleconference focused on the questions posed in this briefing package.
 - **Following comment was conveyed to the sponsor during teleconference:**
The sponsor is requested to submit dissolution profile comparisons between debossed and non-debossed tablets using the selected dissolution method for all strengths (0.5, 1, 2, and 3 mg) of Xanax XR. The sponsor was informed that while dissolution was comparable for tablets with different shapes, the experiments conducted do not evaluate the effect of changes in compression force. Since the Belgian tablets are not debossed in the same manner as the proposed U.S. tablets and since we have no information on the effect of different compression forces on release rate, it is prudent to compare dissolution profiles of debossed and non-debossed tablets.
 - **Note:** The sponsor indicated in the teleconference that they anticipate the debossed tablets will be manufactured and they agreed to submit the requested information as soon as they become available. The requested data were submitted on September 13, 2002.

4.1.3 What is the focus of the current review?

Current review will only focus on the following new information submitted and CPB issues after Agency's last review in 1995:

- (a) New information submitted since last agency's review of Xanax XR. This includes study (protocol P/2002/0017: PK and PD of alprazolam relative to meal timing); dissolution profiles from the newly proposed debossed tablet for all strengths; literature-based metabolism and drug-drug interaction to support the labeling language, and PK data to support the proposed once daily or dosage.
- (b) Are the sponsor proposed dissolution method and specification adequate?
- (c) How does the sponsor respond to the dissolution specification comments from the agency prior to the
- (d) Has the sponsor submitted sufficient information to support the level 3 manufacturing site change?

Only these new information will be thoroughly reviewed by this reviewer. Please refer to Dr. Hossain's previous review for details of remaining individual studies. The source of the review will be clearly indicated throughout this review.

4.1.4 Are the to-be-marketed XR formulations identical to the formulations submitted under

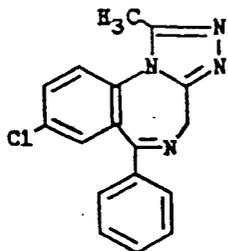
Formulations are unchanged from those submitted: _____ in the original _____

4.2 General Attributes

4.2.1 What are the molecular formula and chemical properties of alprazolam?

Alprazolam (8-chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4] benzodiazepine) is a triazolobenzodiazepine related to the benzodiazepine class of drugs. It is distinct from the other drugs in this class because of a triazole ring fused to the diazepine ring of the benzodiazepine ring system. Alprazolam (molecular formula $C_{17}H_{13}ClN_4$, molecular weight 308.77) occurs as a white to off-white crystalline powder. It is soluble in methanol or ethanol but has no appreciable solubility in water at physiological pH. It has a melting point of about 228-231°C. The octanol:buffer partition ratio for alprazolam is 18, indicating that it is highly lipophilic.

Chemical Structure:



4.2.2 What are the pharmacological properties of alprazolam?

Pharmacologically, the anxiolytic effect of alprazolam is similar to other CNS agents of the 1,4-benzodiazepine class and they presumably exert their effects by binding at stereo specific receptors at several sites within the central nervous system. However, the antidepressive and antipanic mechanisms are less clear. Alprazolam has a higher binding affinity for the benzodiazepine receptors (K_i , affinity constant of alprazolam is 3.4 nM).

4.3 Currently approved formulation and indication

4.3.1.1 Which Xanax formulation and indication are approved?

Xanax is currently marketed as immediate release (IR) tablets (0.25, 0.5, 1, and 2mg) for oral use. Xanax is indicated for (1) the management of anxiety disorder (a condition corresponding most closely to the APA Diagnostic and Statistical Manual [DSM-III-R] diagnosis of generalized anxiety disorder) or the short-term relief of symptoms of anxiety, and (2) the treatment of panic disorder, with or without agoraphobia.

4.3.1.2 What oral dosing regimens of Xanax are recommended for the treatment of panic disorder?

The successful treatment of many panic disorder patients has required the use of XANAX at doses greater than 4 mg daily. In controlled trials conducted to establish the efficacy of XANAX in panic disorder, doses in the range of 1 to 10 mg daily were used. The mean dosage employed was approximately 5 to 6 mg daily. Among the approximately 1700 patients participating in the panic disorder development program, about 300 received XANAX in dosages of greater than 7 mg/day, including approximately 100 patients who received maximum dosages of greater than 9 mg/day. Occasional patients required as much as 10 mg a day to achieve a successful response.

Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses in patients especially sensitive to the drug. Thereafter, the dose can be increased at intervals equal to at least 5 times the elimination half-life (about 11 hours in young patients, about 16 hours in elderly patients). Longer titration intervals should probably be used because the maximum therapeutic response may not occur until after the plasma levels achieve steady state. Dose should be advanced until an acceptable therapeutic response (i.e., a substantial reduction in or total elimination of panic attacks) is achieved, intolerance occurs, or the maximum recommended dose is attained. For patients receiving doses greater than 4 mg/day, periodic reassessment and consideration of dosage reduction is advised. In a controlled postmarketing dose-response study, patients treated with doses of XANAX greater than 4 mg/day for three months were able to taper to 50% of their total maintenance dose without apparent loss of clinical benefit. Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided.

4.3.2 Extended release tablet formulation

4.3.2.1 Why has the sponsor developed a new extended release tablet formulation for oral use?

The sponsor developed this extended-release (XR) alprazolam tablet with a longer duration of action related to slower absorption and intended to decrease the variation in peaks and troughs associated with four-times-daily dosing of IR. Alprazolam XR is expected to provide a more convenient dose regimen and improve patient compliance by allowing less frequent dosing. According to the sponsor, although safe and effective, immediate release (IR) formulation must be taken 3 or 4 times daily, a regimen which is inconvenient and not conducive to patient compliance. In addition, the sponsor received anecdotal reports of interdose or breakthrough anxiety, which required alprazolam IR dosing frequencies of 4 to 5 times per day. However, the attempt to evaluate the improvement of compliance was unsuccessful due to sponsor's concern over the quality of the plasma alprazolam measures in the clinical trials.

4.3.2.2 How is the new extended release tablet formulated and manufactured?

Xanax XR tablets are manufactured with unique shape and color for each strength. It is proposed that tablets will be debossed with a stylized X on one side and tablet strength on the other. All of the formulations are made using

0.5mg	1mg	2mg	3mg
pentagonal, white	square, yellow	round, blue	triangular, green

(highest strength, 3mg) manufactured at Kalamazoo (undebossed) and Puerto Rico sites (with one-sided debossed with tablet strength). (2) Biowaiver can be granted to 3 lower strengths (0.5, 1, & 2mg). The bases are as follows: (a) Similarity in the dissolution profiles in pH 6.0 phosphate buffer [for all strengths (0.5mg, 1mg, 2mg, and 3mg)] and water across two manufacturing sites [(old site, undebossed Vs new site, one-sided debossing with strength (Chou's review)] (section 4.7.3page 35), and (b) All the to-be-marketed Xanax XR tablet formulations (0.5, 1, 2 and 3 mg) are compositionally (both qualitatively and quantitatively) similar. (3) The dissolution profiles comparisons for all 4 strengths are similar between the undebossed and 2-sided debossed XR tablets (Chou's review) (4.7.4.1).

4.4 General Clinical Pharmacology

4.4.1 Which types of clinical studies were performed to assess the new alprazolam XR formulation?

A total of 8 phase II/III clinical studies were conducted with alprazolam XR formulations in patients with panic disorders (Table 4-2 & 4-3). The sponsor has indicated that study M/2000/0369 is the pivotal efficacy trial. As per Dr. Robert Levin, the Medical Officer, this clinical trial was carried out with 1-10 mg once daily given at nighttime with no regard of food intake. Plasma samples for drug analyses were collected in clinical trials (M/2002/0369 & M/200/0271). However, the sponsor did not attempt to explore the exposure-response relationship or provide PK data analysis of XR tablet because of the following reasons: (1) the concerns in quality of lab measures, (2) Population PD of IR had been evaluated, (3) Population PK of XR had been described (Literature-based (Hossain et al)). The efficacy of alprazolam XR tablet is being evaluated by the Clinical Division.

Table 4-2

Table 4. Table of All Phase 2/3 Studies in the Clinical Program

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
M/2000/0369 9152-91-006 [25]	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 6 wk
M/2000/0271 9152-91-005 [26]	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]	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: 87%, 85%, 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/2002/0003 9158-95-014 [28]	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]	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 (36,781) Placebo tablets (36,776) Alp XR up to 4 mg/day or placebo po for 8 wk

Abbreviations: Alp XR=Alprazolam Extended Release; Alp IR=Alprazolam Immediate Release; NA=not available; po=oral; wk=weeks; yr=years
Percentages are based on the number of treated patients. The numbers of randomized, treated, and completed patients are taken from the study reports unless otherwise noted.

* The number completed is from the published literature (see Section 7.2).

Table
 4-3

Table 4. Table of All Phase 2/3 Studies in the Clinical Program (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
M/2002/0015 1340-96-001 [30]	22 Centers 8 Countries (Finland, France, Hungary, Israel, Italy, Portugal, Russia, Spain) April 1993 January 1995	Randomized, Single (Evaluator)-Blind, Active Controlled	263 / 257 / 198 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]	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)
M/2002/0021 a0027679 [32]	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 8 wk

Abbreviations: Alp XR=Alprazolam Extended Release; Alp IR=Alprazolam Immediate Release; NA=not available; po=oral; wk=weeks; yr=years
 Percentages are based on the number of treated patients. The numbers of randomized, treated, and completed patients are taken from the study reports unless otherwise
 noted.

4.4.2 Exposure – response relationships

4.4.2.1 How were the exposure-response relationships of efficacy and safety evaluated for XR or IR tablet, and was there a correlation? (Hossain's & Chou's review)

Overall, alprazolam plasma concentration was not related to control of panic attacks after administering IR tablet.

The sponsor did not properly investigate the PK/PD relationship in the target patient population using clinically relevant endpoint(s) for XR tablet. Specifically, the sponsor conducted several studies (both single dose and multiple doses) to evaluate PK/PD of alprazolam XR and IR tablets. Unfortunately, these studies can not be interpreted meaningfully for the following reasons: (1) Studies did not include control group. (2) Only healthy volunteers were enrolled in the studies to evaluate the relationship between alprazolam plasma concentrations and side effects (psychomotor performance and sedation). (3) Psychomotor performance was evaluated with the digital symbol substitution test (DSST) and card sorting tasks after single and multiple doses. The psychomotor performance was neither measured in clinical studies nor correlated with the clinical efficacy or safety measures.

The sponsor attempted to explore the exposure-response relationship and blood samples were collected in 2 efficacy trials (M/2002/0369 & M/200/0271). However, the sponsor did not provide PK data or PK & PK/PD analysis because of the following reasons: (1) the concerns in quality of lab measures, (2) Population PD of IR had been evaluated, (3) Pop PK of XR had been described. As a result, the exploration of exposure-response was not feasible.

For Xanax IR, on the other hand, the sponsor had investigated the dose- or concentration-response relationship in two of the efficacy trials and results indicated that the efficacy of Alprazolam IR tablets in the treatment of panic disorder has been established. Briefly, the results from study #4432 demonstrated

that patient response, based on the reduction of major panic attacks, was related to alprazolam plasma concentrations determined at steady-state at doses of 2 and 6 mg/day of alprazolam IR tablets in these patients. However, it should be noted that the sponsor indicated in the current submission, "the clinical summary section", that results from analyses from #4432 and another trial #4412 (a short-term study with IR tablet) did not establish a minimum effective alprazolam dose or levels or window of effective doses or levels. In neither of these studies could the alprazolam dose be used to predict the treatment for an individual patient.

4.4.3 Tolerance

4.4.3.1 Has tolerance developed from alprazolam treatment? (Hossain's review: M/2000/0253, R/2002/003, P/2002/0010; R/2002/0002)

Yes, tolerance (both acute and chronic) to the psychomotor function (digital symbol substitution score test =DSST) and sedative effects has been observed from alprazolam treatment in healthy subjects. This phenomenon is independent of route of administration or formulation (iv, IR, XR) or dose (IR 1.5 mg ; XR, 1, 3, 4, 6, 8 or 10mg). The sponsor indicated that tolerance in psychomotor function was suggested when "clockwise" hysteresis was observed when mean percent decrement in DSST was plotted versus the mean log alprazolam concentration. However, psychomotor function measure will not be discussed further since this measure were not evaluated in the clinical trial, or correlated with clinically relevant outcomes. (see section 3.3.2.1)

Acute tolerance developed after single doses of XR tablet. Specifically, the maximal sedation occurred at approximately 2-3 hours, is independent of dose (XR, po, 1, 3, 4, 6, 8 or 10mg), formulation (iv, IR, XR), dosing regimen [XR 6mg/day (qd, bid); IR 1.5mg, qid] or route of administration [iv 1mg; p.o.(IR, XR)] Peak sedative effects were related to the XR dose following single dose administration of 1, 3, or 6mg (the degree of sedation increased with dose), but acute tolerance to the sedative effects occurred at later times following the dose (M/2000/0253). The mean maximum sedation scores for the 8 and 10 mg doses were similar to that observed for the 6 mg doses (R/2002/003).

Chronic tolerance appeared to develop with multiple dosing of IR tablet (P/2002/0010; R/2002/0002) and XR tablet (M/2000/0253; P/2002/0010; R/2002/0002).

- The peak sedation score for the 3 – and 6-mg treatments during the multiple dose administration (steady-state) were significantly lower than the peak sedation scores after single dose administration. The peak sedation during the multiple dose administration of XR (1, 3, or 6mg) was not different among treatments even though there was a 6-fold difference in dose (M/2000/0253).
- After 7 days of multiple dosing (XR 3mg bid, IR 1.5mg qid), subjects developed chronic tolerance to the sedative effect (P/2002/0010). Similar results were observed after 6 days of multiple dosing (XR 6mg qd, IR 1.5mg qid), although the extent of tolerance was not complete for the XR tablet treatment (R/2002/0002).
- Tolerance develops rapidly and to the same extent after multiple dosing from either dosage forms in healthy volunteers [XR 6mg/day (qd or bid); IR 1.5mg qid].

4.4.4 Pharmacodynamics (Safety/efficacy) of XR tablet

4.4.4.1 Does the slow release rate of XR tablet have an effect on the pharmacodynamics (Safety/efficacy) of the compound? (Hossain's review; Pharmacometrics review: Mishina)

Although the PK profiles as well as the calculated PD effects for alprazolam obtained after the administration of IR (1.5mg qid) and XR (3mg bid, 6mg qd) formulation are similar, the conclusion of the

same efficacy and safety of both formulations may be controversial. The results were inconsistent when comparing across the IR and XR tablet treatment groups in clinical trials. Note: all the clinical studies were carried out in once daily dose.

- (1) In the treatment phase: the premature treatment discontinuation in treatment phase was more associated with XR group (28%) than the IR group (10%). The main reason for that was the occurrence of medical events (XR: 16.6% versus IR 4.3%). [M/2000/0271, M/2000/0369, M/20002/0002], M/2002/0003].
- (2) Tapering (discontinuation, 50% dose reduction): A greater percent of patients in XR group(76%) had difficulty in tapering (76% in XR group versus 67% in IR group). At the end of taper, the alprazolam treated patients had greater change in total panic attacks in XR (+3.86) versus IR (+2.92%) versus placebo (+0.33) group. [M/2000/0271]. Opposite result was observed with pooled data [M/2000/0271, M/2000/0369, M/20002/0002, M/2002/0003]: XR formulation performed slightly better than IR formulation (25.3% versus 29.0% of total discontinuation cases.)
- (3) In both treatment and discontinuation phase: Adverse events were inconsistent. Fifty percent of patients in XR group had at least one treatment associated adverse event versus 9% in IR group. However, serious adverse events were 4 times more frequent in IR group (16%) versus XR group (4%).

Acute and chronic tolerance to sedation effect in healthy subjects occurred regardless of the formulations (section 3.1.11.1). Other PD measures such as psychomotor function are not clinically relevant and will not be discussed but appeared to be comparable across IR and XR formulations (4.4.2.1).

4.4.5 General pharmacokinetics

4.4.5.1 What are the PK characteristics of alprazolam following the administration of XR tablet and how do they compare to the administration of IR tablet? (Source: Hossain's review)

Studies comparing single dose and steady-state kinetics of alprazolam after administration of both IR and XR tablets indicated that there is a reduction in absorption rate (lower C_{max} and longer t_{max}) which is to be expected from an extended release formulation. However, the average C_{max} is comparable at the steady-state when comparing PK profiles from IR tablet (1.5mg qid) and XR tablet (6mg qd)(Figure 1). Other PK parameters remained comparable: relative bioavailability, extent of absorption (AUC), distribution (V_d/F), metabolism (AUC ratio of parent:metabolite), or elimination (t_{1/2} & Cl/F) of alprazolam.

Absorption (M/2000/0235; M/2000/253; M/2000/0305; M/2000/0346; M/2000/0275, R/2002/0002; P/2002/0010; P/2002/0013) : **The relative bioavailability of alprazolam is not affected by its release rate (IR versus XR).** Alprazolam is well absorbed from XR tablets, and to the same extent as from IR tablets across various doses when given as single doses of 1, 1.5, 3 or 6mg. The mean absolute bioavailability of alprazolam from XR tablet is approximately 0.86 with 16-34% CV. The results are comparable with the absolute bioavailability of alprazolam from IR tablets, which was reported to be 0.92. The relative bioavailability when compared to the IR tablets ranged from 0.969-1.07 with 10-18% CV.

Distribution (R/2002/0002; P/2002/0010;P/2002/0013): **The apparent volume of distribution (V_d/F) of alprazolam is not influenced by its release rate (IR versus XR).** Alprazolam V_d/F after administration of single dose of 3 mg or 6mg (2x3mg tablet) XR tablets was 1.22 ±0.197 or 1.15±0.171 L/kg, respectively. Alprazolam V_d/F after administration of single dose of 1 or 1.5mg IR tablet was 1.03-1.07 L/Kg with 12-18%CV.

Metabolism (M/2000/0253; R/2002/0002; P/2002/0010; P/2002/0013):

Average plasma clearance of alprazolam after a 1mg iv dose was 0.93mg/min/kg (CV=32%). **The oral clearance of alprazolam is not influenced by its release rate (IR versus XR).** Average alprazolam oral clearance was 1.3 min/ml/kg (CV=32%) and 1.1ml/min/kg (CV=30%) for both single and multiple doses of IR and XR tablet treatment.

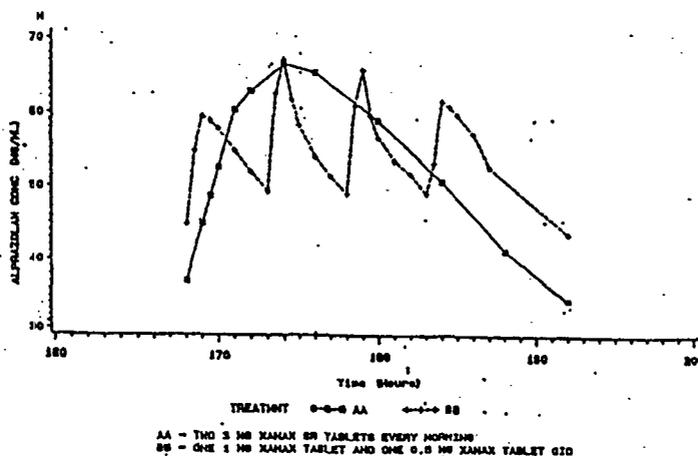
The PK parameters for the two hydroxylated metabolites of alprazolam(4-hydroxyalprazolam and α -hydroxyalprazolam) were comparable between IR and XR treatments at steady-state indicating that the metabolism of alprazolam is not affected by the release rate (IR versus XR). The alprazolam:metabolite AUC ratio did not change with dose providing further evidence that the metabolism of alprazolam was unchanged over the alprazolam recommended dosage range of 2-10mg. Following both IR and XR tablets treatments, the concentrations for 4-hydroxyalprazolam and α -hydroxyalprazolam were always less than 10% and 4% respectively, of unchanged alprazolam concentrations. The reported potencies were 0.20 and 0.66, respectively, for 4-hydroxyalprazolam and α -hydroxyalprazolam in benzodiazepine receptor binding experiments and animal models of induced seizure inhibition.

Elimination: Since the metabolism is the major route of elimination, and metabolism is unchanged by the release rate, the excretion of unchanged alprazolam would also be unchanged. Alprazolam and its metabolites are excreted primarily in the urine. The mean plasma elimination half-life of alprazolam following administration of Xanax XR tablet in healthy adults is more constant than those from Xanax IR tablets [on average, 11.2 hours (range: 6.3-26.9 hours) Vs 11.2-15.8 hours (dependent on the studies)]

Figure 1

Figure 9

Mean Steady-State Alprazolam Plasma Concentrations Following Multiple Oral Doses of Xanax Tablets and Xanax SR Tablets To 20 Healthy Volunteers



4.4.6 Dose-proportionality

4.4.6.1 Has dose proportionality been established for the XR formulations of alprazolam within the therapeutic dose range (0.5-10mg) ? (Hossain's review: M/2000/0253; R/2002/003)

Yes, the pharmacokinetics of alprazolam and two of its major active metabolites (4-hydroxyalprazolam and α -hydroxyalprazolam) are linear and concentrations are proportional up to the recommended maximum daily dose of 10mg given as once daily dose in a single dose study. In addition, XR tablet follows linear kinetics with multiple doses up to once daily dose of 6mg per day. Similar terminal half-life was observed followed administration of both IR and XR tablets. The accumulation ratio calculated as the ratio of Cmax or AUC has been found to be 1.5 and 2-2.5, respectively for alprazolam, 4-hydroxyalprazolam and α -hydroxyalprazolam.

4.4.7 Strength equivalency

4.4.7.1 Has the strength equivalency been demonstrated for the 4 strengths of XR tablets (0.5, 1, 2 and 3 mg) proposed for marketing? (Hossain's review: M/2000/0352; R/2002/0001)

Yes, the strength equivalency between the 0.5mg XR tablet given as a 1mg dose and the 1.0mg XR tablet has been demonstrated in study R/2002/0001. The strength equivalency between the 1.0, 2.0, and 3.0mg XR tablet given as a single oral dose of 6mg of alprazolam has been demonstrated in study M/2000/0352. Ninety percent confidence interval (using two one-sided test) of the ratio of test to reference for the pivotal PK parameters (AUC & Cmax) fell within the recommended goal post of 80-125%.

4.4.8 Sponsor proposed dosing regimen

4.4.8.1 What is the sponsor's proposed dosing regimen for the Xanax XR formulation?

The sponsor proposed once--daily (total daily dose given in divided doses) regimens for the XR tablet for the treatment of panic disorder.

Note: As per Dr. Robert Levin, the pivotal efficacy trial (protocol M/2000/0369 [4452]) for Alprazolam XR tablet was carried out with a once daily regimen. At the pre-NDA meeting, the Clinical Division informed the sponsor " dosing regimen for XR will be acceptable if plasma profiles of XR given bid are completely bracketed by XR (qd) and IR (approved dosing regimen).

4.4.8.2 Are plasma profiles of XR given bid completely bracketed by XR (qd) and IR (approved dosing regimen)? From the Clinical Pharmacology and Biopharmaceutics perspective, are the proposed dosing regimen adequate (once daily or total daily dose given divided doses)? [R/2002/0002& P/2002/0010 (Hossain's review); Pharmacometrics review (Mishina); Antal EJ et al & Greenblatt DJ et al (Chou's review)]

Note:

- Pharmacometrics (PM) consult was requested to evaluate whether it is acceptable regarding sponsor's justification and dosing with XR product [only qd dosing was tested in pivotal clinical trial (#4452)] based on population PK/PD of Xanax IR in the panic disorder patient population, and PK data observed from the once- and twice daily regimens of XR tablets. PM scientist was also asked to look at the potential PD effects if profiles are not completely bracketed. These results along with the single efficacy clinical trial (#4452) have been submitted to support the approval of the Xanax XR (once- and dosing in panic disorders). Complete PM review is attached (Pharmacometrics review, section 7.4, page 70).

- Previously, from the PK perspective, Hossain recommended: ~~not~~ the qd dosing regimen. Specifically, administration of one 3mg XR tablet twice a day resulted in an AUC, Cmax, Cmin and peak to trough fluctuation ratio (lower by 10%) that were not significantly different from the 1.5 mg qid dosing. However, once a day dosing of two 3mg XR tablets results in a 17% lower Cmin and a 32% greater peak to trough fluctuation ratio to a 1.5mg IR tablet qid.

Yes, from the Clinical Pharmacology and Biopharmaceutics perspective, the pharmacokinetic parameters (the overall AUC, Cmax, and Cmin) following the twice daily (bid) dosing are bracketed by those from XR (qd) and IR (qid) regimens if same daily dose is administered. However, these data analyses have some limitations, i.e., the time-course of the effect was not taken into consideration. Specifically, from the steady-state alprazolam plasma concentration profiles, plasma concentrations following XR (bid) dosing are consistently the highest among three treatments (XR bid, XR qd, and IR qid) between the hours of 14-24 over a 24-hour time span if the time-course after the dosing is considered. However, the potential impact on the safety from these sustained higher alprazolam levels is unknown and needs to be further evaluated by the Clinical Division. Summarized below are points to be considered:

- (a) Although the PK profiles as well as the calculated PD effects for alprazolam obtained after the administration of IR (1.5mg qid) and XR (3mg bid, 6mg qd) formulations are similar, the conclusion of the same efficacy and safety of both formulations may be controversial since these comparisons did not take time-course of effect into consideration (Pharmacometrics review, section 7.4, page 70).
- (b) The data analysis such as 90% CI of the overall average PK parameters (AUC, Cmax and Cmin) does not take time-course of effect into consideration.
- (c) The data from the two literature references (Antal EJ et al & Greenblatt DJ et al) the sponsor submitted suggested that the emergency of several side effects, including sedation, was significantly related to alprazolam concentration following IR tablets (1-10mg/day) administration. The frequency of reports on the CNS-depressant side effects (sedation, ataxia, slurred speech, fatigue, and weakness) increased with higher alprazolam plasma concentration. Approximately 14.5% of patients experienced severe sedative effects at alprazolam level of 60ng/ml or greater, compared with 7.2% of the patients at level below 60ng/ml ($p < 0.1$). Total sedation scores differed significantly among plasma level categories, with mean scores increasing in the 2 highest categories (40-59 and 60ng/ml). In addition, the efficacy measures (patient and physician-rated global improvement and Hamilton anxiety and depression scale score reduction) were maximal at 20-39 ng/ml, with no further benefit at higher levels. Although the frequency of total remission of panic attack increased with increasing plasma concentration at week 3 of treatment (20-39, 40-59 and ≥ 60 ng/ml), however, at week 8, there was no significant difference among these 3 plasma concentration categories. This article does not, however, evaluate the impact of differences in time course of plasma concentrations.
- (d) The estimated average plasma Cmax after single 10 mg XR tablet per day taken in the morning is 105.75 ng/ml assuming an accumulation ratio of Cmax is 1.5 and linear kinetics following multiple dose of 10mg/day. The differences in IR to XR could be large in some subjects if we consider the magnitude of the change in Cmax and tmax from the combination of multiple factors that will affect the PK and/PD (safety) of alprazolam. These factors include, but not limited to, the following: (1) Circadian variation [earlier tmax (on average 1 hour) & higher Cmax (on average +30%) after nighttime dose (note: pivotal clinical trial for XR was done as nighttime administration)]; (2) Significant food-effect [prolonged (up to 2hours), dose-dependent (significant at higher dose), shortened tmax (on average -34%) & higher Cmax (on average +26%, range: -12%~+84%)]; and (3) Considerable inter-subject variability (sections 4.5.1.1; 4.6.1).

To iterate further, following tests were performed: (a) The overall average PK parameters (AUC, Cmax and Cmin) at steady-state are similar among three treatments as indicated by the 90% confidence interval analysis of ratio of test to reference which fell within the goal post of 80-125% with the exception of the Cmin from 6mg qd, which had been shown to be efficacious in pivotal clinical trial. (Hossain's review Table 4-4 & Table 4-5). (b) Pharmacometrics analysis of Cmin using population approach reached similar

conclusion (Mishina's review Table 4-6). In addition, the PK/PD model used for the calculation of the probability of decrease in panic attack at the trough plasma alprazolam level for all three treatments overlapped.

Figure 2 Sponsor's justification of XR bid Vs qd dosing.

Note: The concentrations values from study 0010 (for XR and IR) were multiplied by the ratio of 24-hour AUC values from the IR tablet treatment in study 0002 versus study 0010 (1298ng h/ml: 1514 ng hr/ml). The sponsor indicated that using correction factor was justifiable since different subjects were used in the two studies, so that differences in clearance had to be accounted for when comparing the data. The squares (open and closed) denote data from study 0002 and the triangles (open and closed) denote data from study 0010. (Note: alprazolam IR=alprazolam CT which represents alprazolam ~~IR~~ tablets-immediate release)

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

**APPEARS THIS WAY
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Table 4-4 XR 6mg qd (treatment C) Vs IR 1.5mg qid (treatment D)

Table 18

Mean (± standard deviation) Steady-State (Day 8) Alprazolam Pharmacokinetic Parameters Following Administration of Multiple Oral Doses of ASR and ACT Tablets to 20 Healthy Volunteers Parameters Corrected for Mean Assayed Tablet Lot Potency.

Parameter			ANOVA
	Tmt A	Tmt B	
Dose	6 mg QD (ASR)	1.5 mg QID (ACT)	p value
AUC ₀₋₂₄ (ng·hr/mL)	1285 (407) ^a	1298 (442) ^a	0.6954
C _{max} (ng/mL)	70.9 (17.7) ^a	70.3 (20.6) ^a	0.8163
C _{min} (ng/mL)	34.3 (17.5)	41.6 (16.4)	0.0001
C _{avg} (ng/mL) ^b	53.5 (17.0)	54.1 (18.4)	—
Fr ^c	0.739 (0.240)	0.56 (0.129)	0.0001
T _{max} (hr)	6.75 (1.97) ^a	9.15 (4.58)	0.1999
Cl _o (L/kg)	5.12 (1.64)	5.10 (1.60)	0.8859
Cl _o (mL/min/kg)	1.12 (0.372)	1.11 (0.345)	0.7821
Vd/F (L/kg)	1.15 (0.186)	1.10 (0.141) ^a	0.1183
λ (hr ⁻¹)	0.059 (0.017)	0.06 (0.017) ^a	0.4384
r ^d	1.32 (0.125) (r=24)	3.51 (r=5)	—
r (based on C _{max})	1.57 (0.318)	3.29 (0.876)	—
t _{1/2} (hr)	13.0 (4.87)	12.5 (4.03)	—

^a C_{avg} = AUC₀₋₂₄/24
^b C_{max} to C_{min} fluctuation ratio, Fr = (C_{max} - C_{min})/C_{avg}
^c Accumulation factor, r = 1/(1-e^{-λτ})
^d Single dose parameter in Table 17 is significantly different from steady-state parameter, p < 0.05

Table 4-5 XR 3mg bid (treatment D) Vs IR 1.5mg qid (treatment C)

Table 25

Mean (± standard deviation) Steady-State (Day 7) Alprazolam Pharmacokinetic Parameters Resulting From the Administration of Multiple Oral Doses of ASR Tablets and ACT Tablets to 17 Healthy Volunteers and Corrected for Mean Assayed Tablet Lot Potency.

Parameter	C	D	ANOVA
Dose	1.5 mg QID (ACT)	3 mg BID (ASR)	p value
AUC ₀₋₂₄ (ng·hr/mL)	1514 (596) ^a	1574 (610)	0.0490
C _{max} (ng/mL)	82.9 (28.8) ^a	84.1 (35.8) ^a	0.3015
C _{min} (ng/mL) ^b	49.3 (24.7)	48.9 (16.0)	0.0294
C _{avg} (ng/mL) ^c	63.1 (24.1)	65.6 (24.7)	—
Fr ^d	0.570 (0.164)	0.512 (0.220)	0.0893
T _{max} (hr)	7.24 (3.32) ^a	10.1 (6.81)	0.5674
Cl _o (L/hr)	4.38 (1.19)	4.21 (1.16) ^a	0.0632
Cl _o (mL/min/kg)	1.04 (0.331)	1.00 (0.334) ^a	0.0648
Vd/F (L/kg)	1.12 (0.137) ^a	1.14 (0.172)	0.4945
λ (hr ⁻¹)	0.055 (0.013) ^a	0.052 (0.012) ^a	0.0673
t _{1/2} (hr)	13.34 (3.69)	14.21 (4.11)	—
r (based on C _{max}) ^e	3.83 (0.90)	3.38 (1.17)	—
r (based on λ) ^f	3.61 (0.76) (r=5)	2.2 (0.63) (r=12)	—

^a C_{min} for C and D is taken as the lowest C_p value between 0 to 24 hour and not as C_{min0} or C_{min24}.
^b C_{avg} = AUC₀₋₂₄/24
^c C_{max} to C_{min} fluctuation ratio (Fr) = (C_{max} - C_{min})/C_{avg}
^d Accumulation factor
^e Single dose parameter in Table 24 is significantly different from steady-state parameter, p < 0.05

Table 19

90% Confidence Interval Analysis of Single Dose (Day 1) and Steady-State (Day 8) Selected Alprazolam Pharmacokinetic Parameters Following the Administration of XANAX SR Tablets and XANAX CT Tablets to 20 Healthy Volunteers. Parameters Corrected For Mean Assayed Tablet Lot Potency.

Parameter	Treatment ^a	MSE	90% C.I.	Result	Power ^b
AUC ₀₋₂₄ (ng x hr/mL) ^c	A vs B	2284	85.2-102.0	Pass	97
C _{max} (ng/mL) ^d	A vs B	19.8	40.3-62.5	Fail	84
AUC (ng x hr/mL)	C vs D	10,264	94.7-103.3	Pass	99
C _{max} (ng/mL)	C vs D	70.0	94.3-107.4	Pass	99
C _{min} (ng/mL)	C vs D	16.0	77.2-87.7	Fail	99
Fr ^e	C vs D	0.018	119-145	Fail	70

^a A: Xanax SR 6 mg (2 x 3 mg) Given as a Single Dose
^b B: Xanax ACT 1.5 mg (1 & 0.5 mg) Given as a Single Dose
^c C: Xanax SR 6 mg Given Every Morning For 6 Days
^d D: Xanax ACT 1.5 mg Given Every 5 hours For 6 Days
^e Power to detect a 20% difference between treatment and reference means at an α level of 0.05.
^f Fluctuation ratio = (C_{max} - C_{min})/C_{avg}
^g Normalized to a 1.5 mg dose.

Table 26

90% Confidence Interval Analysis (Two One-Sided Test Procedure) of Single Dose (Day 1) and Steady-State (Day 7) Alprazolam Pharmacokinetic Parameters Following the Administration of XANAX SR Tablets and XANAX CT Tablets to 17 Healthy Volunteers. Parameters Corrected For Mean Assayed Tablet Lot Potency.

Parameter	Treatment ^a	MSE	90% C.I.	Result	Power ^b
AUC ₀₋₂₄ (ng·hr/mL) ^c	B vs A	3557	95.3-115.3	Pass	90.57
C _{max} (ng/mL) ^d	B vs A	6.1	50.8-64.4	Fail	99.55
AUC ₀₋₂₄ (ng·hr/mL)	D vs C	8515	100.3-107.6	Pass	>99.9
C _{max} (ng/mL)	D vs C	56.1	96.0-107.0	Pass	99.97
C _{min} (ng/mL)	D vs C	66.5	89.2-109.0	Pass	90.8
Fr ^e	D vs C	0.0232	73.8-106.0	Fail	52.0

^a A: Xanax ACT 1.5 mg (1 & 0.5 mg) Given as a Single Dose
^b B: Xanax SR 3 mg Given as a Single Dose
^c C: Xanax ACT 1.5 mg Given QID (Every 5 hours) For 6 Days
^d D: Xanax SR 3 mg Given Every Morning For 6 Days
^e Power to detect a 20% difference between treatment and reference means at an α level of 0.05.
^f Fluctuation ratio = (C_{max} - C_{min})/C_{avg}
^g Normalized to a 1.5 mg dose.

Table 4-6 Comparison of the observed plasma concentrations measured at trough and calculated effects of alprazolam in studies 0002 and 0010.

Study	0002		0010	
Regimen	IR 1.5 mg QID	XR 6 mg QD	IR 1.5 mg QID	XR 3 mg BID
C _{min} , ng/mL				
Mean (SD)	47.02 (17.42)	36.35 (17.7)	55.28 (25.12)	57.5 (25.73)
Range	—	—	—	—
<i>Probability of major response to alprazolam concentrations at C_{min}, (%)</i>				
Mean	27.38	20.92	32.84	34.36
Range	12.53-65.03	10.29-59.15	19.93-80.38	16.98-81.25

4.5 Intrinsic factors

4.5.1 Chronopharmacokinetics

4.5.1.1 Is PK of alprazolam influenced by circadian variation? If yes, is the effect similar between IR and XR formulations? (Protocol P/2002/007, Hossain's review)

Yes, the PK of alprazolam were influenced by the circadian variation, but the result of this influence was a function of the oral formulation. Specifically, the IR formulation exhibited a delayed and reduced mean peak concentration after nighttime administration while the XR formulation exhibited an earlier and higher mean peak concentration. However, since the pivotal clinical efficacy trial was carried out with 1-10mg XR tablets once daily dose given at nighttime, the clinical relevance of this chronopharmacokinetics is of less concern.

The result from study protocol P/2002/007 is summarized below:

Xanax XR: There is a significant chronological effect on the PK parameters (C_{max} & t_{max}) of Xanax XR. When comparing the PK from single morning (7AM) versus evening (10PM) dose of 3 mg (3x1mg) Xanax XR treatment in male healthy volunteers, a 30% increase in C_{max} (10.4 versus 8.01ng/ml) and 1 hour earlier t_{max} (8.61 hrs versus 9.91 hrs) was observed for the evening dose. AUC is comparable for morning and evening doses. Oral clearance of Xanax XR is not significantly affected by the time of dosing. (Table 4-7; Fig 3)

4-hydroxyalprazolam (major metabolite): There is a significant difference in t_{max} and ratio of alprazolam to 4-hydroxyalprazolam. Although the difference in mean AUC is not statistical significant, there is a 53% reduction in AUC after the evening dose. The mean peak concentration of 4-hydroxyalprazolam from the XR tablet administered in the evening occurred 3.69 hours earlier (8.61 versus 12.3 hours) than the mean peak concentration from the XR tablet administered in the morning. The mean ratio of parent to 4-hydroxyalprazolam from the XR tablet administered in the evening was 38% higher (14.6 versus

10.6) than the mean ratio from the XR tablet administered in the morning. However, the concentration-time profiles of 4-hydroxyalprazolam for the morning and evening doses of XR tablets parallel those of alprazolam. (Figure 3; Figure 4)

Xanax IR: Significant chronological effect on PK parameters (AUC, Cmax, tmax) of the Xanax IR product is also observed, however, the magnitude and trend of changes are different. When comparing the PK from single morning (7AM) versus evening (10PM) dose of 1 mg Xanax IR treatment in male healthy volunteers, small but significant changes were observed in Cmax (a 9% decrease) and AUC (a 6% increase). There is a 2 hour prolongation in tmax (3.61 hrs versus 1.54 hrs) for the evening dose. Oral clearance of Xanax IR is not significantly affected by the time of dosing (Fig 3)

Table 4-7

Treatment A	Treatment B	Treatment C	Treatment D
1mg IR at 7am	3mg XR at 7am	1mg IR at 10 pm	3mg XR at 10pm

Table 4
Mean (±SD) Alprazolam Pharmacokinetic Parameters Resulting from the Single Dose Administration of Morning or Bedtime Doses of XANAX® Tablets 1 mg and XANAX XR® Tablets 3 mg to 23 Healthy Volunteers. Parameters are Corrected for Mean Assayed Tablet Lot Potency.

Parameter	Treatment*				ANOVA pvalue	Multiple Comparisons ^b
	A	B	C	D		
AUC _{0-∞} (ng·hr/mL)	236 (55.5)	773 (191)	250 (66.2)	791 (195)	0.0001	A C B D
AUC ₀₋₄ (ng·hr/mL)	235 (55.5)	258 (63.8)	250 (66.2)	264 (66.0)	0.0018	A B C D
AUC ₀₋₂₄ (ng·hr/mL)	212 (43.6)	861 (151)	224 (53.5)	699 (145)	0.0001	A C B D
AUC ₀₋₂₄ (ng·hr/mL)	212 (43.6)	220 (43.7)	224 (53.5)	233 (48.3)	0.0081	A B C D
C _{max} (ng/mL)	13.8 (2.35)	24.0 (2.78)	12.6 (4.50)	31.1 (5.05)	0.0001	A B C D
C _{max} ^d (ng/mL)	13.8 (2.35)	8.01 (1.26)	2.6 (4.50)	10.4 (1.68)	0.0001	A B C D
T _{max} (hr)	1.59 (0.875)	9.91 (2.21)	3.61 (2.95)	8.61 (1.53)	0.0001	A B C D
V _d (L)	80.7 (12.2)	87.4 (14.1)	77.7 (14.3)	76.7 (12.1)	0.0001	B A C D
V _d (L/kg)	1.03 (0.117)	1.11 (0.119)	0.987 (0.138)	0.977 (0.135)	0.0001	B A C D
Cl _{CR} (L/hr)	4.48 (1.01)	4.10 (0.956)	4.27 (1.16)	4.00 (0.926)	0.0038	A C B D
Cl _{CR} (mL/min/kg)	0.959 (0.233)	0.875 (0.211)	0.913 (0.263)	0.857 (0.219)	0.0028	A C B D
t _{1/2} (hr)	0.056 (0.011)	0.047 (0.010)	0.055 (0.012)	0.052 (0.009)	0.0001	A C B D
ln(C _{tr}) ^c	12.4	14.7	12.8	13.3	—	—

* Treatment A = (1) XANAX® Tablet 1 mg at 7:00 am
 Treatment B = (3) XANAX XR® Tablets 3 mg at 7:00 am
 Treatment C = (1) XANAX® Tablet 1 mg at 10:00 pm
 Treatment D = (3) XANAX XR® Tablets 3 mg at 10:00 pm
^b Multiple comparisons were made using the Waller-Duncan k-Ratio t test. Treatments connected by a line are not significantly different (p < 0.05).
^c Harmonic mean
^d Corrected for mean assay lot potency

XANAX XR STUDY P/2002/0007
ALPRAZOLAM PLASMA CONCENTRATIONS FOLLOWING THE ADMINISTRATION OF SINGLE MORNING OR BEDTIME DOSES OF XANAX TABLETS OR XANAX XR TABLETS TO 23 VOLUNTEERS
MEAN RESULTS

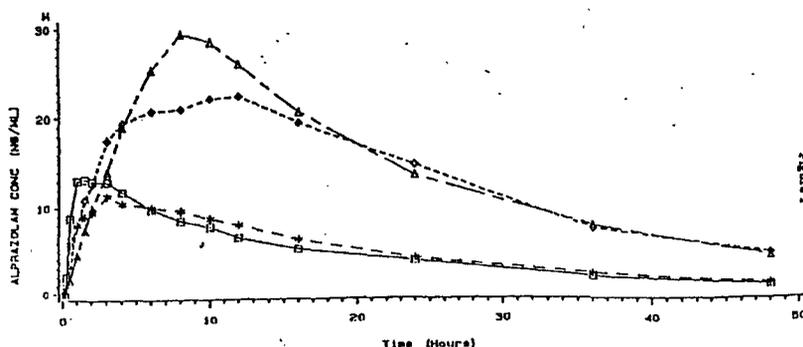


Figure 3

Figure 1

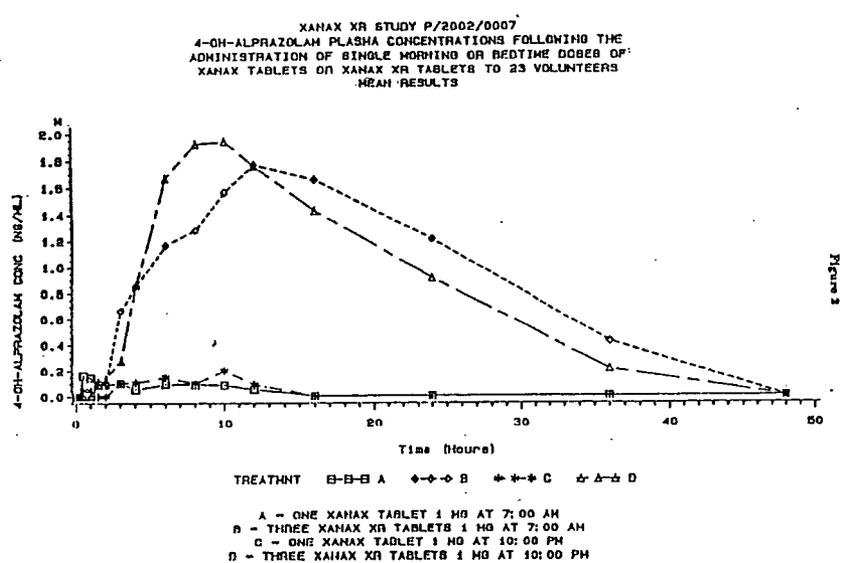
C: \emautop\temp\N21

TREATMENT B-B-B A *-*-* B *-*-* C *-*-* D

A = ONE XANAX TABLET 1 MG AT 7:00 AM
 B = THREE XANAX XR TABLETS 3 MG AT 7:00 AM
 C = ONE XANAX TABLET 1 MG AT 10:00 PM
 D = THREE XANAX XR TABLETS 3 MG AT 10:00 PM

BEST POSSIBLE COPY

Figure 4



4.5.2 Special populations (elderly, pediatrics, hepatic or renal impairment, obesity) (Hossain's review: M/2000/0253; R/2002/0002; P/2002/0010; P/2002/0013):

4.5.2.1 Do the PK and safety/efficacy of alprazolam XR in special populations (elderly, pediatrics, hepatic or renal impairment, obesity) differ from those of alprazolam IR?

No PK or safety/efficacy study was performed in special populations with XR tablet. However, this reviewer agrees with Hossain's conclusion that the factors (such as age, hepatic or renal impairment), which would affect the PK of alprazolam after the administration of IR tablets, would not be expected to change with the administration of XR tablets. This is based on the fact that metabolism of alprazolam is not affected by the release rate (IR versus XR) and alprazolam is extensively metabolized with minimal unchanged drug found in the urine.

The sponsor indicated in clinical data summary section that no clinically important differences were observed between the two patient subgroups (>45 years versus ≤45 years old) in the adverse event profiles during treatment and discontinuation. In the placebo-controlled studies, the incidence of the most commonly reported treatment emergent and discontinuation-emergent adverse events was slightly lower in patients >45 years old than in patients ≤45 years old.

The sponsor is requesting a deferral of study in pediatric patients with panic disorder to be conducted as a Phase IV commitment.

4.5.3 Gender

4.5.3.1 Does gender affect the PK or safety/efficacy of alprazolam? (Hossain et al, Chou's review)

Gender has no effect on the PK of alprazolam (IR and XR). The sponsor submitted a literature article by Hossain et al regarding a population pharmacokinetic (PPK) analysis on data for the IR and XR tablets from normal subjects from a Phase I bioavailability study. Intense plasma sampling to determine plasma levels of alprazolam was undertaken, and a PPK analysis was performed on data from 17 adult healthy

volunteers (7 females and 10 males) who received IR (1.5mg qid) and XR (3mg bid). Eight of the subjects were cigarette smokers. The following covariates were evaluated: gender, age, body weight, body surface area, lean body mass, and cigarette smoking. Only cigarette smoking showed potential effect on alprazolam pharmacokinetics.

Briefly summarized from Clinical Data Summary section, the sponsor did not formally explore the gender-effect on the safety/efficacy measures for XR tablet and there is no information in this regard in the IR tablet (label). However, the by-sex analysis of four clinical trials showed that both males and females treated with Xanax XR tablet had significant greater improvement in their overall clinical condition than males and females treated with placebo. Sex has minimal effect on either the treatment-emergent or discontinuation emergent adverse event. Majority of patients that participated in the four placebo-controlled efficacy trials including pivotal study (#369) were female (~63%).

4.5.4 Pediatrics

4.5.4.1 Did the sponsor investigate the PK and safety/efficacy of Xanax in pediatrics?

No, there is lack of information on PK and safety/efficacy of alprazolam (IR or XR formulation) in pediatrics.

As of today (DFS, 09/09/02), these protocols have not been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). OCPB will review them after the Clinical Division makes a decision on whether or not to grant the deferral of pediatrics studies.

4.5.5 Race (Chou's review & Lin KM et al (1988))

4.5.5.1 Did the sponsor investigate the potential race-effect on the PK and safety/efficacy?

No meaningful comparison of PK or safety/efficacy response by race can be made since the majority of patients that participated in the 4 placebo-controlled efficacy trials including pivotal study (#369) were white ($\geq 85\%$). Similarly, the majority of subjects that participated in BA/BE studies were White.

Comment: The sponsor should further explore the ethnic-effect on the PK and safety/efficacy from the available sources (such as literature & post-marketing experience from over the 50 countries outside of U.S. that XR formulation has been marketed) and incorporate relevant information into the label.

Following are the bases: (a) Ethnic differences in the alprazolam PK parameters (C_{max} , AUC, Cl, $t_{1/2}$) had been reported in the literature (Lin KM et al (1988)*); (b) Ethnic differences in CYP3A4 enzyme activity have been reported in the literature and CYP3A4 pathway is the major route of elimination for alprazolam.

Note: The sponsor indicated that Xanax XR had been marketed in over 50 countries outside of U.S.

* Lin KM et al 1988 Psychopharmacology (Berl) 1988;96(3): 365-9 Comparison of alprazolam plasma levels in normal Asian and Caucasian male volunteers from a PubMed search by this reviewer.

4.6 Extrinsic factors

4.6.1 Food-effect [M/2000/0275 (reviewed by Hossain), P/2002/0013 (reviewed by Hossain), M/2002/0017(reviewed by Chou)]

The sponsor conducted three food effect studies: one on the 1.0 mg XR tablet [M/2000/0275 (Hossain), two on the 3.0mg tablet [P/2002/0013 (Hossain), M/2002/0017(Effect of meal timing, Chou)]. Detailed discussion can be found in section 7.2.1(page 49).

4.6.1.1 Does food affect the bioavailability of the Xanax XR?

Yes, high fat meal when given immediately before or 2 hours before the dosing of 3mg XR tablet significantly affects the bioavailability of Xanax XR tablet by shortening tmax and increasing Cmax (on average, by 21-26%) (Table 4-8; Table 4-9; Table 4-10; Fig 5; Fig 6). The 90% CI of test (fed)-to-reference (fasted) ratio fell outside the 0.80-1.25 goal post for average BE assessment for the log transformed PK parameter [Cmax with 90% CI of 116-128 (M/2002/0017) and 116.16-135.87 (P/2002 0013); 115-127 (P/2002/0017)] and these differences were statistically significant (p<0.0001) (Table 4-8; Table 4-9; Table 4-10). The mean tmax was shortened from 8.1 hours (fasted) to 6.41-6.69 hours (food taken 1-2 hour prior to dosing), 7.52 hours (food taken immediately prior to dosing). The mean AUC and elimination half-lives were comparable. When high-fat meal was given 1 hour after the dosing of 3mg XR tablet, it has no effect on the average PK parameters (AUC and Cmax), but prolonged the mean tmax from 8.1 hours to 10.6 hours:

In addition, the food-effect may dose-dependent (cross-study comparisons). The high-fat meal when taken immediately before the dosing of 1mg XR tablet has minimal effect on the alprazolam PK parameters (AUC, Cmax, tmax) (7.2.1). Note: The 1mg and 3mg XR tablets have same release mechanism and are compositionally very similar.

From the review of individual concentration-time profile for the 3mg XR tablet given with food (1hour after dosing, immediately before dosing, 1or 2 hours before dosing) indicates that in some individuals the dosage form-food interaction may be quite significant: ranging from -34~+84% for Cmax and -63% to +433% for tmax [M/2002/0017(Chou)]. The tmax effect may be inaccurate since in several subjects, the PK profile was flat. Similar magnitude of % change in Cmax (+50~+75%) was observed from study [M/2000/0013 (Hossain)] when XR tablet was given immediately after a high fat meal (Table 4-8).

Table 4-8 Range of % change in Cmax & tmax relative to the reference (3mg in fasted state, treatment E) and 90% CI of AUC & Cmax. Bold indicates outside of goal post (80-125).

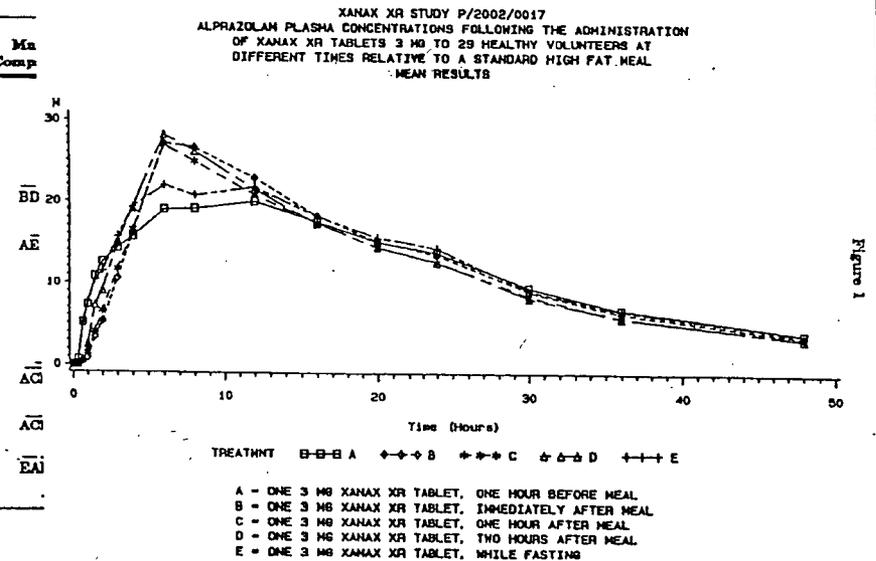
Group		Treatment A	B	C	D	E (Reference)
Treatment		1x 3mg XR (fed)	1x 3mg XR (fed)	1x 3mg XR (fed)	1x 3mg XR (fed)	1x 3mg XR (fasted)
Meal time		1 hour after dosing	Immediately before dosing	1 hour before dosing	2 hours before dosing	Not applicable
AUC	90% CI	92-101	93-102 [87.95-104.9 (P/200/0013)]	88-97	89-98	0
Cmax	90%CI	89-101	116-128 (M/2002/0017) [116.16-135.87 (P/2000/0013)]	109-120	115-127 (M/2002/0017)	0
	Range of % change	-34%~+69.7% (mean -2.6%)	[-12%~+84% (mean+24.7%); [highest +50~+75% (mean +26%, P/200/0013)]	-20~+78% (mean +16.8%)	-12~+67% (mean +22.8%)	0
Tmax	Range of % change	-63%~+433% (mean +55%)	-50~+100% (mean +6.32%) [(mean -34%, P/200/0013)]	-50%~+100 (mean -8%)	-50%~+100% (mean -3.7%)	0

Table 4-9 & Figure 5 [protocol P/2002/0017 (Chou' review)]: Pharmacokinetics and pharmacodynamics of alprazolam relative to meal timing.

TR No.: 7215-93-050

Table 6. Mean (± standard deviation) Alprazolam Pharmacokinetic Parameters Resulting From Single Oral Doses of 3 mg XANAX XR Tablets Administered at Different Times Relative to a Standard High Fat Breakfast to 29 Healthy Volunteers.

Parameter	Treatment ^a					ANOVA p value	Min Comp
	A	B	C	D	E		
AUC (ng x hr/ml)	688 (206)	688 (185)	655 (165)	662 (161)	707 (200)	0.0500	
AUC _{0-∞} (ng x hr/ml)	579 (133)	604 (181)	574 (120)	592 (123)	606 (133)	0.1098	
C _{max} (ng/ml)	22.8 (4.28)	29.1 (4.82)	27.4 (4.81)	29.0 (5.43)	23.9 (4.46)	0.0001	
T _{max} (hr)	10.6 (4.06)	7.52 (2.05)	6.41 (0.988)	6.69 (1.34)	8.10 (3.07)	0.0001	
CL _{0-∞} (L/hr)	4.83 (1.63)	4.73 (1.57)	4.90 (1.86)	4.85 (1.46)	4.61 (1.48)	0.1277	
CL _{0-∞} (ml/min/kg)	1.09 (0.376)	1.07 (0.364)	1.11 (0.342)	1.09 (0.329)	1.06 (0.357)	0.1706	
V _d P (L)	97.3 (25.5)	56.8 (13.6)	93.3 (18.5)	88.0 (14.9)	92.4 (18.0)	0.0087	
V _d P (L/kg)	1.30 (0.280)	1.17 (0.158)	1.25 (0.169)	1.18 (0.124)	1.24 (0.199)	0.0155	
λ (hr ⁻¹)	0.050 (0.014)	0.055 (0.014)	0.053 (0.013)	0.055 (0.012)	0.050 (0.014)	0.0001	
t _{1/2} (hr) ^b	13.9	12.6	13.1	12.6	13.9	-	



Treatment A: one 3 mg XANAX XR Tablet, one hour before meal
 Treatment B: one 3 mg XANAX XR Tablet, immediately after meal
 Treatment C: one 3 mg XANAX XR Tablet, one hour after meal
 Treatment D: one 3 mg XANAX XR Tablet, two hours after meal
 Treatment E: one 3 mg XANAX XR Tablet, fasting
 Multiple comparisons were made using the Waller-Duncan k-ratio t test.
 Treatments connected by a line are not significantly different (p<0.05).
 Elimination half-life, harmonic mean

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Table 4-10; Figure 6: (directly excerpted from Dr. Hossain's review from protocol M/2002/0013: Effects of food on the bioavailability of XR-3mg tablets). Effects of food on the bioavailability of XR-3mg tablets.

Group	Treatment A	B	C
Treatment	1x 3mg XR tablet (fasted)	1x 3mg XR tablet (fed)	1x 3mg IR tablet (fasted)

Results:

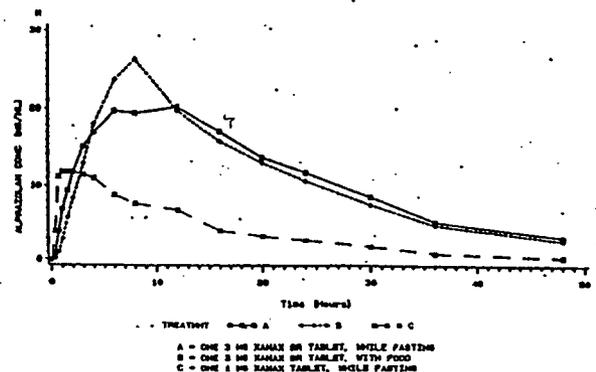
Table 15

Mean (CV, %) Alprazolam Pharmacokinetic Parameters Following Oral Administration of 1-mg ASR Tablets Administered With and Without Food and 1-mg ACT Tablets to 21 Healthy Volunteers

Parameter	Tmt. A Fasting	Tmt. B Fed	Tmt. C Fasting	ANOVA*	W-D MCT ^b
AUC _{0-∞} (ngxh/ml)	229.2 (26)	212.3 (27)	217.3 (33)	NS*	
C _{max} (ng/ml)	8.2 (10)	9.2 (17)	13.4 (18)	0.0001	C B A
T _{max} (hr)	7.2 (39)	7.0 (31)	1.5 (49)	0.0001	A B C
F _{rel}	1.00 (12)	0.97 (8)	1.00 (0)		
T _{1/2} (hr)	14.3 (33.3)	12.4 (30.2)	13.1 (30.7)	NS	
λ (hr ⁻¹)	0.053 (30)	0.062 (34)	0.057 (34)	NS	

* Analysis of variance for latin square design, level of significance.
^b Treatments sharing underhead bars are not significantly different at the 95% confidence interval.
 * No significant differences among treatments (p>0.05).

Figure 19 - Mean Alprazolam Plasma Concentration-Time Profiles



4.6.1.2 Is sponsor's proposed Xanax XR dose administration relative to the food intake adequate? If not, what would be the Agency's recommendation on XR tablet dosing in relation to meals?

Note: As per Dr Robert Levin, the medical officer, the pivotal clinical trial was conducted with 1-10mg XR tablet given once daily at nighttime with no regard of food intake. Based on the PK perspective, Hossain recommended that in order to insure the integrity of the dosage form and to minimize side-effects, XR tablet should be administered on an empty stomach or preferably at least 2 hours after a meal.

Sponsor proposed: Despite the existence of significant food effect, the sponsor proposed no specific instructions regarding XR tablet dosing in relation to meals is warranted.

Comments:

- There is significant food-effect. High-fat meal taken immediately before the dosing of 3mg XR tablet significantly affects the bioavailability of alprazolam by increasing C_{max} (an average of 21-26% with 90% CI of 116-135, which fell outside of goal post) and shortening t_{max} (an average of a 21-34% earlier t_{max}). The food effect is prolonged even when the food was taken 2 hours before the dosing. In addition, in some individuals, the magnitude of % change in C_{max} and t_{max} is quite significant (-34~+84% for C_{max}).
- This reviewer agrees with Hossain's recommendation that separating XR tablet dosing from food intake may be warranted. Ideally, XR tablet should be taken with an empty stomach or preferably at least 1 hour before or 2 hours after a meal.
- However, since the pivotal efficacy trial was conducted with 1-10mg once daily administered at nighttime with no regard of food intake, the significant food-effect on the bioavailability of Xanax XR tablets should be described in the Clinical Pharmacology, Pharmacokinetics section. No specific dosing recommendations related to food are suggested.

4.6.2 Cigarette smoking

4.6.2.1 Does cigarette smoking affect the disposition of alprazolam after Xanax XR? (Hossain et al 1997; Chou's review)

Yes, cigarette smoking showed a potential effect on alprazolam pharmacokinetics. Cigarette smoking was associated with a 100% increase in clearance of alprazolam as compared to non-smokers. The sponsor submitted a literature by Hossain et al regarding a population pharmacokinetic (PPK) analysis on data for the IR and XR tablets from normal subjects from a Phase I bioavailability study. Intense plasma sampling to determine plasma levels of alprazolam was undertaken, and a PPK analysis was performed on data from 17 adult healthy volunteers (7 females and 10 males) who received IR (1.5mg qid) and XR (3mg bid). Eight of the subjects were cigarette smokers. The following covariates were evaluated: gender, age, body weight, body surface area, lean body mass, cigarette smoking. Only cigarette smoking showed potential effect on alprazolam pharmacokinetics.

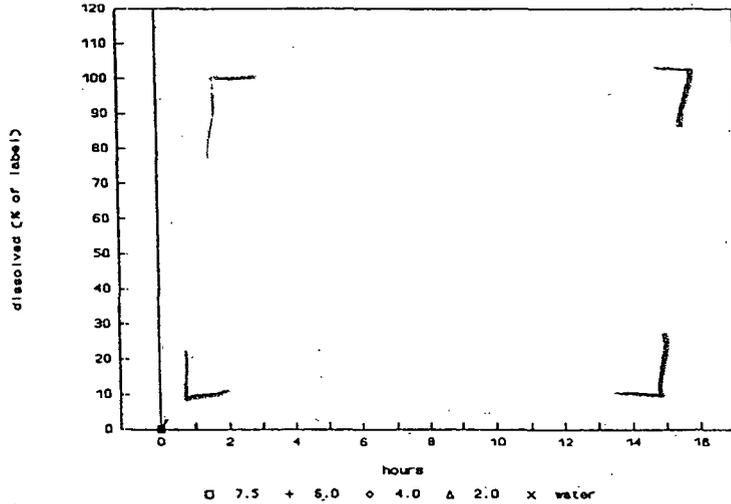
4.6.3 Drug-drug interactions (DDI) (Chou's review)

Note: No drug-drug interaction study was performed with the XR tablet to evaluate the PK or safety/efficacy. The sponsor proposed to use labeling language of marketed Xanax IR (Revised June 2000) as template and incorporate the new literature-based drug-drug interaction information between alprazolam IR and CYP3A4 inhibitors (ketoconazole, itraconazole, and erythromycin), and CYP3A4-inducer (carbamazepine), respectively. This reviewer agrees with Hossain's conclusion that the factor such as drug-drug interaction that may affect the PK of alprazolam after the administration of IR tablets

phosphate buffer over water as dissolution medium may provide some benefits due to the lack of buffer capacity in water.

Figure 7

Figure ILG-2 Dissolution profiles for XANAX XR 1 mg Lot 85,317 with dissolution media of water, pH 2.0, pH 4.0, pH 6.0 and pH 7.5.



- Ideally, one common specification should be used for all 4 different strengths. However, in this specific case, where a strength-dependent drug release phenomenon exists, dissolution specs has to be widened to accommodate all 4 strengths. To justify this widening, an established in-vitro and in-vivo correlation (IVIVC) is required*. Since IVIVC was unsuccessful for XR tablet (4.7.2.1, page 33), the dissolution specifications will be used as QC measures and separate specifications for each strength are acceptable.

*The guidance published in September 1997 "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations"

- This reviewer has evaluated sponsor's proposed dissolution specs at any time point against dissolution profiles from following batches used to establish BA/BE & efficacy, and support a manufacturing site change [Details of individual dissolution profile are attached in section 7.2.3 (page57)]:
 - (a) Batches used in the pivotal PK/BE & efficacy studies manufactured at US site (old site, undebossed) as primary data.
 - (b) Batches manufactured at the Arecibo, Puerto Rico (new site, undebossed) used in the BE study (data submitted under _____) to support the manufacturing site change as primary data. The dissolution profile from the biobatches for this BE study was not available.
 - (c) Dissolution profiles from commercial final formulation (new site, 2-sided debossed) were used as supportive data.
 - (d) Dissolution profiles from final formulation (new site, undebossed).
 - (e) The review chemists (Drs Thomas Oliver & Lorenzo Rocca) were also asked to evaluate the sponsor's proposed dissolution specifications against the stability data.

Final dissolution method and specification:
 USP apparatus I, 100rpm, 37°C, volume 500ml, pH 6.0 buffer

	0.5 mg	1 mg	2 mg	3 mg
1 hour				
4 hours				
8 hours				
16 hours				

4.7.2 In vitro and in vivo drug release comparisons

4.7.2.1 Has the sponsor evaluated the relation between in vitro release and the in vivo performance of Xanax XR? Was the IVIVC properly developed and does it demonstrate satisfactory predictability?

Yes, the sponsor attempted to evaluate the relation between in vitro release and the in vivo performance but failed to establish the IVIVC for Xanax XR tablet. However, the sponsor had indicated during the teleconference (03/22/2002).

As a result, the sponsor did not submit the requested individual data and IVIVC was not reviewed.

4.7.3 Manufacturing site changes (P/2002/0018)

Note:

- During the drug development process, there was a manufacturing site change from Kalamazoo Michigan to Arecibo, Puerto Rico. All the XR tablets used in the PK and clinical studies were manufactured at the Upjohn Kalamazoo facility without debossing. The final commercial production with 2-sided debossing (strength & X) is planned and will be manufactured at Arecibo, Puerto Rico.
- The sponsor submitted a BE study (P/2002/0018) comparing highest strength 3mg XR tablet manufactured from Kalamazoo (lot #26,397) and Puerto Rico (lot #26,437) sites. The existing stability lots made in Puerto Rico in 1991 and 1992 were debossed on one side only (with tablet strength). Ninety-percent confidence interval analysis indicated that tablets manufactured at these sites were BE (90% CI for Cmax, AUC was 98.0-110.6, 95-108.4, respectively) (Table 4-11).
- Previously, the sponsor submitted dissolution profiles (pH 6.0 & H2O) of 3mg tablets made from both sites. For lower strengths (0.5, 1, and 2 mg), only dissolution profiles (pH 6.0 & H2O) from Puerto Rico were submitted. This reviewer has performed an f2 test comparing the dissolution profiles between the batches made from new site and the biobatches for PK/BE/pivotal efficacy trial manufactured at the old site. The dissolution profiles between 2 sites for each strength are similar (f2=50.98-82.9).
- During a teleconference dated May 10, 2002, the sponsor was requested to submit dissolution profile comparisons between debossed (2-sided) and non-debossed tablets using the selected dissolution method for all strengths (0.5, 1, 2, and 3 mg) of Xanax XR. They anticipate the debossed tablets will be manufactured in and they agreed to submit the requested information as soon as they become available. The sponsor indicated in a letter (dated 07/17/02) that these information would be submitted in the week of September 16, 2002. The requested data were submitted on September 13, 2002.

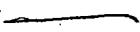
4.7.4 Debossing issues

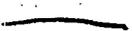
Note:

Xanax XR was submitted for review under current NDA(#21,434) on 12/26/01. Later, on 05/10/02, the sponsor submitted a request for teleconference along with three questions regarding stability and debossing issues for discussion. The sponsor proposed that XANAX XR Tablets will be debossed with a stylized "X" on one side and tablet strength on the other. This represents a change from the debossing associated with stability lots. Most of the stability lots reported in NDA 21-434 were  with no debossing and all of the confirmatory stability lots will be  with no debossing. It should be noted that neither clinical nor biopharmaceutical studies were conducted using to-be-marketed debossed tablet.

Sponsor: The sponsor argued that although addition of debossing has the potential of substantially influencing drug release from modified-release dosage forms, the addition of the proposed debossed markings to XANAX XR Tablets is not expected to alter the drug release characteristics of these products. This conclusion is based on scientific studies conducted during product development that examined the effect on drug release of tablet surface area and tablet volume variations associated with different tablet shapes. Pharmacia & Upjohn proposes that addition of the proposed debossed markings is well within the surface area and tablet volume variations studied.

Following comment was conveyed to the sponsor during teleconference:

The sponsor is requested to submit dissolution profile comparisons between debossed and non-debossed tablets using the selected dissolution method for all strengths (0.5, 1, 2, and 3 mg) of Xanax XR. The sponsor was informed that while dissolution was comparable for tablets with different shapes, the experiments conducted do not evaluate the effect of changes in . Since the Belgian tablets are not debossed in the same manner as the proposed U.S. tablets and since we have no information on the effect of different  on release rate, it is prudent to compare dissolution profiles of debossed and non-debossed tablets.

Note: The sponsor indicated in the teleconference that they anticipate the debossed tablets will be manufactured  and they agreed to submit the requested information as soon as they become available. Later, on September 13, 2002, the sponsor submitted the comparisons of debossed with undebossed tablets from 1 full scale lot of each strength. The stability data were also submitted and reviewed by Chemist, Lorenzo Rocca, Ph.D.

4.7.4.1 Are the dissolution profiles similar between debossed and non-debossed tablets using the selected dissolution method for all strengths (0.5, 1, 2, and 3 mg) of Xanax XR?

Yes, the dissolution profiles are similar between the debossed (commercial production) and undebossed tablets using the selected dissolution method for all 4 strengths (0.5, 1, 2, and 3 mg) of Xanax XR. An f_2 test performed by the sponsor indicated all f_2 values for 0.5mg, 1mg, 2mg and 3mg strengths are greater than 80. The results summarized in table below indicate that the debossing does not affect the drug release from the tablets of all 4 strengths (Table 4-13). Details of dissolution profiles can be found in section 7.2.3(page 57).

Table 4-13 Dissolution profile comparisons of debossed and undebossed for all 4 strengths of XR tablets

pH 6.0 phosphate buffer											
0.5mg			1mg			2mg			3mg		
Lot # (debossed)	Lot # (un-debossed)	f2	Lot # (debossed)	Lot # (un-debossed)	f2	Lot # (debossed)	Lot # (un-debossed)	f2	Lot # (debossed)	Lot # (un-debossed)	f2
65565	65517	87	65568	65520	81	65571	65523	85	65574	65526	86
	65518	84		65521	81		65524	100		65527	80
	65519	87		65522	96		65525	84		65528	67

4.8 Analytical Section

4.8.1 Which analytical methods were used in the plasma analyses? Are the methods acceptable? [Hossain’s review; protocol P/2002/0017 (Chou’s review)]

Alprazolam and its primary metabolites, 4-hydroxyalprazolam and α -hydroxyalprazolam, were quantified in human serum or plasma by high performance liquid chromatography (HPLC). The same method was used to measure all three analytes, but only alprazolam was measured in some of the studies included in the PK/BIO development program for XR tablets. The limit of quantification for all three analytes was . Minor modifications were made in the method during the XR tablet development program. Absolute recoveries were determined by comparing peak heights of extracted calibration standards with the peak heights of pure injection standards at each concentration of the calibration curve. Mean recoveries for all three analytes ranged from 78% to 107%; average recovery for the internal standard ranged from 88% to 91%. Overall, the method validation was found to be acceptable in terms of reproducibility, specificity, sensitivity, linearity, precision and accuracy. Details of bioanalytical assay can be found in section 7.3 (page 68)

4.9 DSI inspection (Division file,)

4.9.1 Is the Division of Scientific Investigation inspection requested? Were the results from the Division of Scientific Investigation inspection satisfactory? (Hossain’s review, Division file)

Yes, previously DSI inspection was requested for 3 studies [BE of XR 3mg bid and IR(P/2002/0010); food study (P/2002/0013), BE of 1, 2, and 3mg XR(M/2000/0352)]. The results were found satisfactory.

5 LABELING

5.1 What changes have been made to the approved Xanax IR label that are unique for this XR tablet? Are these changes acceptable?

The sponsor proposed a separate label for the Xanax XR tablet. The sponsor used the label for the marketed Xanax IR formulation as a template and made revisions. The sponsor’s proposed label is included in the Appendix, Section 7.5, page 76).

Text associated with ~~_____~~ dosing should only be included if clinical division agrees to this ~~_____~~ dosing. Text in the "Dosage & Administration" should be modified (see below) if ~~_____~~ dosing is acceptable.

Text associated the significant food effect on the bioavailability of XR tablet should be incorporated in the Pharmacokinetics section.

Text associated the significant circadian variation on the PK profiles of XR tablet should be incorporated in the Pharmacokinetics section.

The sponsor is asked to:

- Insert separate headers of Pharmacodynamics and Pharmacokinetics under the heading of "Clinical Pharmacology" and organize text accordingly.
- Insert headers in the Pharmacokinetics section (Absorption, Distribution, Metabolism, and Elimination) in the label and organize the pharmacokinetics section in this order, then followed by food, diurnal variation (nighttime administration of XR tablet), special populations (such as elderly, pediatrics, hepatic impairment, renal impairment, obesity), gender, race, cigarette smoking, drug-drug interaction. Incorporate information in these regards in the label.
- Incorporate information regarding the interaction between pharmacodynamics (safety/efficacy) and clinical covariates (such as special populations, age, race, drug-drug interaction, food) from the available sources. Sources include, but not limited to, literature and post-marketing experience over the 50 countries outside of U.S. where XR tablet has marketed. We also note some of these information were provided in the Clinical Summary Section of the submission.
- Insert information regarding dose-proportionality and strength equivalency in Pharmacokinetics section.

In addition, the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) proposes the following revisions to the sponsor's proposed label based on the information submitted (unless noted, the proposed text is acceptable to OCPB). Single Strike-through text marks deletions or sponsor's proposed revision from IR label, OCPB's changes of deletion are marked as double strikethrough and new proposed text are marked in bold (in some instance, bold & underlined), unchanged paragraphs in a smaller font size with OCPB proposed text is marked in bold & underlined and normal font size. The text within the bracket "[]" explains the proposed changes, or references. These should not be included in the final label.

CLINICAL PHARMACOLOGY

~~_____~~

~~_____~~

~~_____~~

3 pages redacted from this section of
the approval package consisted of draft labeling

(E)

6 SIGNATURES

Wen-Hwei Chou, Pharm.D., Ph.D. _____

RD/FT initialed by Ramana Uppoor, Ph.D. _____

Division of Pharmaceutical Evaluation I,
Office of Clinical Pharmacology and Biopharmaceutics

OCPB Briefing Date: September 30, 2002

Briefing Attendees: Laughren T; Mehta M; Sahajwalla C; Uppoor R; Gobburu, J; Mishina.E; Chou W

c.c.: NDA 21-346, HFD-120 (Laughren, Levin), HFD-860 (Mehta, Sahajwalla, Uppoor, Gobburu,
Mishina, Chou)

**APPEARS THIS WAY
ON ORIGINAL**