CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-726

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
SUPPLEMENTAL NEW DRUG APPLICATION - REVIEW

NDA:	21-726
Submission Types; Code:	N (AZ) - Major Amendment – Mulitple Discipines Response to Approvable Letter
Submission Date:	November 19, 2004
Generic Name:	Alprazolam Orally Disintegrating Tablets
Trade Name:	NIRIVAM™
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Acting Team Leader:	Sally Yasuda, Pharm.D.
OCPB Division:	Division of Pharmaceutical Evaluation 1 (DPE1) HFD-860
ORM division:	Division of Neuropharmacologic Drug Products (DNDP) HFD-120
Relevant INDs:	63,934
Sponsor:	Schwarz Pharma Milwaukee, WI
Formulation; Strengths:	Orally Disintegrating Tablets; 0.25 mg, 0.5 mg, 1 mg, 2 mg
Route of Administration:	Oral
Indications:	• Short-term relief of the symptoms of anxiety • Management of generalized anxiety disorder • Anxiety associated with depression • Panic disorder, with or without agoraphobia.

1 EXECUTIVE SUMMARY

1.1 CONTENTS OF SUBMISSION

This submission contains the sponsor's complete response to the approvable letter dated October 19, 2003.

The approvable letter included the following items applicable to OCPB that the sponsor has responded to:

- Regulatory Dissolution Method, Specifications, and Acceptance Criteria
- A Phase IV Commitment Request
- Three proposals for additional literature searches and studies to be performed at the sponsor's discretion
- Labeling

The labeling was submitted in electronic format and the remainder of the submission was provided as a hard-copy.

1.2 RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation I (OCPB/DPE-1) has reviewed NDA # 21-726 N(BZ) SN 007 submitted November 19, 2004 and finds this application acceptable provided that satisfactory agreement is reached between FDA and the sponsor regarding labeling.

Phase IV commitments may be found in section 2.2 on page 2, and should be recorded in the appropriate regulatory databases.

Labeling comments may be found in section 2.4 beginning on page 3 and should be communicated to the sponsor as appropriate. In addition, in the 6 column formatted table certain paragraph breaks to indicate a physical space separation in the printed labeling have been removed and should be reinserted as appropriate when the table is converted back to text.

2 REVIEW OF SPONSOR'S RESPONSES

2.1 DISSOLUTION METHOD, SPECIFICATIONS, AND ACCEPTANCE CRITERIA

The sponsor has accepted the following dissolution method, specifications, and acceptance criteria.

Table 1 Dissolution Method, Specifications, and Acceptance Criteria

Apparatus:	USP Apparatus 2, (paddles)
Medium:	70 mM Potassium phosphate buffer, pH 6.0
Temperature:	37.0°C ± 0.5°C
Volume:	500 mL
Rotation Speed:	50 rpm
Sampling Times:	10 minutes
Acceptance Criteria:	Per USP 27– NF 22 <711> Dissolution Acceptance Table for Unit Samples; Q = —

2.2 PHASE IV COMMITMENTS

The sponsor has agreed to the following phase IV request and to fulfill it within 1 year of approval.

/

2.3 ADDITIONAL INFORMATION REQUESTED

1. In addition to proton pump inhibitors, drug interaction studies with other drug classes that raise gastric pH would also provide useful information. However, such studies are not being requested as a phase IV commitment and may be performed at the sponsor's discretion. These other classes include antacids and H2 antagonists.

- The sponsor has agreed to evaluate performing such studies after the results of the phase IV study [redacted] are known.

2. Since dry mouth due to concomitant drugs or other causes might effect the disintegration of the tablets [redacted], the effect of anticholinergic drugs on absorption rate both when administered with and without water is of interest. However, this is not being requested as a phase IV commitment and may be performed at the sponsor's discretion.

- The sponsor has agreed to FDA proposed labeling regarding dry mouth, and may or may not perform *in vivo* studies at their disfcretion.

3. It is recommended that the sponsor perform a literature search examining what changes occur in esophogeal transit, saliva flow and composition, (i.e. pH and ionic composition) in the healthy elderly and what potential effects any differences found in the elderly, or in diseases that commonly occur in the elderly, may have on absorption of alprazolam ODT. The sponsor should also propose labeling changes and/or studies as appropriate. However, studies are not being requested as a phase IV commitment.

- The sponsor will consider the above request.

2.4 LABELING

2.4.1 BACKGROUND AND REGULATORY HISTORY

In the original NDA submission on December 19, 2003 the sponsor proposed labeling that was based on the then available labeling for the innovator's immediate release product, Xanax™. At the time of submission of the ODT NDA the innovator had previously submitted 3 separate labeling supplements that were still under review. Subsequently, these 3 labeling supplements were approved prior to the completion of the review of the alprazolam ODT tablets.

The OCPB reviewer for the ODT tablets was unaware of these labeling supplements for the innovator's tablets and thus did not use the latest labeling as a basis for review. However, the medical division did send the sponsor a labeling proposal in the approvable letter that incorporated the latest changes in the innovator's product labeling as well as most of OCPB's comments for the ODT tablets.

The sequence of these various labeling proposals is shown in Table 2.

Table 2 Timetable of Various Recent Alprazolam Labeling Proposals

NDA	Suppl	Drug Name	Submission Date	Description	OCPB Review	Approval Date
21-726	—	NIRAVAM™ (alprazolam) orally disintegrating tablets	Dec 19, 2003 Mar 25, 2004	Original NDA Submission	Sep 24, 2004	Oct 19, 2004[1]
18-276	SLR 039	Xanax™ (alprazolam) IR Tablets	Oct 1, 2003	Revisions to various additional sections of the Xanax IR Tablet labeling to be consistent with Xanax XR labeling.	—	Apr 2, 2004
18-276	SLR 038	Xanax™ (alprazolam) IR Tablets	Apr 2, 2003	Update to PRECAUTIONS/Drug Interactions section of labeling to include potential drug interactions of alprazolam with sertraline and paroxetine.	Sept 30, 2003	Apr 2, 2004
21-434	SLR 001	Xanax™ XR (alprazolam) Extended-Release Tablets	Mar 11, 2003			Apr 2, 2004

1 Date of approvable letter.

2.4.2 LABELING COMMENTS

The basis of the labeling for the Sponsor's current Alprazolam ODT labeling proposal is thus based on 4 different versions of labeling:

a) The innovator's available labeling for alprazolam IR (Xanax™) tablets
b) The sponsor's proposed changes for alprazolam ODT tablets.
c) OCPB's proposed labeling changes for alprazolam ODT tablets
d) The approved changes to the labeling for the innovator's alprazolam IR (Xanax™) tablets

After the approvable letter was sent the FDA provided an electronic version of FDA's proposed labeling and informed the sponsor that the sponsor only needed to indicate their proposed modifications to the FDA's proposal. However, for ease of comparison and review, this review contains a side by side comparision of the various pertinent versions of labeling along with comments in a 6-column format in section 2.4.3Professional Labeling – 6 Column Format on page 6.

A description of the five versions of labeling included in the side-by-side 6 column formatted table may be found in Table 3 below. In addition, Table 3 provides a guide to how changes are variously highlighted for each version of labeling in the side-by-side 6 column formatted table.

Table 3 Descriptions of Labeling Included in the 6 column Side-by-Side Comparison Along with How Various Proposed Changes are High-lighted

Column	Description	Comments
1	Sponsor's Original Proposed Labeling (Dec 19, 2003) with OCPB Edits (Sept 24, 2004)	• Yellow highlighting indicates differences for the sponsor's proposed labeling compared to the innovator's available labeling for Xanax™ IR tablets. • [redacted] • [redacted] • [redacted]
2	Approved Xanax IR Tablet Labeling as of April 2, 2004	
3	FDA Labeling Proposal from Approvable Letter (Oct 19, 2004)	• FDA comments are included in [red text enclosed in brackets]. • N.B. FDA proposed changes are not otherwise highlighted.
4	Sponsor's Latest Labeling Proposal (Nov 19, 2004))	• Red text highlights sponsor's proposed changes. • [Red text enclosed in brackets indicates comments]. • Single underline indicates the sponsor's proposed addition to labeling • Single ~~strikethrough~~ indicates the sponsor's proposed deletion to labeling
5	OCPB Review of Sponsor's Latest Nov 19, 2004 Labeling Proposal	• Green text highlights additions and deletions proposed by OCPB. • Single underline indicates the reviewer's proposed addition to sponsor's proposed labeling • Single ~~strikethrough~~ indicates the reviewer's proposed deletion to sponsor's proposed labeling
6	Comments	• Comments in greenish-blue text are in reference to the latest OCPB, (current), labeling proposals. • Comments in royal blue text describe changes in the currently approved Xanax™ IR labeling from the previous version of Xanax™ IR labeling that the sponsor and OCPB originally worked from.

The side-by-side 6 column formatted table that includes OCPB's latest proposed labeling revisions may be found in section 2.4.3 Professional Labeling – 6 Column Format on the following pages.

Due to space limitations adverse event tables are not duplicated for each version of labeling.

40 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

__✓ § 552(b)(4) Draft Labeling

3 SIGNATURES

Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D. — Date
Senior Reviewer
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

Sally Yasuda, Pharm.D. — Date
Acting - Team Leader
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

CC List:

NDA 21-726	(orig., 1 copy)
HFD-120	(TalyorR, TeleC, OliverT, LevinR, LaughrenT, KatzR)
HFD-860	(KavanaghR, YasudaS, BawejaR, RahmanA, MehtaM)
CDR	(Barbara Murphy)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ron Kavanagh
1/12/05 11:19:58 AM
BIOPHARMACEUTICS

Sally Yasuda
1/12/05 11:34:03 AM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
NEW DRUG APPLICATION - REVIEW

NDA:	21-726
Submission Types; Code	N N(C) BB
Submission Dates:	December 19, 2003 - N March 25, 2004 - N(C) September 15, 2004 - BB
Brand Name	— (Proposed)
Generic Name	Alprazolam Orally Disintegrating Tablets
Reviewer	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Acting Team Leader	Sally Yasuda, Pharm.D., Ray Baweja, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation 1 (DPE1) HFD-860
ORM division	Division of Neuropharmacologic Drug Products (DNDP) HFD-120
Relevant INDs	63,934
Sponsor	Schwarz Pharma Milwaukee, WI
Formulation; Strengths	Orally Disintegrating Tablets; 0.25 mg, 0.5 mg, 1 mg, 2 mg
Route of Administration	Oral
Indications	• Short-term relief of the symptoms of anxiety • Management of generalized anxiety disorder • Anxiety associated with depression • Panic disorder, with or without agoraphobia.

1 EXECUTIVE SUMMARY

1.1 BACKGROUND

1.1.1 PRIOR REGULATORY HISTORY

Alprazolam is a benzodiazepine that is currently approved as immediate release tablets in strengths of 0.25 mg, 0.5 mg, 1 mg, and 2 mg as Xanax® from Pharmacia-UpJohn.

Alprazolam is indicated for the management of anxiety disorders, including generalized anxiety disorder, (GAD), anxiety associated with depression, and panic disorder with or without agoraphobia.

Dosing is initiated with a dose of 0.5 mg three times daily, and depending on the response, the dose may be increased at intervals of 3 to 4 days in increments of no more than 1 mg per day. For GAD and anxiety associated with depression the maximum labeled dose is 4 mg/day. For panic attacks the maximum approved dose is 10 mg/day in 3 – 4 divided doses distributed as evenly as possible throughout the waking hours.

1.1.2 PRESENT SUBMISSION

The present submission is for a new dosage formulation of alprazolam, i.e. an orally disintegrating tablet in the same strengths as the approved immediate release tablets. In contrast to regular immediate release tablets, orally disintegrating tablets disintegrate when placed in the mouth and are intended to be taken with or without water.

Other orally disintegrating tablets have been formulated as lyophilized tablets. In contrast alprazolam ODT is formulated by

The sponsor proposes approval based on bioequivalence criteria. Since this isn't the same dosage formulation as the reference product this review is conducted by the Office of Clinical Pharmacology and Biopharmaceutics rather than the Office of Generic Drugs. Consequently, no clinical efficacy or safety studies have been submitted for a clinical section and the only human data that this NDA contains is included in the HUBIO clinical pharmacolgy section.

The sponsor of the present submission references the innovator's pharmacology/toxicology and clinical data to the maximum extent allowable.

The two lower strengths and the two higher strengths of the proposed product use different % weight qualitative/quantitative compositions. Consequently, 2 bioequivalence studies to the innovator's product have been performed, each utilizing an orally disintegrating tablet with a different % weight qualitative / quantitative composition, and waiver requests have been submitted for the other two compositionally proportionate strengths.

Each bioequivalence study has been performed with the orally disintegrating tablet administered with and without water. In addition, a food effect study has also been performed with a single orally disintegrating tablet strength.

1.2 RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation I (OCPB/DPE-1) has reviewed NDA # 21-726 submitted December 19, 2003 and March 25, 2004.

OCPB finds this application acceptable provided that satisfactory agreement is reached between FDA and the sponsor regarding the dissolution method, specifications, and labeling.

Comments should be communicated to the sponsor as appropriate:

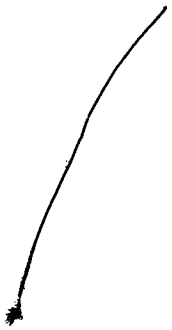
(See Section 3.2 on page 6).

Labeling comments should also be communicated to the sponsor as appropriate:

(See Section 3.3 Labeling Comments on page 7).

1.3 PHASE IV COMMITMENTS

The sponsor is requested to commit to the following phase IV request;



2 CPB FINDINGS

How does the formulation used in the pivotal bioequivalence studies compare to the to-be-marketed product?

The qualitative / quantitative compositions of the alprazolam orally disintegrating tablets used in the pivotal clinical bioequivalence studies and the food effect study are the same as the to-be-marketed formulation.

Are alprazolam 1 mg orally disintegrating tablets bioequivalent to the Reference Labeled Drug; (Xanax™ 1 mg IR tablets)?

Yes. The mean Cmaxs and AUCs of the 1 mg orally disintegrating tablet are in the range of 92.5% to 95% of the reference labeled drug whether administered with or without water. There were minor differences in median Tmax, (difference of medians 0.2 – 0.4 hours), that are unlikely to be clinically significant.

Are alprazolam 0.5 mg orally disintegrating tablets bioequivalent to Xanax™ 0.5 mg IR tablets?

Yes. The mean Cmaxs and AUCs of the 1 mg orally disintegrating tablet are in the range of 89.0% to 96% of the reference labeled drug whether administered with or without water. There were differences in median Tmax, (difference of medians 0.56 – 0.88 hours), that are unlikely to be clinically significant.

How does administration with and without water affect the rate of absorption of alprazolam orally disintegrating tablets, and are differences likely to be clinically significant?

The rate of absorption as indicated by Tmax is fastest for Xanax™ IR tablets, slightly slower for alprazolam orally disintegrating tablets when taken with water, and even slower when taken without water. However, the differences in the Tmaxs are not very large as shown below:

Table 1 Comparison of Tmax for Aprazolam ODT to Tmax for Xanax IR Tablets

Tablet Strength	Median Tmax and Ranges (hours)			Median Difference in Tmax with Alprazolam ODT Compared to Xanax IR Tablets (hours)	
	Xanax	Alprazolam ODT			
		With Water	Without Water	With Water	Without Water
0.5 mg	1.775	2.0	2.25	0.25	0.38
1 mg	0.75	1.5	2.0	0.5	0.75

As alprazolam is administered in divided daily doses for anxiety and panic attacks rather than on an as needed basis, (i.e. prn), it's *unlikely that the differences in Tmax are clinically important.* This is supported by studies demonstrating the effectiveness of Xanax XR sustained release tablets being efficacious for panic attacks with and without agoraphobia, as Xanax XR, tablets have a Tmax of around 7 hours with relatively constant concentrations between 5 and 11 hours post dose. Although there were failed studies with Xanax XR, these studies limited the dosage range to lower doses of up to only 4 mg or 6 mg as per the reviews for Xanax XR, (NDA 21-434).

Is a biowaiver appropriate for the 0.25 mg and 2 mg strengths of alprazolam orally disintegrating tablets?

Biowaivers are granted based on the following criteria:

- The 0.25 mg and 0.5 mg tablet strengths and the 1 and 2 mg tablet strengths are compositionally proportional.
- Tablet dissolution is comparable between different strengths
- Alprazolam pharmacokinetics appear to be linear from 0.5 to 10 mg po

What is the effect of food on the bioavailability of alprazolam orally disintegrating tablets and is it likely clinically significant?

When the 1 mg ODT was administered with food there was *no change in the extent* of absorption, however there was approximately *a 25% decrease in the Cmax, (range 16 – 31%), that is apparently due to a slower rate of absorption that also results in an average delay in Tmax of over 2 hours.*

There are also secondary delays in the Tlag and Tmax for hydroxy-alprazolam.

The degree of clinical significance of the food effect is hard to assess from the available information, but *should be manageable with descriptive labeling*. It has been suggested in the literature by Greenblatt et al. that efficacy of alprazolam may be related to plasma concentrations and that these should be monitored. However, labeling for Xanax™ XR indicated that it has a Tmax that is several hours later than for Xanax™ IR tablets and that there is a food effect resulting in a shorter Tmax and 25% increase in Cmax, yet when the formulation is switched dosing is kept the same and dosage is retitrated if necessary. Since the PK differences when Xanax™ formulations are switched are likely in the same range as the food effect with alprazolam ODT and since efficacy is likely time averaged. It appears that descriptive labeling that gives the prescriber guidance regarding the magnitude of the food effect should be sufficient.

How do various intrinsic and extrinsic factors affect bioavailability?

After the filing meeting a request was sent to the sponsor to address the effect of salivary pH, and also dry mouth due to anticholinergic effects on absorption rate; as alprazolam's solubility is pH dependent and since patients with anxiety disorders may also be taking drugs that have anticholinergic side effects.

Salivary pH

Alprazolam orally disintegrating tablet are formulated differently than other orally disintegrating tablet formulations.

Other orally disintegrating tablets have been formulated as lyophilized tablets, thus in the presence of dry mouth when taken without water the drug substance may take several hours, (5 – 6 hours) before drug reaches the small intestines and absorption begins.

In contrast alprazolam ODT is formulated by

The average pH of saliva has been variously reported as between 5.5 and 7.5, with it most commonly reported in the low 7s. Standard deviations are generally small, on the order of 0.1 pH unit. Since the ——— ., the pH of the mouth could effect disintegration rate and possibly dissolution rate. The biggest problem would be if dissolution is enhanced and higher peaks are produced due to oral mucosal absorption. Although the BE study suggests this isn't a problem in healthy volunteers.

Dry Mouth and Anticholinergics

Alprazolam orally disintegrating tablets are likely to be administered concurrently with tricyclic antidepressants in patients with depression and GAD. Since TCAs have significant anticholinergic effect,s dry mouth in patients taking alprazolam ODT would not be unusual. *Dry mouth might effect the disintegration of the tablets ....* ——— ——— *./. Currently, the effect of anticholinergics on oral disintegration, mouth feel, and absorption rate when taken both with and without water is unknown.* Management has suggested that the sponsor may wish to pursue this at the sponsor's discretion.

Drugs that Affect Gastric pH

Due to the pH dependency of the dissolution rate of alprazolam orally disintegrating tablets, *drugs that raise gastric pH may effect absorption rate and should be examined to determine the extent of the effect, and to guide possible labeling changes.* Drug classes that would be of interest include the following:

- Proton Pump Inhibitors
- H2 Antagonists
- Antacids

Drugs of particular interest include those that might raise gastric pH for durations long enough such that all the pareils might pass out of the gut and into the small intestine where they might not be dissolved, i.e. proton pump inhibitors, although effects of all three drug classes would be interest.

Gender

There was no effect of gender.

Race

There were too few non-Caucasians of other races to determine if there was an effect.

Age

There was no effect of age over the range of 18 to 50 years old. However, subjects greater than 50 years of age were not studied. A brief pubmed search revealed that although stimulated salivary flow is decreased, baseline salivary flow is unchanged in the elderly. Thus salivary volume is not a concern in the healthy elderly. This pubmed search also revealed that there might be changes in salivary pH and composition. Plus there is a possibility that esopheal motility might change in the elderly. The information available from the abstracts in pubmed was too incomplete to form any opinions on whether any of these factors are truly linked to increasing age or to comorbid diseases, the degree of any changes, or if they're likely to effect bioavailability. Consequently, it would be useful if the sponsor could perform a literature review to help address these potential issules. Management has suggested that the sponsor may wish to pursue this at the sponsor's discretion.

Smoking

All subjects were non-smokers so the influence of smoking could not be determined.

Are there any adverse effects specific to this formulation and method of administration?

This issue is being addressed by the medical safety reviewer.

Are the proposed dissolution method and acceptance criteria acceptable?

The dissolution method is largely acceptable. However, *the single point sampling time should be 10 minutes rather than 30 minutes as proposed*, with a Q of —.

3 COMMENTS FOR SPONSOR

3.1 COMMENTS ALREADY CONVEYED

None.

3.2 COMMENTS TO BE CONVEYED

3.2.1 GENERAL COMMENTS

Biowaivers for the 0.25 mg and 2 mg alprazolam orally disintegrating tablet strengths are granted.

3.2.2 DISSOLUTION METHOD, SPECIFICATIONS, AND ACCEPTANCE CRITERIA

Please adopt the following dissolution method, specifications, and acceptance criteria for all strengths of alprazolam orally disintegrating tablets.

Table 2 Dissolution Method, Specifications, and Acceptance Criteria

Apparatus:	USP Apparatus 2, (paddles)
Medium:	70 mM Potassium phosphate buffer, pH 6.0
Temperature:	500 mL
Volume:	37.0°C ± 0.5°C
Rotation Speed:	50 rpm
Sampling Times:	10 minutes
Acceptance Criteria:	Per USP 27– NF 22 <711> Dissolution Acceptance Table for Unit Samples; Q = —

3.2.3 PHASE IV COMMITMENTS

The sponsor is requested to commit to the following phase IV request and to fulfill it within 1 year of approval or approvability, whichever is earlier.

3.2.4 ADDITIONAL INFORMATION REQUESTED

1. In addition to proton pump inhibitors, drug interaction studies with other drug classes that raise gastric pH would also provide useful information. However, such studies are not being requested as a phase IV commitment and may be performed at the sponsor's discretion. These other classes include antacids and H2 antagonists.

2. Since dry mouth due to concomitant drugs or other causes might effect the disintegration of the tablets [redacted] the effect of anticholinergic drugs on absorption rate both when administered with and without water is of interest. However, this is not being requested as a phase IV commitment and may be performed at the sponsor's discretion.

3. It is recommended that the sponsor perform a literature search examining what changes occur in esophogeal transit, saliva flow and composition, (i.e. pH and ionic composition) in the healthy elderly and what potential effects any differences found in the elderly, or in diseases that commonly occur in the elderly, may have on absorption of alprazolam ODT. The sponsor should also propose labeling changes and/or studies as appropriate. However, studies are not being requested as a phase IV commitment.

3.3 LABELING COMMENTS

Labeling comments in a three-column format follow:

The first column is the innovator's current approved labeling. The second column is the sponsor's proposed labeling and the third column contains comments.

The following editorial marks are used in the labeling comments to indicate various changes:

Places where the innovator's current approved labeling and the sponsor's proposed labeling differ are indicated by [redacted], and yellow highlighting for the sponsor's proposed labeling. Additions and deletions proposed by OCPB are highlighted in blue.

Differences between the sponsor's proposed labeling and the innovator's labeling generally tend to be either those that are related to differences in the products themselves, or minor changes in formatting. Not all changes in formatting are highlighted or noted.

Regarding the reviewer's proposed changes.

Single underline indicates the reviewer's proposed addition to sponsor's proposed labeling
Single ~~strikethrough~~ indicates the reviewer's proposed deletion to sponsor's proposed labeling

35 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

__ § 552(b)(4) Draft Labeling

4 SIGNATURES

Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D. — Date
Senior Reviewer
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

Sally Yasuda, Pharm.D. — Date
Acting - Team Leader
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

4.1 OCPB BRIEFING MEETING:

Date:	September 20, 2004
Time:	Noon
Location:	WOC2 Conference Room C
Level:	Optional Intra-division
Attendees:	Atrakchi, Aisar; Levin, Robert; KavanaghR, YasudaS, KofiK RahmanA, MehtaM, UppoorR

4.2 CC LIST:

NDA 21-726	(orig., 1 copy)
HFD-120	(TalyorR, LevinR, TeleC, OliverT, AndreasonP, LaughrenT, KatzR)
HFD-860	(KavanaghR, YasudaS, BawejaR, RahmanA, MehtaM)
CDR	(Barbara Murphy)

Table of Contents

LIST OF TABLES

LIST OF FIGURES

5 REVIEW

5.1 STUDIES SUBMITTED AND REVIEWED

The sponsor has submitted 3 clinical studies, 2 bioequivalence studies relative to the reference drug product Xanax® (alprazolam Immediate release tablets), and a food effect study.

Table 3 Clinical Studies with Alprazolam Orally Disintegrating Tablets – (N21-726)

Study	Title
SP765	A Pharmacokinetic Study to Evaluate the Bioequivalence of a Unique New Formulation (Test), Orally Disintegrating Tablet (ODT) of Alprazolam 0.5 mg, Administered with and Without Water, Compared to a Marketed Immediate Release Alprazolam 0.5 mg Tablet Formulation (Reference), Xanax® by Pharmacia and UpJohn
SP691	A Pharmacokinetic Study to Evaluate the Bioequivalence of a Unique New Formulation (Test), Orally Disintegrating Tablet (ODT) of Alprazolam 1 mg, Administered with and Without Water, Compared to a Marketed Immediate Release Alprazolam 1 mg Tablet Formulation (Reference), Xanax® by Pharmacia and UpJohn
SP766	A Pharmacokinetic Study to Evaluate the Effect of Food on the Bioavailability of a 1.0 mg Alprazolam Orally Disintegrating Tablet

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

5.2.2.1 Appearance

Table 4 Appearance of Proposed Alprazolam Dosage Forms

Strength	0.25 mg	0.5 mg	1 mg	2 mg
Dosage Form	Orally Disintegrating Tablet	Orally Disintegrating Tablet	Orally Disintegrating Tablet	Orally Disintegrating Tablet
Release	Immediate Release	Immediate Release	Immediate Release	Immediate Release
Tablet Diameter	¼"	5/16"	5/16"	3/8"
Tablet Weight	100 mg	200 mg	200 mg	400 mg
Tablet Shape	round	round	round	round
Tablet Press Tooling				
Tablet Color	Yellow	Yellow	White	White
Tablet Coating	None	None	None	None
Tablet Engravure (top side)	SP321	SP322	SP323	SP324
Tablet Engravure (bottom side)	0.25	0.5	1	2
Tablet Scored	Yes	Yes	Yes	Yes

APPEARS THIS WAY
ON ORIGINAL

5.2.2.2 Qualitative / Quantitative Formulations

5.2.2.2.1 Coated Alprazolam Intermediate

The qualitative / quantitative composition and batch formula of the alprazolam [redacted] are shown in Table 5.

Table 5 Qualitative / Quantitative composition and Batch Formula of Alprazolam [redacted] Active)

Ingredient	Reference	Role	% w/w	Quantity (mg/g)	Quantity per Batch (Kg)
Alprazolam	USP	Active pharmaceutical ingredient			
[redacted]					
Magnesium Stearate,	NF/EP/JP				
[redacted]					
Total	—	—	100.00	1000.00	

1

Selected in-house acceptance criteria for the alprazolam [redacted] are shown in Table 6.

Table 6 Selected In-House Attributes and Acceptance Criteria for Alprazolam [redacted]

Attribute	Acceptance Criteria	Method
Alprazolam Content (% w/w)		562
Dissolution of [redacted]		587
Particle Size		SOP

1 This corresponds to a range of [redacted] of the theoretical % weight of [redacted]
2

5.2.2.2.2 Final Dosage Form

5.2.2.2.2.1 To Be Marketed Formulations

The sponsor's claimed qualitative / quantitative compositions of the commercial tablets and their batch formulae are shown in Table 7. According to the sponsor any discrepancies between the % weight and the total batch quantity information presented and information obtained via calculations are due to rounding.

Table 7 Qualitative / Quantitative Compositions of Alprazolam Orally Disintegrating Tablets

Ingredient	Reference	Role	Quantity per Tablet (mg)				% w/w				Quantity per Batch (kg)			
Tablet Strength (mg)			**0.25**	**0.5**	**1**	**2**	**0.25**	**0.5**	**1**	**2**	**0.25**	**0.5**	**1**	**2**
Alprazolam (Active)[1]	—	Active												
Mannitol	USP													
Mannitol	USP/EP/JP													
Crospovidone	NF/EP/JPE													
Microcrystalline Cellulose,	NF/EP/JP													
Magnesium Stearate,	NF/EP/JP													
Natural & Artificial Orange Flavor	—	Flavor												
Sucralose	NF	—												
Colloidal Silicon Dioxide	NF/EP/JP	—												
Yellow Iron Oxide	—	Color												
Total	—	—	**100.00**	**200.00**	**200.00**	**400.00**	100.00	100.00	100.00	100.00				
Number of Tablets per Batch	—	—	—	—	—	—	—	—	—	—				

1

2

5.2.2.2.3 Clinical Trial Formulations

The qualitative / quantitative compositions of the alprazolam orally disintegrating tablets used in the pivotal clinical bioequivalence studies and the food effect study are shown in Table 8. As indicated by the numbers in bold in Table 8 there is a discrepancy between the sponsor's claimed drug content and the actual drug content that results in slightly different dosages than being administered in the pivotal studies than the dosages claimed. These discrepancies of — o are unlikely to alter the finding of regarding bioequivalence.

Table 8 Qualitative / Quantitative Composition of Alprazolam Orally Disintegrating Tablets Used in Pivotal Clinical Bioequivalence Studies

Ingredient	Amount (mg/tablet)		% w/w		Reference
Strength	**0.5 mg**	**1 mg**	**0.5 mg**	**1 mg**	
Lot Number	720395B1	720397B1	720395B1	720397B1	—
Studies Used In	Pivotal 0.5 mg (SP765) & 1.0 mg (SP691) BE Studies & Food Effect Study (SP766, 1.0 mg)				—
Alprazolam Lot Number Used	720564	720565	—	—	—
Batch Size			—	—	—
Alprazolam Content			—	—	—
alculated amount of s needed					—
Calculated amount of Mannitol needed					—
Amount of alprazolam used compared to calculated amount			—	—	—
Alprazolam[1]					—
Mannitol					USP
					USP/EP/JP
Crospovidone					NF/EP/JPE
Microcrystalline Cellulose					NF/EP/JP
Magnesium Stearate					NF/EP/JP
Natural & Artificial Orange Flavor					—
Sucralose					N
Colloidal Silicon Dioxide					NF/EP/JP
Yellow Iron Oxide					—
Total	200.00	200.00	100.00	100.00	—

1 According to sponsor amount is based on actual potency of alprazolam
2 According to sponsor amount is based on actual potency of alprazolam

5.2.2.3 Dissolution

5.2.2.3.1 Sponsor's Proposed Dissolution Method and Selected Acceptance Criteria

The sponsor's proposed dissolution method and selected acceptance criteria are shown in Table 9 and Table 10 respectively. For comparison, Table 9 also shows the USP method (USP XXVII / NF 22) for alprazolam IR tablets. Differences between the two methods are *italicized and highlighted*.

Table 9 Comparison of Sponsor's Proposed Dissolution Method for Alprazolam Orally Disintegrating Tablets and USP Method for Alprazolam Immediate Release Tablets

Parameter	Proposal for Oral Disintegrating Tablets	USP Method for Alprazolam IR Tablets
Apparatus:	*USP Apparatus 2, paddles*	*USP Apparatus 1, basket*
Medium:	70 mM Potassium phosphate buffer, pH 6.0	70 mM Potassium phosphate buffer, pH 6.0
Volume:	500 mL	500 mL
Temperature:	37.0°C ± 0.5°C	37.0°C ± 0.5°C
Paddle Speed:	*50 rpm*	*100 rpm*
Sampling Time (Single):	30 minutes	30 minutes
Sampling Time (Profile):	5, 15, 30, and 45 minutes	
Sampling Volume:	5 mL	

The proposed dissolution sample sizes and specification limits shown in Table 10 are consistent with USP requirements for immediate release formulations.

Table 10 Sponsor's Proposed Specifications for Alprazolam Orally Disintegrating Tablets:

Test	Specification	Method
Assay	label claim	ATM-561
Content Uniformity		ATM -561
Disintegration Time	Average NMT	ATM-213
Dissolution	Q= at 30 minutes 1) NMT than (n=6) 2) Average NLT , NMT , (n=12) 3) Average NLT NMT and NMT , (n=24)	ATM-571

5.2.2.3.1.1 Dissolution Method Development

Development of the dissolution method began with the USP method for alprazolam IR tablets with varying media, i.e. 50 ml of media in USP apparatus I (basket) at 100 rpm, utilizing the highest and next to lowest strength tablets, i.e. 2 mg and 0.5 mg tablets.

Figure 1 and Figure 2 show the results of these experiments. Based on the data from Figure 1 for the 0.5 mg tablets, the sponsor eliminated pH 4.5 and below as it resulted in too rapid dissolution and lack of discrimination, and pH 7.4 due to insolubility. Between these extremes dissolution was pH dependent.

Based on the data from Figure 2 for 2.0 mg tablets the sponsor claimed that the pHs above 6.0 were not feasible as drug was not totally released. However, the volume was only 500 ml and could have been increased. Based on these experiments the sponsor also switched to USP apparatus 2, (paddle), as there was

However, data from Figure 3 for 2.0 mg tablets using type 2 apparatus, (paddle), indicates that the lack of complete dissolution is at least partly artifactual as comparison of dissolution data for 2.0 mg tablets at pH 6.2 and 100 rpm shows that complete dissolution can be achieved with simply a change in apparatus. In addition, the much slower dissolution at pH 6.6 might be minimized by using a larger volume of media. Figure 4 indicates that pHs at 6.2 are too acidic for the 0.5 mg tablets as dissolution is essentially complete by 15 minutes for 0.5 mg tablets.

Thus going to a pH higher than 6.2 and a volume greater than 500 ml is a logical next step in order to try to achieve a discriminatory method for all tablet strengths. However, it should be noted that the lowest strength 0.25 mg tablets were not examined. Thus even if the method is discriminatory for the 0.5 mg tablets, there may still be too rapid dissolution of the 0.25 mg tablets and a lack of discriminatory power. Thus it's likely that slight differences in the dissolution methods used for the 0.25 mg and 0.5 mg tablets as compared with the method for the 1.0 mg and 2.0 mg tablets would be appropriate.[2]

5.2.2.3.1.2 Dissolution Data for Pivotal Bioequivalence Batches

The sponsor provided comparative dissolution profiles for all four tablet strengths using the proposed dissolution method, and using the proposed method with varying media. The media used included pH 1.0 HCl, and pH 4.5 and 6.8 buffers as recommended in the pre-NDA meeting. The 0.5 mg and 1.0 mg tablet experiments utilized tablets from the pivotal bioequivalence studies.

The results are shown in Table 11. Unfortunately, the sponsor did not examine appropriate pH ranges for comparison, (i.e. between 6.0 to 6.8 in 0.1 – 0.2 unit increments). As expected pH 1.0 and 4.5 media resulted in essentially complete dissolution within 5 minutes and nondiscriminatory profiles as would be expected based upon the previously available information. In addition, 500 ml of pH 6.8 media failed to give complete dissolution at 60 minutes for any strength.

In additional comments to the sponsor to a teleconference held June 26, 2003, pre-NDA meeting package submitted 05/22/2003, [Reference - DFS File: PIND 63,934 M 000 April 23, 2003]; the sponsor was encouraged to reevaluate whether the dissolution sampling times of less than 30 minutes, i.e. 15 minutes would be appropriate.

In the current submission, the sponsor's proposed regulatory method, (i.e. 70 mM pH 6.0 phosphate buffer at 30 minutes), is totally nondiscriminatory as dissolution is essentially complete by 10 minutes. However, a 5 minute sampling point might allow sufficient discriminatory power to detect manufacturing problems for all but the 0.25 mg tablets. In general dissolution for this product is so rapid that only very, very large delays in dissolution are likely to have any effect on absorption characteristics. Upon discussion with OCPB management it was decided that a 10 minute dissolution time would be proposed

2 n = 3 tablets per experiment

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

5.2.2.3.1.3 Half-Tablet Dissolution

The need for dissolution data for half-tablets was discussed with the sponsor during the pre-NDA phase of development as all strengths are scored and justification for not providing such data was requested. However, no such justification was provided.

In this reviewer's opinion there is no need for half-tablet dissolution profiles, for the following reasons:

- Alprazolam orally disintegrating tablets disintegrate rapidly in the oral cavity
- Dissolution likely does not occur until reaching the stomach and then occurs within minutes
- Absorption of dissolved drug is likely rate limited by GI transit to the duodenum

Consequently, there should be no clinically significant difference in dissolution and absorption *in vivo* whether half-tablets or whole tablets are taken.

N.B. All strengths of the innovator's IR tablets are scored.

5.2.2.4 Disintegration – *In Vitro*

Disintegration has been measured both *in vitro* and *in vivo*. The sponsor's *in vitro* internal specification is a mean of NMT —— . As dissolution is so rapid and is used as a specification there is no need for a regulatory disintegration specification for OCPB's purposes.

5.2.3 BIOANALYSIS

All 3 studies utilized the same assay method and the assay validation is acceptable, (see Appendix 1).

Based on the QC plots there appears to be some minor systematic intraassay bias that occurs on a cyclic basis. However the degree of bias is typically only a few percent. Consequently, the assayed samples are acceptable.

QC plots of diluted QC samples with concentrations higher than the highest standard, (i.e. > 15 ng/ml), indicate that dilution and quantitation of those samples with concentrations higher than the upper limit of the standard curve are acceptable.

5.2.3.1 DSI Inspection Report

On September 23, 2004 OCPB received a memo from the Division of Scientific Investigations to Dr. Russell Katz dated September 10, 2004 regarding study SP691, the pivotal bioequivalence study to the reference labeled drug, Xanax 1 mg.

DSI found that 1 of 2 low QC samples for Hydroxy-alprazolam were unacceptable in 5 out of 21 analytical runs, (76% of runs) They also noted that the concentrations of the low QC samples were 0.15 ng/ml whereas the average peak concentrations were around 0.45 ng/ml. Thus the hydroxy-alprazolam concentrations and metrics cannot be considered reliable.

Although hydroxy-alprazolam might have some activity, both hydroxy-alprazolam mean peak concentrations and total exposures are less than 5% of those of alprazolam. Thus hydroxy-alprazolam is unlikely to significantly add to the pharmacologic effects of alprazolam. Second, hydroxy-alprazolam is likely formation rate limited thus exposure to it is likely driven by alprazolam's kinetics. Finally, metabolite kinetics are inherently more variable than the kinetics of parent drugs thus metabolite kinetics are generally not used to establish bioequivalence, unless there is a compelling reason, e.g. they produce a major portion of the pharmacologic effects.

In conclusion, the issues identified with the analysis of hydroxy-alprazolam should not alter the conclusion of bioequivalence.

Although there were no comments on the other pivotal BE study for the 0.5 mg tablets, considering the type of findings in this report, the biopharmaceutic properties of the drug, the dose proportionality, and clinical use. No clinically significant problems are expected.

5.3 PHARMACOKINETICS

5.3.1 BIOEQUIVALENCE WITH AND WITHOUT WATER

5.3.1.1 Bioequivalence - 1.0 mg Tablets – Study SP691

The reference labeled drug is Xanax™ (alprazolam) 1.0 mg IR tablets.

The 1.0 mg Alprazolam Orally Disintegrating Tablets administered both with and without water were bioequivalent to Xanax™ 1.0 mg tablets with respect to both Cmax and AUC∞. Although, the Cmaxs and AUC∞s for the ODTs did tend to be 5 – 7.5% lower on average than for Xanax™ tablets. There was also a clear lengthening in the time to reach Tmax, going from a median of 1.775 hours with Xanax 1.0 mg tablets to 2.0 hours with the ODT formulation administered with water, to 2.25 hours when the ODT formulation was administered without water, (see Table 12). This delay in Tmax is most likely due to differences in the rate of absorption.

As alprazolam is administered in divided daily doses for anxiety and panic attacks rather than on an as needed basis, (i.e. prn), it's unlikely that the differences in Tmax observed under these conditions are clinically important. This is supported by studies demonstrating the effectiveness of Xanax XR sustained release tablets being efficacious for panic attacks with and without agoraphobia, as Xanax XR, tablets have a Tmax of around 7 hours with relatively constant concentrations between 5 and 11 hours post dose. Although there were failed studies with Xanax XR, these studies limited the dosage range to lower doses of up to only 4 mg or 6 mg, (see reviews for NDA 21-434).

Pharmacokinetic metrics for hydroxy-alprazolam were also similar between the 3 treatments, (see Table 14).

N.B. After completion of the OCPB breifing an amendment to the NDA was received. The sponsor reports that some of the data in study SP691for hydroxy-alprazolam was reported incorrectly, although the data for alprazolam is correct. This was verified for the pharmacokinetic metrics but not for the raw concentration data. Table 13 and Table 15 contain the corrected summary statistics. The minior discrepancies for alprazolam are due to rounding errors, whereas differenences for hydroxy-alprazolam are due to minor changes in the data as well as rounding errors. Comparison of the corrected data with the original data in Table 12 and Table 14 indicate that the differences are too small to result in any change in conclusions.

Table 12 Comparative Pharmacokinetic Metrics of Alprazolam after Administration of Alprazolam ODT 1.0 mg with and without Water, and Xanax® 1.0 mg - Protocol SP691[1]

	Summary Statistics			LN Means			Geometric Mean Ratios (90% CI)	
	C	A	B	C	A	B	A:C	B:C
	Xanax 1 mg	Alprazolam ODT 1 mg with H_2O	Alprazolam ODT 1 mg without H_2O	Xanax 1 mg	Alprazolam ODT 1 mg with H_2O	Alprazolam ODT 1 mg without H_2O	Alprazolam ODT 1 mg with H_2O : Xanax 1mg	Alprazolam ODT 1 mg without H_2O : Xanax 1 mg
	Reference	Test A	Test B	Reference	Test A	Test B	Test A : Reference	Test B : Reference
Tlag (hours)	0.26 ± 0.06 (21.3) 0.25 - 0.5 [0.25]	0.25 ± 0.0 (0.0) 0.25 - 0.25 [0.25]	0.28 ± 0.09 (31.0) 0.25 - 0.5 [0.25]	—	—	—	—	—
Tmax (hours)	1.71 ± 0.84 (49.6) 0.5 - 3.01 [1.775]	1.91 ± 0.87 (45.69) 0.75 - 4.00 [2.00]	2.1 ± 1.06 (50.4) 0.25 - 4.0 [2.25]	—	—	—	0.21 ± 1.3 (622.8) -2.26 - 3.0 [0.25]	0.40 ± 1.4 (344.4) -2.76 - 3.50 [0.38]
Cmax (ng/ml)	15.5 ± 2.2 (14.1) [15.2]	14.4 ± 2.1 (14.7) [14.4]	14.5 ± 2.6 (17.9) [14.7]	2.73	2.65	2.66	92.5 87.9 - 97.4	93.1 88.4 - 98.0
AUC(0-inf) (ng/ml x hr^{-1})	267.7 ± 76.0 (28.4) 152.1 - 476.2 [244.7]	249.0 ± 69.7 (28.0) 140.0 - 399.3 [245.0]	254.7 ± 76.1 (29.9) 142.7 - 454.9 [238.1]	5.56	5.48	5.51	92.7 89.6 - 96.0	94.8 91.6 - 98.2
AUC(0-t) (ng/ml x hr^{-1})	259.0 ± 66.8 (25.8) 148.4 - 430.4 [241.8]	241.5 ± 64.2 (26.6) 137.4 - 372.0 [242.0]	246.6 ± 69.1 (28.0) 140.4 - 420.8 [232.8]	—	—	—	—	—
Ratio AUC(0-t) : AUC(0-inf)	0.97 ± 0.02 (2.35) 0.90 - 0.99 [0.98]	0.97 ± 0.02 (1.80) 0.93 - 0.99 [0.98]	0.97 ± 0.02 (1.81) 0.93 - 0.99 [0.98]	—	—	—	—	—
t½ (hours)	12.8 ± 3.28 (25.7) 8.68 - 21.4 [11.5]	12.4 ± 3.1 (25.0) 8.0 - 18.8 [11.8]	12.5 ± 3.05 (24.5) 7.9 - 19.2 [11.6]	—	—	—	—	—

1 Values are Mean ± SD, (%CV), range, [median]

Table 13 Corrected Comparative Pharmacokinetic Metrics of Alprazolam after Administration of Alprazolam ODT 1.0 mg with and without Water, and Xanax® 1.0 mg - Protocol SP691[1]

	Summary Statistics			LN Means			N
	C	A	B	C	A	B	
	Xanax 1 mg	Alprazolam ODT 1 mg with H_2O	Alprazolam ODT 1 mg without H_2O	Xanax 1 mg	Alprazolam ODT 1 mg with H_2O	Alprazolam ODT 1 mg without H_2O	
	Reference	Test A	Test B	Reference	Test A	Test B	
Tlag (hours)	—	—	—	—	—	—	20 / 20 / 21
Tmax (hours)	1.71 ± 0.84 (49.6) 0.50 - 3.01 [1.78]	1.91 ± 0.87 (45.7) 0.75 - 4.00 [2.00]	2.15 ± 1.05 (49.1) 0.25 - 4.00 [2.50]	—	—	—	20 / 20 / 21
Cmax (ng/ml)	15.48 ± 2.19 (14.1) [15.23]	14.39 ± 2.12 (14.7) [14.42]	14.49 ± 2.53 (17.5) [14.66]	2.73 ± 0.13 (4.9) [2.72]	2.66 ± 0.15 (5.7) [2.67]	2.66 ± 0.17 (6.5) [2.68]	20 / 20 / 21
AUC(0-inf) (ng/ml x hr^{-1})	267.66 ± 75.96 (28.4) 152.10 - 476.16 [244.69]	249.03 ± 69.73 (28.0) 139.95 - 399.27 [245.03]	252.87 ± 74.63 (29.5) 142.74 - 454.91 [235.93]	5.55 ± 0.27 (4.8) 5.02 - 6.17 [5.50]	5.48 ± 0.28 (5.2) 4.94 - 5.99 [5.50]	5.49 ± 0.28 (5.1) 4.96 - 6.12 [5.46]	20 / 20 / 21
AUC(0-t) (ng/ml x hr^{-1})	259.01 ± 66.80 (25.8) 148.42 - 430.44 [241.80]	241.50 ± 64.23 (26.6) 137.43 - 372.03 [242.02]	245.07 ± 67.69 (27.6) 140.43 - 420.82 [231.25]	5.53 ± 0.25 (4.5) 5.00 - 6.06 [5.49]	5.45 ± 0.27 (5.0) 4.92 - 5.92 [5.49]	5.47 ± 0.27 (4.9) 4.94 - 6.04 [5.44]	20 / 20 / 21
Ratio AUC(0-t) : AUC(0-inf)	0.973 ± 0.023 (2.3) 0.904 - 0.993 [0.979]	0.973 ± 0.018 (1.8) 0.932 - 0.994 [0.977]	0.97 ± 0.02 (1.8) 0.93 - 0.99 [0.98]	—	—	—	20 / 20 / 21
t½ (hours)	12.8 ± 3.3 (25.7) 8.7 - 21.4 [11.5]	12.4 ± 3.1 (25.0) 8.0 - 18.8 [11.8]	12.38 ± 2.98 (24.1) 7.94 - 19.21 [11.53]	—	—	—	20 / 20 / 21

1 Values are Mean ± SD, (%CV), range, [median]

Table 14 Comparative Pharmacokinetic Metrics of Hydroxy-Alprazolam after Administration of Alprazolam ODT 1 mg with and without Water, and Xanax® 1 mg - Protocol SP691[1]

	C	A	B
	Xanax 1 mg	Alprazolam ODT 1 mg with H_2O	Alprazolam ODT 1 mg without H_2O
	Reference	Test A	Test B
Tlag (hours)	0.50 ± 0.11 (22.9) 0.25 - 0.75 {0.5}	0.49 ± 0.1 20.8 0.25 - 0.75 [0.5]	0.54 ± 0.25 46.0 0.25 - 1.0 [0.5]
Tmax (hours)	1.8 ± 0.8 (45.5) 0.5 - 3.0 [2.0]	2.77 ± 2.30 (82.9) 0.75 - 12.0 [2.5]	3.33 ± 2.78 (83.5) 0.50 - 12.0 [2.5]
Cmax (ng/ml)	0.49 ± 0.17 (34.2) [0.48]	0.45 ± 0.15 (33.2) [0.43]	0.43 ± 0.15 (34.6) [0.41]
AUC(0-inf) (ng/ml x hr^{-1})	10.6 ± 2.7 (25.6) 5.8 - 16.0 [9.7]	9.54 ± 1.95 (20.5) 6.64 - 13.82 [9.30]	9.54 ± 2.21 (23.2) 6.58 - 13.91 [9.17]
AUC(0-t) (ng/ml x hr^{-1})	8.6 ± 2.8 (33.0) 3.9 - 14.3 [7.9]	7.56 ± 2.25 (29.8) 4.08 - 12.84 [7.62]	7.70 ± 2.38 (30.9) 2.38 - 12.69 [7.36]
Ratio AUC(0-t) : AUC(0-inf)	0.83 ± 0.09 (11.3) 0.55 - 0.92 [0.87]	0.82 ± 0.08 (9.9) 0.61 - 0.93 [0.82]	0.81 ± 0.15 (18.3) 0.23 - 0.93 [0.84]
t½ (hours)	14.7 ± 4.08 (27.7) 8.92 - 23.8 [14.0]	14.9 ± 4.9 (32.7) 7.7 - 28.7 [14.2]	15.0 ± 5.4 (36.1) 8.8 - 30.5 [14.3]

1 Values are Mean ± SD, (%CV), range, [median]

Table 15 Corrected Comparative Pharmacokinetic Metrics of Hydroxy-Alprazolam after Administration of Alprazolam ODT 1 mg with and without Water, and Xanax® 1 mg - Protocol SP691[1] – Provided by Sponsor in Submission Dated Sept 14, 2004

	C	A	B	N
	Xanax 1 mg	Alprazolam ODT 1 mg with H_2O	Alprazolam ODT 1 mg without H_2O	
	Reference	Test A	Test B	
Tlag (hours)	—	—	—	—
Tmax (hours)	1.82 ± 0.86 (47.2) 0.50 - 3.00 [2.00]	2.75 ± 2.31 (84.1) 0.75 - 12.00 [2.50]	3.29 ± 2.71 (82.4) 0.50 - 11.99 [2.50]	20 / 20 / 21
Cmax (ng/ml)	0.49 ± 0.17 (34.1) [0.48]	0.45 ± 0.15 (33.7) [0.43]	0.43 ± 0.15 (34.3) [0.44]	20 / 20 / 21
AUC(0-inf) (ng/ml x hr⁻	10.59 ± 2.72 (25.7) 5.77 - 15.98 [9.72]	9.54 ± 1.96 (20.5) 6.64 - 13.82 [9.30]	9.67 ± 2.25 (23.3) 6.58 - 13.89 [9.25]	19 / 17 / 21
AUC(0-t) (ng/ml x hr⁻	8.57 ± 2.83 (33.0) 3.94 - 14.26 [7.86]	7.55 ± 2.26 (29.9) 4.05 - 12.84 7.62]	7.88 ± 2.47 (31.4) 2.38 - 12.69 [7.42]	20 / 20 / 21
Ratio AUC(0-t) : AUC(0-inf)	0.83 ± 0.09 (11.3) 0.55 - 0.92 [0.87]	0.816 ± 0.081 (9.9) 0.605 - 0.929 [0.817]	0.81 ± 0.15 (18.0) 0.23 - 0.93 [0.83]	19 / 17 / 21
t½ (hours)	14.73 ± 4.08 (27.7) 8.92 - 23.77 [14.00]	14.9 ± 4.9 (32.7) 7.7 - 28.7 [14.2]	14.80 ± 5.35 (36.2) 8.81 - 30.45 [13.63]	19 / 17 / 21

1 Values are Mean ± SD, (%CV), range, [median]

5.3.1.2 Bioequivalence - 0.5 mg Tablets – Study SP765

The 0.5 mg Alprazolam Orally Disintegrating Tablets administered both with and without water were bioequivalent to Xanax™ 0.5 mg tablets with respect to both Cmax and AUC∞. Although, the Cmaxs and AUC∞s for the ODTs did tend to be 5 – 10% lower on average than for Xanax™ tablets. There was also a clear lengthening in the time to reach Tmax, going from a median of 0.75 hours with Xanax 0.5 mg tablets to 1.5 hours with the ODT formulation administered with water, to 2.0 hours when the ODT formulation was administered without water, (see Table 16). This delay in Tmax is most likely due to differences in the rate of absorption.

As alprazolam is administered in divided daily doses for anxiety and panic attacks rather than on an as needed basis, (i.e. prn), it's unlikely that the differences in Tmax observed under these conditions are clinically important. This is supported by studies demonstrating the effectiveness of Xanax XR sustained release tablets being efficacious for panic attacks with and without agoraphobia, as Xanax XR, tablets have a Tmax of around 7 hours with relatively constant concentrations between 5 and 11 hours post dose. Although there were failed studies with Xanax XR, these studies limited the dosage range to lower doses of up to only 4 mg or 6 mg, (see reviews for NDA 21-434).

Pharmacokinetic metrics for hydroxy-alprazolam were also similar between the 3 treatments, (see Table 17).

Table 16 Comparative Pharmacokinetic Metrics of Alprazolam after Administration of Alprazolam ODT 0.5 mg with and without Water, and Xanax® 0.5 mg - Protocol SP765

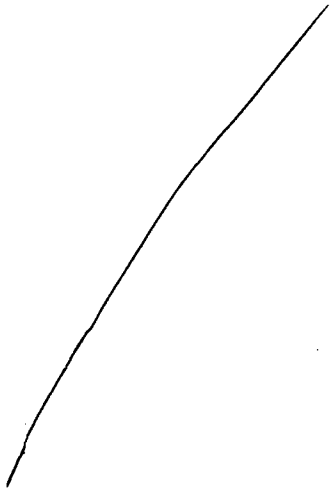
	Summary Statistics[a]			LN Means			Geometric Mean Ratios (90% CI)[b]	
	C	A	B	C	A	B	A : C	B : C
	Xanax 0.5 mg	Alprazolam ODT 0.5 mg with H_2O	Alprazolam ODT 0.5 mg without H_2O	Xanax 0.5 mg	Alprazolam ODT 0.5 mg with H_2O	Alprazolam ODT 0.5 mg without H_2O	Alprazolam ODT 0.5 mg with H_2O : Xanax 0.5 mg	Alprazolam ODT 0.5 mg without H_2O : Xanax 0.5 mg
	Reference	Test A	Test B	Reference	Test A	Test B	Test A : Reference	Test B : Reference
Tlag (hours)	0.27 ± 0.06 (24.2) 0.25 - 0.5 [0.25]	0.33 ± 0.12 (36.6) 0.25 - 0.5 [0.25]	0.33 ± 0.12 (36.6) 0.25 - 0.5 [0.25]	—	—	—	—	—
Tmax (hours)	1.07 ± 0.70 (65.0) 0.50 - 3.02 [0.75]	1.63 ± 0.80 (49.1) 0.74 - 3.00 [1.50]	1.95 ± 0.97 (49.9) 0.50 - 4.00 [2.00]	—	—	—	0.56 ± 0.73 (130.5) -0.78 - 2.0 [0.49]	0.88 ± 0.70 (79.6) -0.02 - 2.0 [0.75]
Cmax (ng/ml)	8.63 ± 1.62 (18.7) [9.07]	7.73 ± 1.78 (23.1) [7.88]	8.34 ± 1.80 (21.5) [8.77]	2.137	2.021	2.097	89.0 (81.6 - 97.1)	96.0 (88.0 - 104.7)
AUC(0-inf) (ng/ml x hr^{-1})	137.56 ± 40.34 (29.3) 76.27 - 204.41 [132.62]	133.25 ± 49.48 (37.1) 65.63 - 253.06 [126.98]	127.70 ± 46.36 (36.3) 59.45 - 242.02 [122.58]	4.882	4.832	4.789	95.1 (89.6 - 100.9)	91.0 (85.8 - 96.6)
AUC(0-t) (ng/ml x hr^{-1})	132.62 ± 39.02 (29.4) 73.29 - 195.50 [129.25]	127.11 ± 46.80 (36.8) 63.75 - 239.56 [122.70]	122.19 ± 43.63 (35.7) 56.69 - 227.63 [119.61]	4.845	4.786	4.746	94.3 89.0 - 99.8	90.6 85.5 - 95.9
Ratio AUC(0-t) : AUC(0-inf)	0.963 ± 0.015 (1.5) 0.938 - 0.988 [0.962]	0.955 ± 0.012 (1.2) 0.940 - 0.972 [0.951]	0.958 ± 0.015 (1.5) 0.937 - 0.985 [0.963]	—	—	—	—	—
t½ (hours)	12.62 ± 2.32 (18.3) 9.16 - 16.47 [12.24]	12.56 ± 2.77 (22.0) 9.31 - 17.45 [11.79]	12.51 ± 2.68 (21.4) 8.90 - 17.78 [11.98]	—	—	—	—	—

a Values are Mean ± SD, (%CV), range, [median]
b For Tmax values are Mean ± SD, (%CV), range and [median] of differences in Tmax

Table 17 Comparative Pharmacokinetic Metrics of Hydroxy-Alprazolam after Administration of Alprazolam ODT 0.5 mg with and without Water, and Xanax® 0.5 mg - Protocol SP765[a]

	C	A	B
	Xanax 0.5 mg	Alprazolam ODT 0.5 mg with H_2O	Alprazolam ODT 0.5 mg without H_2O
	Reference	Test A	Test B
Tlag (hours)	0.52 ± 0.06 (12.5) 0.5 - 0.75 [0.5]	0.62 ± 0.16 (25.9) 0.5 - 1 [0.5]	0.72 ± 0.28 (39.3) 0.5 - 1.5 [0.75]
Tmax (hours)	2.43 ± 2.01 (82.4) 0.50 - 8.00 [2.00]	2.89 ± 1.93 (66.7) 0.75 - 8.05 [2.50]	3.00 ± 2.74 (91.2) 0.50 - 12.00 [2.50]
Cmax (ng/ml)	0.24 ± 0.07 (29.7) [0.22]	0.22 ± 0.06 (25.9) [0.21]	0.23 ± 0.05 (23.7) [0.24]
AUC(0-inf) (ng/ml x hr^{-1})	6.15 ± 1.81 (29.5) 3.40 - 9.77 [5.85]	5.72 ± 1.37 (24.0) 3.33 - 7.36 [6.09]	5.82 ± 1.57 (26.9) 3.38 - 9.65 [5.29]
AUC(0-t) (ng/ml x hr^{-1})	3.86 ± 1.36 (35.2) 1.95 - 6.69 [3.80]	3.35 ± 1.17 (34.9) 1.48 - 5.77 [3.21]	3.58 ± 1.35 (37.7) 2.15 - 6.76 [3.23]
Ratio AUC(0-t) : AUC(0-inf)	0.666 ± 0.140 (21.1) 0.358 - 0.851 [0.720]	0.617 ± 0.137 (22.1) 0.398 - 0.799 [0.622]	0.626 ± 0.134 (21.4) 0.309 - 0.813 [0.667]
t½ (hours)	18.97 ± 6.61 (34.8) 12.94 - 34.79 [17.08]	18.95 ± 6.66 (35.1) 10.76 - 33.47 [17.74]	20.70 ± 9.06 (43.8) 11.23 - 44.53 [18.67]

a Values are Mean ± SD, (%CV), range, [median]



5.3.2 DOSE LINEARITY

The PK data from the BE studies with the 0.5 mg and 1.0 mg dosages indicates dose proportionality over this range of single doses. This is in agreement with the present labeling for Xanax® IR tablets.

The reason for the differences in the half-lives reported for hydroxy-alprazolam between the studies is not readily apparent.

5.3.3 BIOWAIVERS

Biowaivers for the 0.25 mg and 2 mg tablets are granted.

In OCPB review of a teleconference held June 26, 2003, pre-NDA meeting package submitted 05/22/2003, [Reference - DFS File: PIND 63,934 M 000 April 23, 2003]; OCPB indicated that biowaivers for the 0.25 mg and 2 mg orally disintegrating tablets may be granted based on the PK of the 0.5 mg and 1 mg tablets respectively, so long as dissolution data from all strengths in 3 media (pH 1.0, 4.5 and 6.8) are comparable between appropriate strengths, as:

- The recommended dose for Xanax is 0.25mg to 10mg per day in divided doses.
- Alprazolam (Xanax) exhibits dose proportionality over the range of 0.5 to 3.0mg.
- The sponsor's justifications are considered reasonable.

Since, the 0.25 mg and 0.5 mg tablets and the 1 mg and 2 mg tablets are qualitatively and quantitatively proportional and the dissolution data is comparable between the strengths the biowaivers are granted.

---

[3] OCPB Review - Wen-Hwei Chou, Pharm.D., Ph.D.: NDA: 18,276 / SCS-037 (Xanax IR tablets - Pharmacia & Upjohn) Submitted: May 21, 2002.

5.3.4 FOOD EFFECT – STUDY SP766

When the 1 mg ODT was administered with food there was no change in the extent of absorption, however there was approximately a 25% decrease in the Cmax, (range 16 – 31%), that is apparently due to a slower rate of absorption that also results in an average delay in Tmax of over 2 hours, (see Table 18).

There are also secondary delays in the Tlag and Tmax for hydroxy-alprazolam, (see Table 19).

In response to the protocol submission, (PIND 63,934 M001 (GC) Submitted July 17, 2003), OCPB recommended that it would be preferable to use the highest strength for a food effect study, especially as it would be approvable based on a biowaiver. Although the highest strength was not used, the results are likely applicable to all other proposed strengths.

Table 18 Effect of Food on Alprazolam Bioavailability after Administration of Alprazolam ODT 1 mg - Protocol SP766[a]

	Alprazolam ODT 1 mg Fasted	Alprazolam ODT 1 mg Fed	LN Means		Geometric Mean Ratio (90% CI)
	Reference	Test			
Tlag (hours)	0.25 ± 0.00 (0.00) 0.25 - 0.25 [0.25]	0.3 ± 0.1 (44.4) 0.0 - 0.5 [0.3]	—	—	—
Tmax (hours)	2.21 ± 0.97 (43.87) 0.75 - 4.01 [2.52]	4.36 ± 1.25 (28.66) 2.53 - 6.03 [4.01]	—	—	2.14 ± 1.61 (75.18) -0.01 - 5.01 [1.77]
Cmax (ng/ml)	16.1 ± 3.5 (21.9) [15.9]	12.4 ± 3.1 (25.0) [12.1]	2.76	2.48	76.0 68.8 - 84.0
AUC(0-inf) (ng/ml x hr^{-1})	256.9 ± 96.1 (37.4) 105.5 - 524.2 [248.0]	268.1 ± 121.0 (45.1) 102.0 - 628.3 [252.6]	5.49	5.51	102.5 97.7 - 107.4
AUC(0-t) (ng/ml x hr^{-1})	247.0 ± 81.9 (33.2) 100.5 - 448.8 [242.6]	255.1 ± 100.8 (39.5) 99.9 - 539.6 [246.3]	5.46	5.47	101.9 97.3 - 106.7
t½ (hours)	13.1 ± 4.4 (33.4) 8.2 - 26.7 [12.0]	13.5 ± 4.3 (31.7) 8.0 - 24.7 [12.9]	—	—	—

a Values are Mean ± SD, (%CV), range, [median]

Table 19 Effect of Food on Hydroxy-Alprazolam Pharmacokinetic Metrics after Administration of Alprazolam ODT 1 mg - Protocol SP766[a]

	Alprazolam ODT 1 mg Fasted	Alprazolam ODT 1 mg Fed
	Reference	Test
Tlag (hours)	0.48 ± 0.11 (22.8) 0.25 - 0.75 [0.5]	0.91 ± 0.33 (36.1) 0.5 - 1.5 [0.75]
Tmax (hours)	3.01 ± 1.17 (39.02) 1.50 - 6.00 [3.00]	5.88 ± 2.75 (46.71) 3.00 - 12.00 [6.00]
Cmax (ng/ml)	0.5 ± 0.3 (52.1) [0.5]	0.4 ± 0.2 (53.2) [0.4]
AUC(0-inf) (ng/ml x hr^{-1})	11.8 ± 5.4 (46.0) 6.9 - 28.2 [10.2]	11.6 ± 6.2 (53.3) 4.9 - 29.8 [10.1]
AUC(0-t) (ng/ml x hr^{-1})	9.4 ± 5.5 (58.7) 2.5 - 26.7 [8.0]	9.4 ± 5.7 (60.4) 3.2 - 27.7 [8.2]
t½ (hours)	16.3 ± 4.3 (26.6) 10.5 - 26.2 [15.7]	16.2 ± 4.1 (25.5) 9.5 - 23.4 [15.7]

a Values are Mean ± SD, (%CV), range, [median]

5.3.5 GENDER EFFECT

There do not appear to be any gender differences.

In the 0.5 mg BE study the women tended to have higher exposures than the men, but there were only 3 women. In contrast both studies with 1 mg tablets enrolled closer numbers of men and women and in these studies men tended to have higher exposures, (see Table 20 to Table 22 and Figure 9 to Figure 12).

a Values are Mean ± SD, (%CV), range, [median]
b DWN – Dose and Weight Normalized

Table 20 Summary of Demographic Information and Pharmacokinetic Metrics Including Dose & Weight Normalized Metrics by Gender and Treatment for 1 mg BE Study – SP691[a]

Treatment		Sex	N	Race	Age	Weight	Tlag	Cmax	Tmax	AUCinf	t1/2	DWN Cmax[b]	DWN AUCinf[b]
				W/B/A/H/AI	(years)	(kg)	(hrs)	(ng/ml)	(hrs)	ng/ml x hr^{-1}	(hrs)	pg/ml/(mg/kg)	pg/ml x hr^{-1}/(mg/kg)
A	1 mg ODT With Water	F	7	7/0/0/0/0	28.9 ± 9.3 (32.2) 20.0 - 41.0 [26.0]	68.3 ± 8.8 (12.9) 58.6 - 85.0 [67.3]	0.25 ± 0.00 (0.00) 0.25 - 0.25 [0.25]	14.8 ± 1.5 (10.1) — [14.5]	2.1 ± 0.7 (32.2) 1.0 - 3.0 [2.5]	223.1 ± 35.1 (15.7) 178.4 - 268.5 [219.8]	10.8 ± 1.8 (16.5) 8.6 - 13.8 [10.3]	221.7 ± 45.7 (20.6) 168.1 - 308.8 [216.2]	3302.8 ± 623.9 (18.9) 2652.0 - 4193.0 [3039.3]
		M	13	10/1/1/1/0	27.8 ± 8.2 (29.4) 19.0 - 44.0 [27.0]	77.6 ± 8.3 (10.6) 63.6 - 89.5 [78.6]	0.25 ± 0.00 (0.00) 0.25 - 0.25 [0.25]	14.2 ± 2.4 (17.0) — [14.4]	1.79 ± 0.96 (53.73) 0.75 - 4.00 [2.00]	263.0 ± 80.5 (30.6) 140.0 - 399.3 [277.8]	13.4 ± 3.3 (25.0) 8.0 - 18.8 [12.7]	185.7 ± 44.7 (24.1) 126.4 - 275.7 [188.7]	3454.9 ± 1163.2 (33.7) 1620.5 - 4748.1 [3868.4]
B	1 mg ODT Without Water	F	7			—	0.25 ± 0.00 (0.00) 0.25 - 0.25 [0.25]	15.4 ± 2.2 (14.6) — [15.5]	2.29 ± 0.70 (30.57) 1.00 - 3.00 [2.50]	227.9 ± 24.2 (10.6) 183.6 - 252.0 [235.9]	10.9 ± 1.3 (12.0) 9.1 - 12.5 [10.4]	230.4 ± 52.8 (22.9) 164.1 - 287.4 [230.1]	3390.5 ± 611.1 (18.0) 2643.3 - 4096.9 [3671.1]
		M	13			—	0.29 ± 0.10 (33.36) 0.25 - 0.50 [0.25]	14.0 ± 2.7 (19.4) — [14.7]	2.00 ± 1.23 (61.27) 0.25 - 4.00 [2.00]	269.1 ± 90.7 (33.7) 142.7 - 454.9 [244.7]	13.3 ± 3.4 (25.8) 7.9 - 19.2 [11.6]	183.5 ± 47.1 (25.7) 125.5 - 306.9 [167.4]	3543.7 ± 1322.5 (37.3) 1652.8 - 5409.7 [3406.9]
C	1 mg IR Tablet (Xanax™)	F	7	—	—	—	0.29 ± 0.09 (33.07) 0.25 - 0.50 [0.25]	16.1 ± 2.1 (13.0) — [15.3]	1.72 ± 0.69 (40.32) 1.00 - 3.00 [1.55]	234.1 ± 26.5 (11.3) 203.9 - 280.5 [225.7]	11.3 ± 1.3 (11.7) 9.5 - 13.4 [11.2]	240.6 ± 56.4 (23.4) 160.6 - 345.6 [243.0]	3484.9 ± 653.4 (18.8) 2653.5 - 4315.9 [3378.1]
		M	13			—	0.25 ± 0.00 (0.00) 0.25 - 0.25 [0.25]	15.2 ± 2.3 (14.9) — [14.7]	1.7 ± 0.9 (55.6) 0.5 - 3.0 [2.0]	285.8 ± 88.1 (30.8) 152.1 - 476.2 [266.2]	13.5 ± 3.8 (27.9) 8.7 - 21.4 [12.6]	197.3 ± 34.1 (17.3) 147.9 - 276.7 [189.4]	3753.9 ± 1263.4 (33.66) 1761.2 - 5662.4 [3706.2]

a Values are Mean ± SD, (%CV), range, [median]
b DWN – Dose and Weight Normalized

Table 21 Summary of Demographic Information and Pharmacokinetic Metrics Including Dose & Weight Normalized Metrics by Gender and Treatment for 0.5 mg BE Study – SP765[a]

Treatment		Sex	N	Race	Age	Weight	Tlag	Cmax	Tmax	AUCinf	T1/2	DWN Cmax[b]	DWN AUCinf[b]
				W/B/A/H/AI	(years)	(kg)	(hrs)	(ng/ml)	(hrs)	ng/ml x hr^{-1}	(hrs)	pg/ml/(mg/kg)	pg/ml x hr^{-1}/(mg/kg)
A	0.5 mg ODT With Water	F	3	3/0/0/0/0	36.3 ± 10.1 (27.7) 27.0 - 47.0 [35.0]	61.8 ± 12.4 (20.0) 48.6 - 73.2 [63.6]	0.3 ± 0.1 (43.3) 0.3 - 0.5 [0.3]	10.00 ± 2.01 (20.1) — [9.05]	1.8 ± 1.0 (56.7) 1.0 - 3.0 [1.5]	169.9 ± 72.0 (42.4) 127.2 - 253.1 [129.5]	12.7 ± 4.25 (33.5) 9.4 - 17.4 [11.2]	329.8 ± 73.2 (22.2) 247.3 - 386. [355.3]	5574.6 ± 2227.0 (39.9) 3539.0 - 7953.2 [5231.6]
		M	12	9/2/1/0/0	28.8 ± 6.7 (23.5) 20 - 41 [29]	78.7 ± 12.4 (15.8) 62.7 - 96.8 [80.2]	0.33 ± 0.12 (36.93) 0.25 - 0.50 [0.25]	7.2 ± 1.2 (17.4) — [7.0]	1.58 ± 0.78 (49.33) 0.74 - 3.00 [1.75]	124.1 ± 41.4 (33.4) 65.6 - 198.2 [118.3]	12.5 ± 2.5 (20.3) 9.3 - 16.7 [12.0]	190.2 ± 60.5 (31.8) 114.0 - 271.8 [163.2]	3366.1 ± 1592.8 (47.3) 1362.1 - 6320.0 [2857.8]
B	0.5 mg ODT Without Water	F	3	—	—	—	0.25 ± 0.00 (0.0) 0.25 - 0.25 [0.25]	9.2 ± 0.4 (4.4) — [9.0]	2.16 ± 0.76 (35.09) 1.50 - 2.99 [2.0]	137.4 ± 36.6 (26.6) 110.6 - 179.1 [122.3]	12.5 ± 3.9 (31.0) 8.9 - 16.6 [12.1]	307.4 ± 79.3 (25.8) 244.8 - 396.6 [280.8]	4507.2 ± 1142.9 (25.4) 3343.5 - 5628.2 [4549.9]
		M	12	—	—	—	0.35 ± 0.13 (36.3) 0.25 - 0.5 [0.25]	8.1 ± 2.0 (24.1) — [8.3]	1.90 ± 1.04 (54.88) 0.50 - 4.00 [2.00]	125.3 ± 49.6 (39.6) 59.4 - 242.0 [123.1]	12.5 ± 2.5 (20.2) 9.7 - 17.8 [12.0]	214.4 ± 68.4 (31.9) 95.2 - 309.9 [210.4]	3413.4 ± 1818.4 (53.3) 1228.0 - 7716.7 [2926.2]
C	0.5 mg IR Tablet (Xanax™)	F	3	—	—	—	0.33 ± 0.14 (43.3) 0.25 - 0.5 [0.25]	10.3 ± 0.9 (8.4) — [10.4]	0.92 ± 0.14 (15.8) 0.75 - 1.0 [1.0]	152.5 ± 45.4 (29.8) 120.3 - 204.4 [132.6]	12.9 ± 3.6 (27.8) 9.2 - 16.3 [13.3]	345.4 ± 100.9 (29.2) 255.1 - 454.2 [326.9]	4999.1 ± 1400.7 (28.0) 3624.3 - 6424.4 [4948.6]
		M	12	—	—	—	0.25 ± 0.00 (0.0) 0.25 - 0.25 [0.25]	8.2 ± 1.5 (18.4) — [8.3]	1.11 ± 0.78 (70.17) 0.50 - 3.02 [0.75]	133.8 ± 40.3 (30.1) 76.3 - 189.9 [131.2]	12.5 ± 2.1 (16.8) 10.3 - 16.5 [12.0]	217.9 ± 66.2 (30.4) 113.2 - 321.6 [213.5]	3616.1 ± 1573.6 (43.5) 1583.0 - 6056.1 [3119.5]

a Values are Mean ± SD, (%CV), range, [median]
b DWN – Dose and Weight Normalized

Table 22 Summary of Demographic Information and Pharmacokinetic Metrics Including Dose & Weight Normalized Metrics by Gender and Treatment for 1 mg Food Effect Study – SP766[a]

Treatment	Sex	N	Race	Age	Weight	Tlag	Cmax	Tmax	AUC(0-Inf)	T1/2	DWN Cmax[b]	DWN AUCinf[b]
			W/B/A/H/AI	(years)	(kg)	(hrs)	(ng/ml)	(hrs)	ng/ml x hr^{-1}	(hrs)	pg/ml/(mg/kg)	pg/ml x hr^{-1}/(mg/kg)
Fasting	F	9	8/0/0/0/1	31.9 ± 11.5 (36.1) 20.0 - 48.0 [31.0]	65.2 ± 4.9 (7.5) 58.2 - 75.5 [63.6]	0.25 ± 0.00 (0.00) 0.25 - 0.25 [0.25]	16.6 ± 4.4 (26.4) — [15.9]	2.0 ± 0.9 (42.9) 1.0 - 3.0 [2.5]	226.8 ± 75.1 (33.1) 105.5 - 337.1 [225.5]	11.4 ± 2.1 (18.8) 8.2 - 14.8 [10.9]	257.6 ± 74.1 (28.8) 115.9 - 378.7 [257.8]	3503.4 ± 1223.2 (34.9) 1546.8 - 5374.5 [3323.7]
	M	7	6/1/0/0/0	37.6 ± 9.2 (24.4) 24.0 - 50.0 [37.0]	80.5 ± 7.9 (9.9) 66.8 - 89.1 [80.0]	0.25 ± 0.00 (0.00) 0.25 - 0.25 [0.25]	15.5 ± 2.1 (13.8) — [15.9]	2.5 ± 1.1 (44.9) 0.7 - 4.0 [3.0]	295.7 ± 111.6 (37.7) 186.0 - 524.2 [256.9]	15.2 ± 5.7 (37.1) 10.8 - 26.7 [13.9]	193.3 ± 27.3 (14.1) 138.2 - 217.9 [199.2]	3662.6 ± 1226.9 (33.5) 2495.5 - 6006.8 [3410.0]
Fed	F	9		31.9 ± 11.5 (36.1) 20.0 - 48.0 [31.0]	65.2 ± 4.9 (7.5) 58.2 - 75.5 [63.6]	0.25 ± 0.00 (0.00) 0.25 - 0.25 [0.25]	12.0 ± 3.6 (30.0) — [11.7]	4.9 ± 1.4 (27.8) 3.0 - 6.0 [6.0]	230.4 ± 69.8 (30.3) 102.0 - 312.8 [231.7]	11.7 ± 2.3 (19.5) 8.0 - 14.2 [12.8]	184.3 ± 54.7 (29.7) 65.4 - 256.5 [192.1]	3546.5 ± 1080.9 (30.5) 1496.5 - 5022.5 [3491.4]
	M	7		37.6 ± 9.2 (24.4) 24.0 - 50.0 [37.0]	80.5 ± 7.9 (9.9) 66.8 - 89.1 [80.0]	0.3 ± 0.2 (58.8) 0.0 - 0.5 [0.3]	13.0 ± 2.5 (19.3) — [13.2]	3.6 ± 0.6 (17.0) 2.5 - 4.0 [4.0]	316.6 ± 158.9 (50.2) 171.5 - 628.3 [262.9]	15.9 ± 5.3 (33.4) 10.5 - 24.7 [14.8]	162.1 ± 28.1 (17.4) 120.1 - 190.6 [178.2]	3906.2 ± 1781.6 (45.6) 2300.9 - 7199.7 [3044.3]

a Values are Mean ± SD, (%CV), range, [median]
b DWN – Dose and Weight Normalized

5.3.6 EFFECT OF AGE, RACE, AND GENDER

As shown in Figure 5 to Figure 12 there does not appear to be any effect of age from 18 to 50 years old, gender, or race on the pharmacokinetics of alprazolam ODT although there are too few non-Caucasians to reach a firm conclusion regarding race. In addtion, there are no elderly subjects so no conclusions about age can be made.

A quick literature search indicates that baseline salivary flow is not diminished with age in the healthy elderly although stimulated flow is reduced. However, there are a number of conditions that increase in incidence with age that do effect salivary flow. In addition, the composition of the saliva appears to change with age.

Consequently, no study on the effect of decreased salivary flow in the elderly is needed. With regard to salivary composition; since a review of the literature is beyond the scope of this review it's prudent to ask the sponsor to review the literature and to submit the results to ascertain if there are any changes in salivary compostion with age that might effect disintegration or dissolution of the — (e.g. pH or buffering capacity).

N.B. Figure 9 to Figure 12 show dose-normalized data that in the present case tends to suggest a gender difference which is not present in the raw data.

APPEARS THIS WAY
ON ORIGINAL

Figure 5 ɔr Alprazolam ODT in Men by Race and Treatment

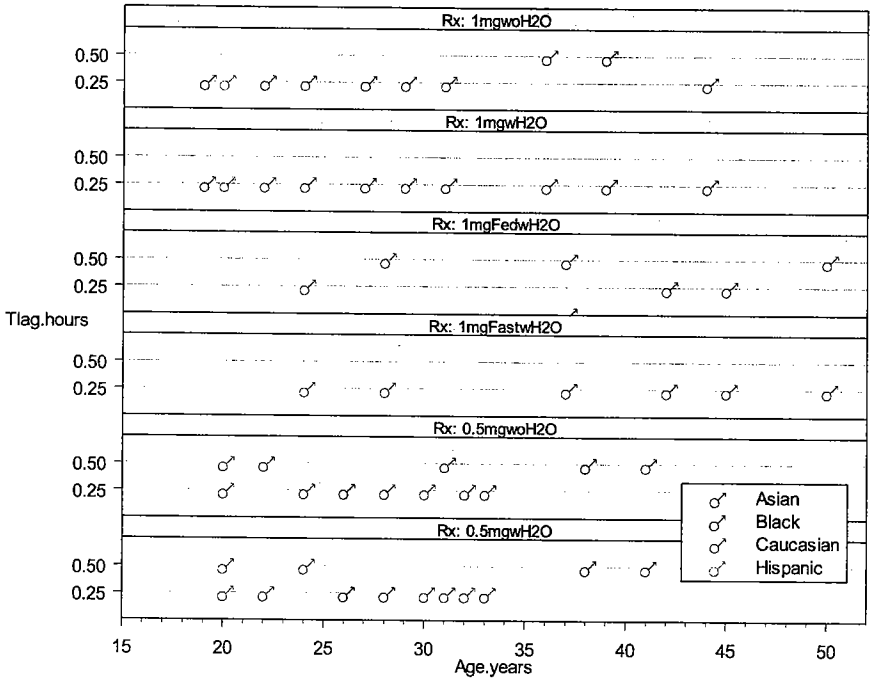


Figure 6 Tlag for Alprazolam ODT in Women by Race and Treatment

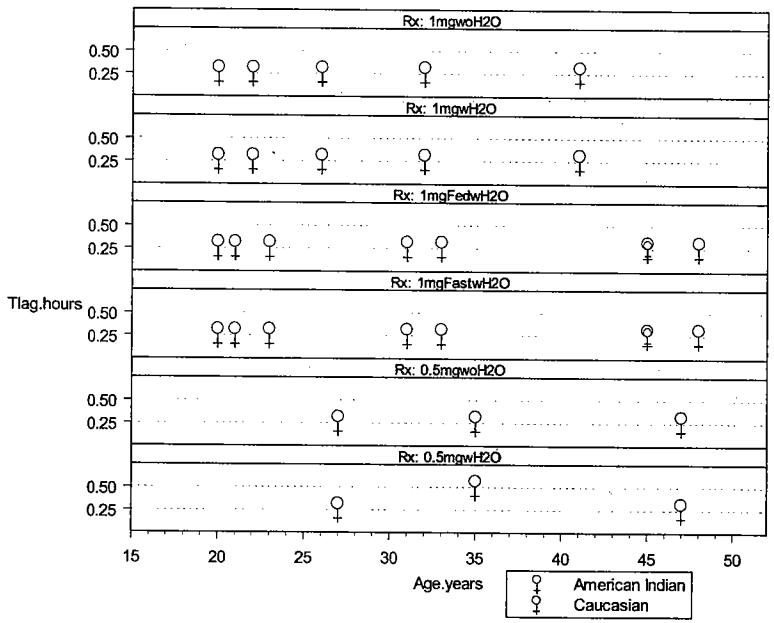


Figure 7 Tmax for Alprazolam ODT in Men by Race and Treatr

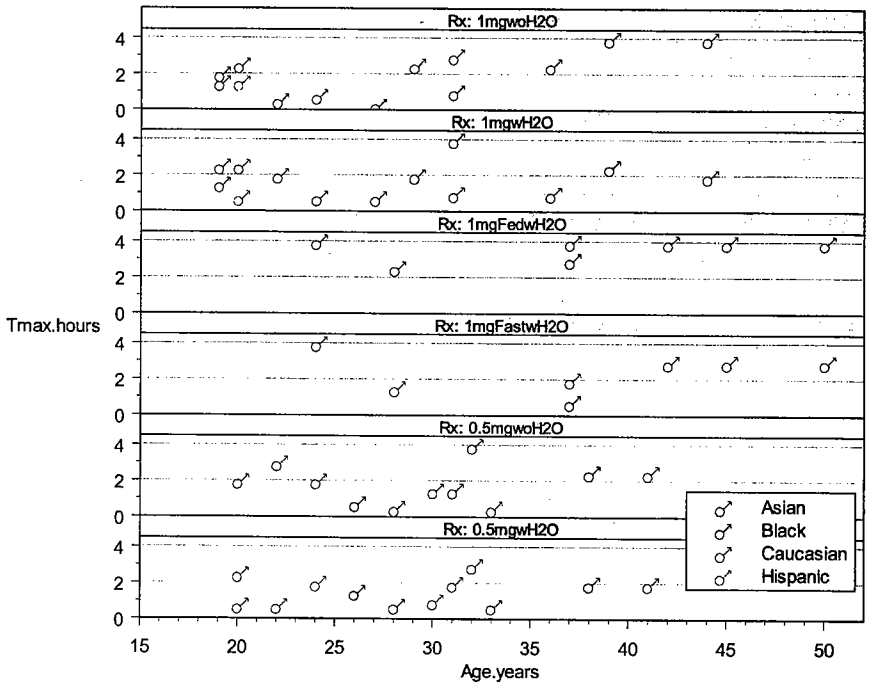


Figure 8 Tmax for Alprazolam ODT in Women by Race and Treatment

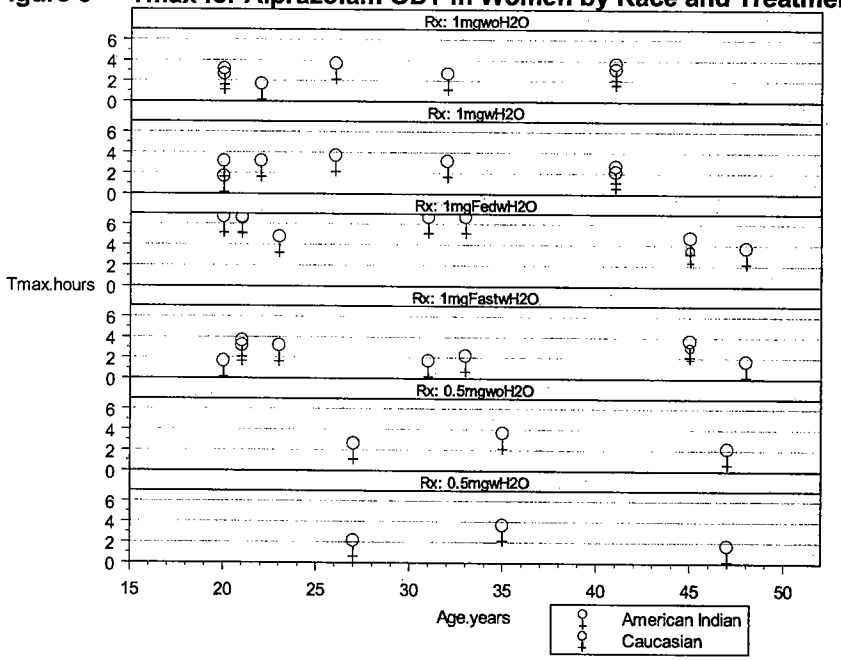


Figure 9 **Dose and Weight Normalized Cmax for Alprazolam ODT in Men by Race and Treatment**

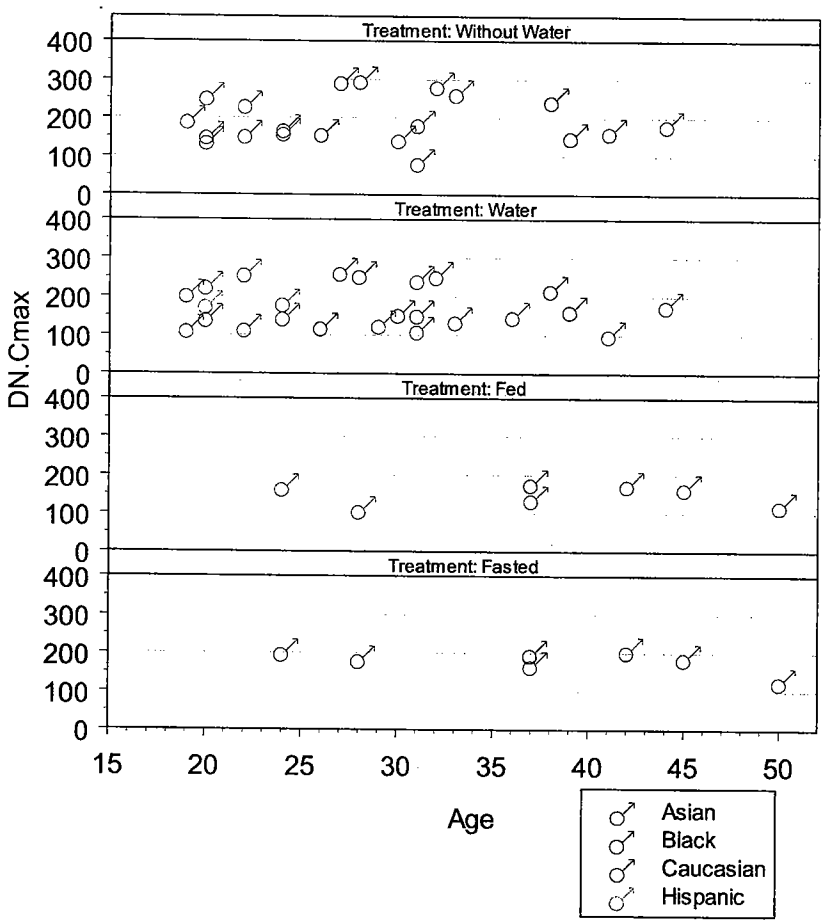


Figure 10 **Dose and Weight Normalized Cmax for Alprazolam ODT in Women by Race and Treatment**

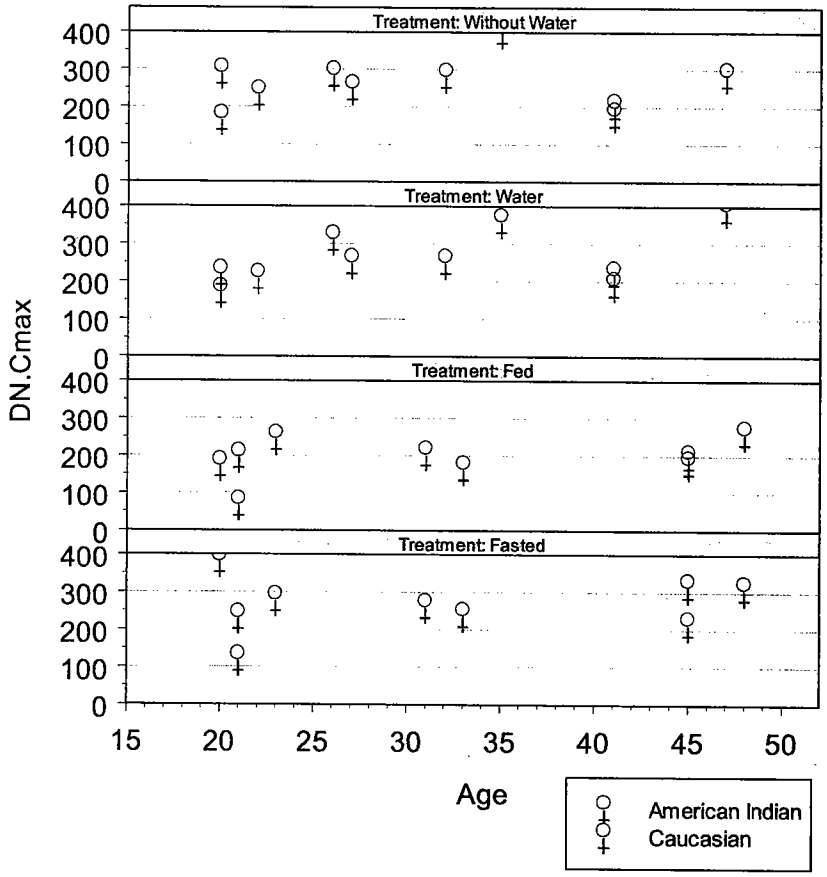


Figure 11 Dose and Weight Normalized AUC∞ for Alprazolam ODT in Men by Race and Treatment

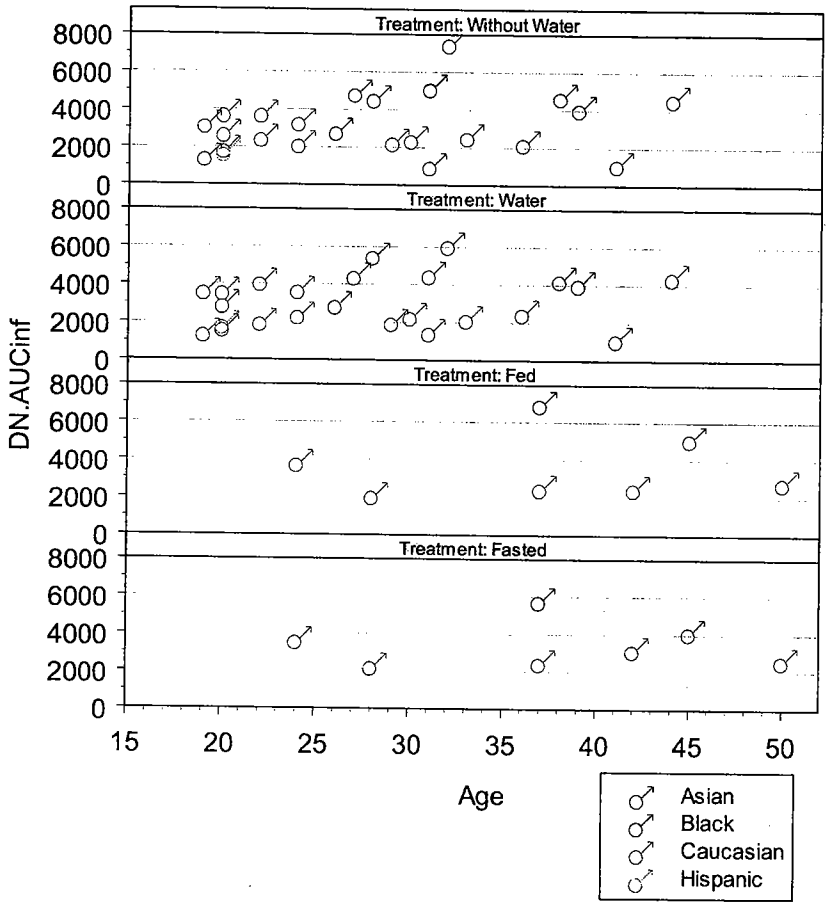
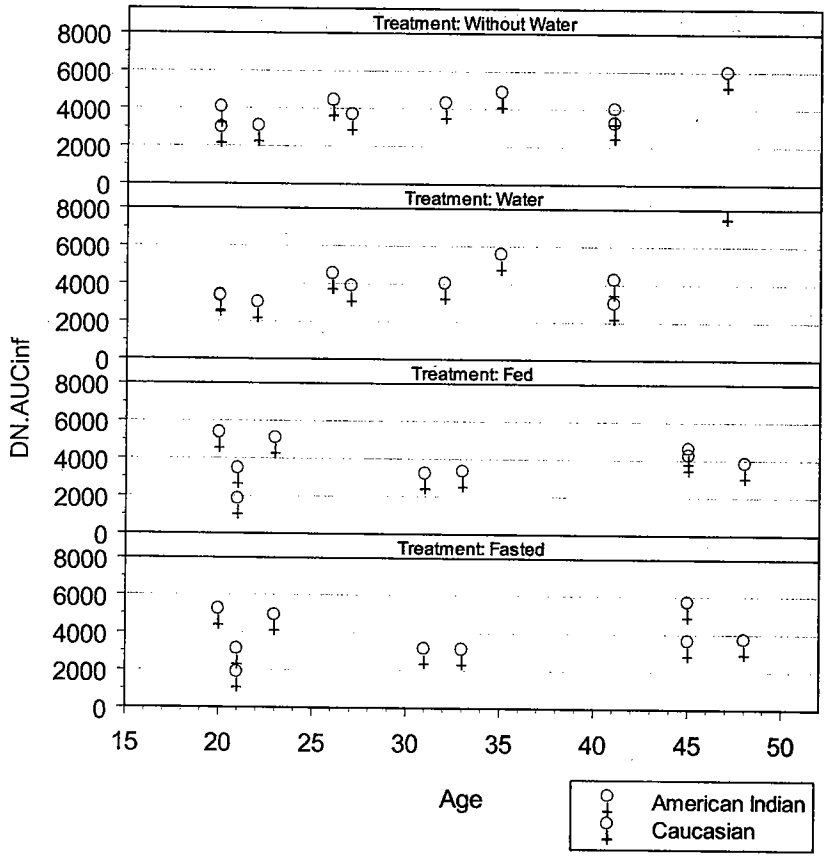


Figure 12 Dose and Weight Normalized AUC∞ for Alprazolam ODT in Women by Race and Treatment



5.3.7 EFFECT OF SMOKING

All subjects were non-smokers.

5.3.8 DISINTEGRATION – IN VIVO

Disintegration times were measured in all three studies. Tablets were placed on the subject's tongue by a clinic staff member. The subject allowed the ODT to disintegrate on the tongue without chewing or swallowing. No water was administered and the subject was asked to notify the clinical staff when the tablet had completely disintegrated. The time when the tablet had completely disintegrated was recorded and verified by the clinic staff upon visual inspection of the subject's mouth. After the tablet has disintegrated and is verified, the subject was instructed to swallow the disintegrated tablet followed by drinking a glass of water, or not, as appropriate to the study. Summary statistics are shown in Table 23.

Table 23 ***In Vivo*** **Disintegration Times**

Study	SP-691		SP-765		SP-766		Total
	1 mg BE Study		0.5 mg BE Study		Food Effect Study		
Treatment	With Water	Without Water	With Water	Without Water	Fasted With Water	Fed With Water	
N	20	21	15	15	16	16	103
	In Vivo **Disintegration Time (Seconds)**						
Mean ± SD (CV%) Range [Median]	63.9 ± 38.0 (59.5) [55]	55.9 ± 23.6 (42.2) [54]	179.6 ± 178.4 (99.3) [120]	127.7 ± 96.7 (75.7) [85]	101.9 ± 52.9 (51.8) [97]	106.4 ± 60.2 (56.6) [77.5]	
	In Vivo **Disintegration Time (Minutes)**						
	1.1 ± 0.6 (59.5) [0.9]	0.9 ± 0.4 (42.2) [0.9]	3.0 ± 3.0 (99.3) [2.0]	2.1 ± 1.6 (75.7) [1.4]	1.7 ± 0.9 (51.8) [1.6]	1.8 ± 1.0 (56.6) [1.3]	
N ≥ 1 minute	9	8	14	11	11	14	67
% ≥ 1 minute	45.0%	38.1%	93.33%	73.33%	68.75%	87.5%	**65.0%**
N ≥ 2 minutes	2	1	8	5	5	5	26
% ≥ 2 minutes	10.0%	4.76%	53.33%	22.81%	23.81%	23.81%	**25.2%**

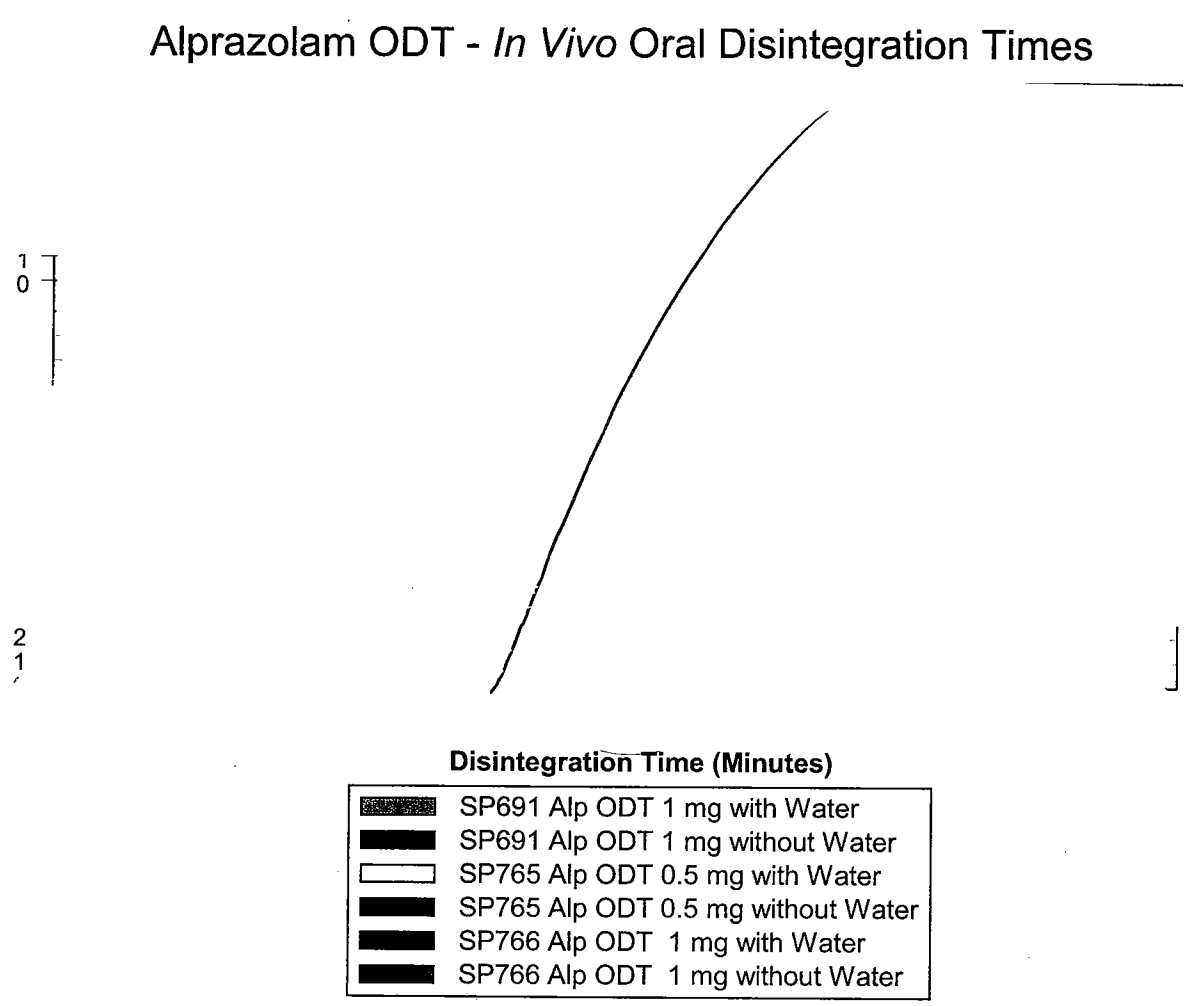
Disintegration times generally averaged 1 to 2 minutes with disintegration times ranging up to 11.8 minutes. Three of the 15 subjects administered the 0.5 mg tablets without water had especially long disintegration times, with disintegration times of — minutes respectively. Long disintegration times occur frequently as shown by the number and percent of oral disintergration times greater then 1 minute, (65% overall), and greater than 2 minutes, (25% overall), (see Table 23 and Figure 13).

These slow disintegration times do not appear to be rate limiting in these individuals with normal saliva production as the time to reach peak concentrations with the 0.5 mg tablets is sooner than for the 1 mg

tablets. This may be due to several factors. In addition, as discussed earlier the differences observed in Tmax should not be clinically significant. However, the situation when there is a lack of saliva may be different and needs to be examined.

Other issues with these long distegration times are whether these tablets meet the definition of an orally disintegrating tablet formulation, and whether the *in vitro* test for orally disintegrating tablet formulation is truly representative of the *in vivo* situation.

Figure 13 Frequency of Alprazolam ODT *In Vivo* Oral Disintegration Times



5.4 CLINICAL PHARMACOLOGY

5.4.1 DRUG-DRUG INTERACTIONS

After the filing meeting a request was sent to address the effect of salivary pH, and also dry mouth due to anticholinergic effects on absorption rate, as alprazolam's solubility is pH dependent and since patients with anxiety disorders may also be taking drugs that have anticholinergic side effects.

5.4.1.1 Anticholinergics and Salivary pH

Alprazolam orally disintegrating tablet are formulated differently than other orally disintegrating tablet formulations.

Other orally disintegrating tablets have been formulated as lyophilized tablets. When these formulations are taken without water in the presence of dry mouth, the drug substance may take several hours, (5 – 6 hours) before drug reaches the small intestines and absorption begins.

In contrast alprazolam ODT is formulated by

According to the sponsor since the pH of saliva is between 6 and 7 and alprazolam will not be released in the oral cavity. Consequently, based on the characteristics of the formulation salivary pH should not be rate limiting with respect to dissolution and absorption.

However, the sponsor's conclusion does not appear to be completely accurate. as shown by the dissolution experiments the rate of dissolution decreases mostly over the range of pH 6.0 – pH 6.8. Thus the , will at least partially dissolve in the oral cavity, (at least enough to result in rapid disintegration most of the time). Since the pH of saliva is generally between 6 and 7 and can go lower or higher it would be expected to effect disintegration somewhat on occasion. Although so long as there is sufficient salivary flow to move to the stomach, this shouldn't be rate limiting with respect to absorption.

However, since dry mouth might effect both the disintegration of the tablets , the effect of anticholinergics on absorption rate when administered without water still needs to be addressed.

5.4.1.2 Drugs that Affect Gastric pH

The sponsor's response to the issue of the effect of salivary pH on dissolution rate raises the question of whether drugs that raise gastric pH might also affect dissolution and absorption rate. Drug classes that would be of interest include the following:

- Proton Pump Inhibitors
- H_2 Antagonists
- Antacids

This issue also needs to be addressed.

6 APPENDICES

Appendix 1 Bioanalytic Assay Validation

Table 24 Assay Validation – Alprazolam/Alpha-Hydroxy-Alprazolam in Human Plasma

Laboratory			
Report	Alprazolam and alpha-hydroxy-alprazolam in Human K3EDTA Plasma Validation		
Report #	AA03784_1		
Date	May 30, 2003		
Analyst(s)			
Method Description	LC-MS/MS		
Method Protocol			
Analyte	Alprazolam		
Internal Standard			
Range	0.1 – 15.0 ng/ml		
Volume			
Structural Model			
Error Model			
Software			
Software Validation			
Matrix			
Sample Storage Method			
Matrix Effects			
LLOQ	0.1 ng/ml		
Conc's (ng/ml)	0.3	3.0	11.5
Bias - Intra assay	-3.7%	5.3%	0.9%
Bias - Inter assay	-6.3%	3.7%	0.0%
Overall Precision	4.4%	5.1%	6.6%
Intra assay Precision	3.6%	1.0%	1.0%
Inter (Between) assay Precision			
Selectivity **Endogenous Substances** **Internal Standard** **OTC Drugs** **Dietary – e.g. Caffeine** **Drugs – Rx**	10 lots OK		
Stability - Blood			
Stability - Plasma **RT** **Refrigerated** **Long Term (-20 °C)** **Long Term (-80 °C)** **Stability Freeze/Thaw**	 24 hours 5 weeks 8 days 5 cycles		
Stability - Extracted **RT** **Refrigerated** **On Machine**	 11 days		

Table 25 Assay Validation - Alpha-Hydroxy-alprazolam

Reason for Partial Validation	alpha-hydroxy-alprazolam		
Laboratory	/		
Report	Alprazolam and alpha-hydroxy-alprazolam in Human K3EDTA Plasma Validation		
Report #	AA03784_1		
Date	May 30, 2003		
Analyst(s)	—		
Original Full Validation Report			
Original Full Validation Report #			
Original Full Validation Date			
Method Description	LC-MS/MS		
Method Protocol			
Analyte	alpha-hydroxy-alprazolam		
Internal Standard			
Range	0.05 – 7.50 ng/ml		
Volume			
Structural Model			
Error Model			
Software			
Software Validation			
Matrix			
Sample Storage Method			
Matrix Effects	*Appears to be interference via bias*		
LLOQ	0.05 ng/ml		
Conc's (ng/ml)	0.15	1.5	5.75
Bias - Intra assay	4.7%	10.7%	10.8%
Bias - Inter assay	-4.7%	3.3%	6.3%
Overall Precision	*6.3%*	*5.1%*	*6.1%*
Intra assay Precision	6.5%	2.3%	3.4%
Inter (Between) assay Precision			
Selectivity **Endogenous Substances** **Internal Standard** **OTC Drugs** **Dietary – e.g. Caffeine** **Drugs – Rx**	10 lots OK		
Stability - Blood			
Stability - Plasma **RT** **Refrigerated** **Long Term (-20 °C)** **Long Term (-80 °C)** **Stability Freeze/Thaw**	 24 hours 5 weeks 8 days 5 cycles		
Stability - Extracted **RT** **Refrigerated** **On Machine**	 11 days		

Appendix 2 Demographic Information

Table 26 Summary of Demographic Information by Study

Trait	1 mg BE Study - SP691			0.5 mg BE Study – SP765			Food Effect Study – SP766		
Gender	**Female**	**Male**	**Overall**	**Female**	**Male**	**Overall**	**Female**	**Male**	**Overall**
Female	8	—	21	3	—	15	9	—	16
Male	—	13		—	12		—	7	
Race									
Caucasian	8	10	18	3	9	12	8	6	14
Black.	—	1	1	—	2	2	—	1	1
Asian	—	1	1	—	1	1	—	—	—
Hispanic.	—	1	1	—	—	—	—	—	—
American Indian	—	—	—	—	—	—	1	—	1
Frame Size									
Small	—	1	1	—	3	3	2	—	2
Medium	1	9	10	3	8	11	7	7	14
Large	7	3	10	1	1	2	—	—	—
Age[a] (years)	28.9 ± 9.3 (32.2) 20.0 - 41.0 [26.0]	27.8 ± 8.2 (29.4) 19.0 - 44.0 [27.0]	—	36.3 ± 10.1 (27.7) 27.0 - 47.0 [35.0]	28.8 ± 6.7 (23.5) 20.0 - 41.0 [29.0]	—	31.9 ± 11.5 (36.1) 20.0 - 48.0 [31.0]	37.6 ± 9.2 (24.4) 24.0 - 50.0 [37.0]	—
Weight (kg)[a]	68.3 ± 8.8 (12.9) 58.6 - 85.0 [67.3]	77.6 ± 8.3 (10.6) 63.6 - 89.5 [78.6]	—	61.8 ± 12.4 (20.0) 48.6 - 73.2 [63.6]	78.7 ± 12.4 (15.8) 62.7 - 96.8 [80.2]	—	65.2 ± 4.9 (7.5) 58.2 - 75.5 [63.6]	80.5 ± 7.9 (9.9) 66.8 - 89.1 [80.0]	—
Height (in)[a]	67.0 ± 1.7 (2.6) 64.0 - 69.0 [67.0]	70.2 ± 2.3 (3.3) 66.0 - 74.0 [71.0]	—	64.7 ± 5.5 (8.5) 61.0 - 71.0 [62.0]	70.4 ± 3.3 (4.7) 66.0 - 76.0 [69.5]	—	66.8 ± 1.7 (2.5) 63.0 - 68.0 [67.0]	70.9 ± 2.7 (3.9) 67.0 - 75.0 [71.0]	—

a Values are Mean ± SD, (%CV), range, [median]

Appendix 3 OCPB Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
NDA Number	21-726	**Brand Name**	Alprazolam Orally Disintegrating Tablets
Related NDAs	None	**Generic Name**	Alprazolam Orally Disintegrating Tablets
OCPB Division (I, II, III)	I HFD-860	**Drug Class**	Benzodiazepine
Medical Division	Neuropharmacology HFD-120	**Indication(s)**	Generalized Anxiety Disorder
OCPB Reviewer	R. Kavanagh, B.S.Pharm., Pharm.D., Ph.D.	**Dosage Form**	Orally Disintegrating Tablets
OCPB Team Leader	Raman Baweja, B.S. Pharm., Ph.D.	**Strengths:**	0.25 mg, 0.5 mg, 1 mg, 2 mg
Date of Submission	December 19, 2003	**Dosing Regimen**	0.75 mg – 4 mg daily in 2 – 3 divided doses
PDUFA Due Date	October 19, 2004	**Route of Administration**	Oral
Division Due Date	August 25, 2004	**Sponsor**	Schwarz Pharma Inc.
Estimated Due Date of OCPB Review	August 14, 2004	**Priority Classification**	S

Clinical Pharmacology and Biopharmaceutic Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				

PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X	1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	The approval of this application will be based upon bioequivalence to the referenced labeled drug.
Comments to be sent to firm	X	In addition to alprazolam orally disintegrating tablets the patient population with generalized anxiety disorder may be taking concomitant medications with anticholinergic side effects, (e.g. dry mouth). Since, alprazolam solubility is pH dependent and since drug substances that are not buccally absorbed may have a several hour lag time when administered as rapidly disintegrating tablets, the sponsor should address the effect of saliva pH and dry mouth on bioavailability when water is not co-administered. The office of clinical pharmacology and biopharmaceutics is available to discuss ways that these issues might be addressed.
QBR questions (key issues to be considered)	Bioequivalence Food Effect Effect of salivary pH and dry mouth due to anticholinergic side effects Biowaiver upwards and downwards for the 2 mg and 0.25 mg strengths. PK is linear. Dissolution	
Other comments or information not included above	An inspection for the pivotal bioequivalence study has been requested. See appendices.	
Primary reviewer Signature and Date	**February 3, 2004**	
Secondary reviewer Signature and Date	**February 3, 2004**	

CC: NDA 21-726
HFD-850 (P. Lee)
HFD-120 (TaylorR)
HFD-860 (KavanaghR, BawejaR, MehtaM, SahajwallaC)
CDR

Appendix 4 Inspection Request

From: Baweja, Raman K
Sent: Tuesday, February 03, 2004 5:00 PM
To: Taylor, Richardae
Cc: Katz, Russell G; Laughren, Thomas P; Ware, Jacqueline H; Kavanagh, Ronald E; Baweja, Raman K
Subject: NDA 21,726, Alprazolam Orally Disintegrating Tablets (ODT) - Inspection Request

Richardae
Re: Inspection Request for Study SP691 (1 mg BE study) in NDA 21,726, Alprazolam ODT

OCPB requests that Study SP691 (1 mg BE study; see exact title below) in NDA 21,726, Alprazolam ODT, be inspected by DSI. Please see details regarding the Inspection Request in Ron's email below and forward this request to DSI.
Thank you
Ray

Ricardae

NDA 21-726 is for Alprazolam Orally Disintegrating Tablets for general anxiety disorder. Approval will be based on bioequivalence to the reference labeled drug Xanax™ 1 mg tablets. Consequently, an inspection is requested for the pivotal bioequivalence study. Information on this study is attached below:
Thanks,

Ron

INSPECTION REQUEST

N21-726	**Alprazolam Orally Disintegrating Tablet (ODT)**
Sponsor:	Schwarz Pharma, Inc. 6140 West Executive Dr. Mequaon, WI 53092
Contact Information:	Donna K. Multhauf, Director of Regulatory Affairs 262-238-5171
Pivotal Study:	A Pharmacokinetic Study to Evaluate the Bioequivalence of a Unique New Formulation (Test), Orally Disintegrating Tablet (ODT) of Alprazolam 1 mg, Administered with and Without Water, Compared to a Marketed Immediate Release Alprazolam 1 mg Tablet Formulation (Reference), Xanax® by Pharmacia and UpJohn
Study Number:	SP691
Contractor:	
Clinical Investigator:	
Clinical Study Site:	

Project No.:	AA03436
Contact Information:	/
	/
Bioanalytic Site:	(Location, contact information and project number same as clinical site)
Principal Scientist:	—
Study Report Location:	Volumes 12, 13, and 14 The bioanalytic report is located in appendix 4

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ron Kavanagh
9/24/04 09:30:11 AM
BIOPHARMACEUTICS

Sally Yasuda
9/24/04 09:35:15 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
NDA Number	21-726	**Brand Name**	Alprazolam Orally Disintegrating Tablets
Related NDAs	None	**Generic Name**	Alprazolam Orally Disintegrating Tablets
OCPB Division (I, II, III)	I HFD-860	**Drug Class**	Benzodiazepine
Medical Division	Neuropharmacology HFD-120	**Indication(s)**	Generalized Anxiety Disorder
OCPB Reviewer	R. Kavanagh, B.S.Pharm., Pharm.D., Ph.D.	**Dosage Form**	Orally Disintegrating Tablets
OCPB Team Leader	Raman Baweja, B.S. Pharm., Ph.D.	**Strengths:**	0.25 mg, 0.5 mg, 1 mg, 2 mg
Date of Submission	December 19, 2003	**Dosing Regimen**	0.75 mg – 4 mg daily in 2 – 3 divided doses
PDUFA Due Date	October 19, 2004	**Route of Administration**	Oral
Division Due Date	August 25, 2004	**Sponsor**	Schwarz Pharma Inc.
Estimated Due Date of OCPB Review	August 14, 2004	**Priority Classification**	S

Clinical Pharmacology and Biopharmaceutic Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X	1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	The approval of this application will be based upon bioequivalence to the referenced labeled drug.
Comments to be sent to firm	X	In addition to alprazolam orally disintegrating tablets the patient population with generalized anxiety disorder may be taking concomitant medications with anticholinergic side effects, (e.g dry mouth). Since, alprazolam solubility is pH dependent and since drug substances that are not buccally absorbed may have a several hour lag time when administered as rapidly disintegrating tablets, the sponsor should address the effect of saliva pH and dry mouth on bioavailability when water is not co-administered. The office of clinical pharmacology and biopharmaceutics is available to discuss ways that these issues might be addressed.
QBR questions (key issues to be considered)	Bioequivalence Food Effect Effect of salivary pH and dry mouth due to anticholinergic side effects Biowaiver upwards and downwards for the 2 mg and 0.25 mg strengths. PK is linear. Dissolution	
Other comments or information not included above	An inspection for the pivotal bioequivalence study has been requested. See appendices.	
Primary reviewer Signature and Date	**February 3, 2004**	
Secondary reviewer Signature and Date	**February 3, 2004**	

CC: NDA 21-726
HFD-850 (P. Lee)
HFD-120 (TaylorR)
HFD-860 (KavanaghR, BawejaR, MehtaM, SahajwallaC)
CDR

Appendix 1

Table 1 Studies Submitted

Study	Title	Description
SP691	A Pharmacokinetic Study to Evaluate the Bioequivalence of a Unique New Formulation (Test), Orally Disintegrating Tablet (ODT) of Alprazolam 1 mg, Administered with and Without Water, Compared to a Marketed Immediate Release Alprazolam 1 mg Tablet Formulation (Reference), Xanax® by Pharmacia and UpJohn	Pivotal BE Study 1 mg Fasted BE with and without water ODT vs IR
SP765	A Pharmacokinetic Study to Evaluate the Bioequivalence of a Unique New Formulation (Test), Orally Disintegrating Tablet (ODT) of Alprazolam 0.5 mg, Administered with and Without Water, Compared to a Marketed Immediate Release Alprazolam 0.5 mg Tablet Formulation (Reference), Xanax® by Pharmacia and UpJohn	0.5 mg Fasted BE with and without water ODT vs IR
SP766	A Pharmacokinetic Study to Evaluate the Effect of Food on the Bioavailability of a 1.0 mg Alprazolam Orally Disintegrating Tablet	Food Effect 1 mg ODT

Biowaiver request for 0.25 mg and 2 mg strengths

Instructions for Use/Handling Tradename™

Just prior to administration, remove the tablet from the bottle with dry hands. Immmediately place theTradename™ Tablet on top of the tongue where it will dissolve in seconds, then swallow with saliva. Administration with liquid is not necessary.

Dissolution is pH dependent:

pH	Time	Approximate % Dissolved
1	5 minutes	100%
4.5	5 minutes	100%
6	5 minutes	93%
6.8	5 minutes	50%
6.8	15 minutes	85%

Comments:

Studies were performed with and without water in healthy normal volunters. The patient population with generalized anxiety disorder may be taking concomitant medications with anticholinergic side effects in addition to alprazolam orally disintegrating tablets. Consequently, the amount of saliva and salivary pH may be different than in healthy normal volunteers. Since, alprazolam solubility is pH dependent and since drug substances that are not buccally absorbed may have a several hour lag time when administered as a rapidly disintegrating tablets, the sponsor should address the effect of saliva pH and dry mouth on bioavailability when water is not administered.

The office of clinical pharmacology and biopharmaceutics is available to discuss ways that these issues might be addressed.

Appendix 2 — Inspection request

N21-726	Alprazolam Orally Disintegrating Tablet (ODT)
Sponsor:	Schwarz Pharma, Inc. 6140 West Executive Dr. Mequaon, WI 53092
Contact Information:	Donna K. Multhauf, Director of Regulatory Affairs 262-238-5171
Pivotal Study:	A Pharmacokinetic Study to Evaluate the Bioequivalence of a Unique New Formulation (Test), Orally Disintegrating Tablet (ODT) of Alprazolam 1 mg, Administered with and Without Water, Compared to a Marketed Immediate Release Alprazolam 1 mg Tablet Formulation (Reference), Xanax® by Pharmacia and UpJohn
Study Number:	SP691
Contractor:	
Clinical Investigator:	
Clinical Study Site:	
Project No.:	AA03436
Contact Information:	
Bioanalytic Site:	(Location, contact information and project number same as clinical site)
Principal Scientist:	
Study Report Location:	Volumes 12, 13, and 14 The bioanalytic report is located in appendix 4

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ron Kavanagh
2/4/04 12:00:24 PM
BIOPHARMACEUTICS

Raman Baweja
2/4/04 03:25:25 PM
BIOPHARMACEUTICS
OCPB NDA Filing and Review Form -- Memo to File