

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-726**

**MEDICAL REVIEW(S)**

## Clinical Review of Response to Approvable Letter

**Sponsor:** Schwarz Pharma, Inc  
**Drug:** Alprazolam Orally Disintegrating Tablet (NIRAVAM)  
**NDA:** 21,726 Amendment 007  
**Material Submitted:** Safety Data, Proposed Labeling  
**Correspondence Date:** November 18, 2004  
**Date Received:** November 23, 2004  
**Drug Category:** Anxiolytic  
**Forms available for proposed study:** 0.25, 0.5, 1.0, 2.0 mg tablet

### I. Background and Summary

Alprazolam Orally Disintegrating Tablet (NIRAVAM) is a new formulation of alprazolam. The sponsor seeks indications for NIRAVAM in the treatment of Panic Disorder and Generalized Anxiety Disorder, based on bioequivalence data and previously established efficacy results of alprazolam conventional tablet in the treatment of these anxiety disorders. The Division concluded that the sponsor had established bioequivalence between the new orally disintegrating tablet and the conventional alprazolam tablet. Thus, the Division issued an Approvable letter to the sponsor by fax on October 19, 2004.

We requested additional clinical safety information regarding the 6 normal subjects treated with NIRAVAM who developed abnormal clinical laboratory findings. In my opinion, the sponsor has submitted a complete response. Furthermore, the laboratory findings do not appear to be clinically significant, and they would not change the conclusion that the submission is approvable. In addition, the sponsor's proposed labeling (containing minimal changes) is acceptable.

### II. Clinical Laboratory Findings

Safety data were gathered and submitted for all of the 52 healthy subjects enrolled in the bioequivalence studies. The extent of safety data are relatively limited, since the studies involved a small number of subjects, and each subject received only one or two doses of the study drug. Moreover, the study drug was not evaluated in the target populations (patients with Panic Disorder or Generalized Anxiety Disorder). Nevertheless, the safety assessment was adequate and appropriate, given the objectives of the clinical program. The total exposure to alprazolam ODT was 125 person-days for a total of 52 healthy adult male and female subjects.

Three subjects (5.8%) in the Alprazolam ODT group developed elevated ALT levels after dosing. There was no placebo group for comparison. None of the subjects in the alprazolam conventional tablet group had elevated ALT levels. There were no other cases of other liver function test abnormalities. One subject (2%) in the alprazolam ODT group had hyperglycemia. None in the alprazolam conventional tablet group had

hyperglycemia. Two subjects (4%) in the ODT group had low hemoglobin concentrations, compared to none in the conventional tablet group.

In most cases, the laboratory abnormalities were mild and transient, and no specific interventions were required. In one case of decreased hemoglobin, the subject was treated with supplemental iron. No subject was discontinued from the study due to a clinical laboratory abnormality. Subjects with abnormal LFTs had only isolated increases in ALT, without abnormalities of other LFTs. In the cases of decreased hemoglobin, the subjects did not have decreased hematocrit. It is possible that abnormal LFTs were related to drug treatment, but it is unlikely that decreased hemoglobin or hyperglycemia were related to treatment. It is possible that the clinical symptoms listed were related to the clinical laboratory abnormality; however, it is also quite likely that most of the symptoms were related to alprazolam treatment (lethargy, tiredness, drowsiness, dizziness). The table below illustrates some of the details of the 6 cases.

Sub. No.	Test	Result	Normal Range	Severity	SAE	Recovery	Action	Relation To AODT	Clinical Symptoms
8	ALT	52	1-39	Mild	No	Complete	None	Possible	None
11	ALT	47	1-39	Mild	No	Complete	None	Possible	None
6	ALT	47	1-39	Mild	No	Complete	None	Possible	Lethargic, poor appetite
3	Gluc	121	73-113	Mild	No	Complete	None	Unlikely	None
11	Hb	11.5		Mild	No	Complete	None	Unlikely	Tired, drowsy
13	Hb	10.7		Mild	No	Complete	Iron suppl.	Unlikely	Tired. Dizzy

### III. Sponsor's Labeling Changes

The sponsor has incorporated all of the Division's requested changes to labeling. Most of the sponsor's proposed changes in labeling are minimal (inserting "NIRAVAM," grammar clarification, etc). The sponsor has proposed two additions.

In the "Information for Patients" section, the sponsor would like to add the following language: — remove NIRAVAM™ tablets from the bottle until just prior to dosing. — immediately placed on the tongue — and be swallowed with the saliva.

#### The sponsor has added: **Instructions for Use/Handling NIRAVAM™ Tablets**

Just prior to administration, remove the tablet from the bottle. Immediately place the NIRAVAM™ tablet on top of the tongue where — swallow with saliva. Administration with liquid is not necessary.

#### **IV. Conclusions**

The sponsor has responded adequately to the Division's request for additional information regarding clinical laboratory results. The additional information has been helpful. At this point, I do not have any particular safety concerns regarding NIRAVAM treatment and the potential development of clinical laboratory abnormalities. We will need to monitor for such potential adverse events during the post-marketing period.

In my opinion, the sponsor's proposed labeling is acceptable.

#### **V. Recommendations**

From a clinical perspective, I recommend that the Division take an Approval action for NDA 21,726.

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Robert Levin, M.D., December 6, 2004  
Medical Reviewer,  
FDA CDER ODE1 DNDP HFD 120

cc: HFD 120  
T Laughren  
P Andreason  
C Taylor

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Robert Levin  
12/6/04 04:48:47 PM  
MEDICAL OFFICER

Thomas Laughren  
1/13/05 01:15:18 PM  
MEDICAL OFFICER

I agree that this application can now be approved--TPL

**MEMORANDUM      DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:**            October 18, 2004

**FROM:**            Thomas P. Laughren, M.D.  
Team Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120

**SUBJECT:**        Approvable Action for Alprazolam ODT (0.25, 0.5, 1, and 2 mg)

**TO:**                File for NDA 21-726  
[Note: Should be filed with 12-19-03 original submission.]

**Background**

Alprazolam, a benzodiazepine, is currently available in immediate release oral tablet strengths of 0.25, 0.5, 1, and 2 mg for the treatment of anxiety and panic disorder. This application provides data in support of an orally disintegrating tablet formulation of this drug in the same strengths, for the same indications. The clinical program for this new formulation consisted of 3 pharmacokinetic studies. These studies were conducted under IND 63,934. We held a preNDA meeting with the sponsor on 6-26-03 and reached agreement on what would be needed for the NDA.

The pharmacokinetic data in this application have been reviewed by Ronald Kavanagh, Ph.D., from OCPB, and the clinical data have been reviewed by Robert Levin, M.D., from the clinical group. Although no pharm/tox data were submitted as part of this application, Aisar Atrakchi, Ph.D., from the pharmacology group, has commented on concerns related to \_\_\_\_\_, an excipient of this new formulation. The CMC data for this application have been reviewed by Chhagan Telle, Ph.D., from the chemistry group.

**Pharmacokinetic Findings**

The clinical program for this new formulation consisted of 3 pharmacokinetic studies, including 2 bioequivalence studies (SP691 and SP765), that compared the new ODT formulation with Xanax as the reference product, both in a fasted state. Both were 3-way crossover studies, comparing a single dose of Xanax with the same dose of ODT, with and without water. SP691 compared 1 mg strengths and SP765 compared 0.5 mg strengths. OCPB concluded that both studies demonstrated bioequivalence, and that the lowest and highest strengths (0.25 and 2 mg) can be waived due to compositional proportionality. The third study (SP766) examined food effect, showing that a high fat meal decreased the Cmax but did not change the AUC.

DSI audited 1 of the bioequivalence studies (SP691) and concluded that the alprazolam data were acceptable. However, they concluded that the alpha-hydroxyalprazolam (AOH) data were not acceptable, due, in the view of DSI, to the failure of the testing facility to select appropriate quality controls for the AOH. I've discussed this issue with OCPB, and they do not feel that the AOH data are relevant to this application (AOH is less than 5% of circulating alprazolam, and its PK depends less on formulation than does that of alprazolam).

Given the pH dependence for this product, Dr. Kavanagh has recommended that the sponsor commit to \_\_\_\_\_

\_\_\_\_\_ He has also recommended a study on the effect of anticholinergic drugs on absorption, and a literature search on other issues related to absorption. These are recommendations, and not phase 4 commitments, and I agree. In addition, OCPB has proposed an alternative dissolution specification.

### Pharmacology/Toxicology Findings and Issues

\_\_\_\_\_, are present as impurities at levels of \_\_\_\_\_. Dr. Atrakchi comments that, although the safety profile of \_\_\_\_\_ is known, it is not for \_\_\_\_\_. A small amount of information is available for \_\_\_\_\_ but little to none for \_\_\_\_\_. The pharm/tox group has recommended that the level of specification be reduced for \_\_\_\_\_. We have also asked the sponsor to justify the safety of the \_\_\_\_\_ that would be present, given the current specification.

### CMC Issues

This ODT formulation was made by \_\_\_\_\_

There are several CMC issues that would need to be addressed prior to final approval of this product, and these are detailed in the approvable letter.

The originally proposed name was considered acceptable by DMETS, but not by DDMAC, since they considered it promotional. The sponsor has proposed an alternative name, i.e., Niravam, and this has been deemed to be acceptable.

### PREA Requirements

We are recommending waiving these requirements \_\_\_\_\_

## **Clinical Review**

The safety database for this new formulation was quite limited, since there were only the 3 SD pk studies. The only findings of potential interest were some laboratory abnormalities reported for ODT patients but not for Xanax patients:

- 3 subjects (6%) with increased SGPT for ODT, none for Xanax
- 2 subjects (4%) with hyperglycemia for ODT, none for Xanax
- 4 subjects (8%) with anemia for ODT, none for Xanax

I checked with Dr. Levin, and he indicated that no further details on the extent of the abnormalities in these parameters were provided. While it seems highly unlikely that this change in formulation would alter the safety profile, we need to ask for more details on these cases, as part of the approvable action.

There was no need for efficacy data since efficacy was extrapolated from existing data.

## **Labeling**

OCPB has recommended some very modest changes to labeling, and I have no objection to these changes.

## **Conclusions/Recommendations**

I agree that this application is approvable, and I recommend that we issue the attached approvable letter with draft labeling, in anticipation of final approval.

cc:

Orig NDA 21-726/Alprazolam ODT

HFD-120/DivFile

HFD-120/TLaughren/RKatz/RLevin/RTaylor

**DOC:** Memo Alprazolam ODT AE1.doc

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/s/

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Thomas Laughren  
10/18/04 03:44:53 PM  
MEDICAL OFFICER

## CLINICAL REVIEW

Application Type NDA  
Submission Number 21,726

Letter Date December 19, 2003  
Stamp Date December 23, 2003  
PDUFA Goal Date October 19, 2004

Reviewer Name Robert Levin, M.D.  
Review Completion Date September 20, 2004

Established Name Alprazolam Orally  
Disintegrating Tablets  
(Proposed) Trade Name Niravam;  
Therapeutic Class Anxiolytic; benzodiazepine  
Applicant Schwarz Pharma Inc.  
Priority Designation S

Formulation 0.25, 0.5, 1, and 2 mg Orally  
Disintegrating Tablets  
Dosing Regimen 0.25- 4 mg/day

Indications Panic Disorder, Generalized  
Anxiety Disorder  
Intended Population Adults with above Anxiety  
Disorders

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**1 EXECUTIVE SUMMARY**

**1.1 Recommendation on Regulatory Action**

I recommend that the Division take an approvable action for NDA 21,726 for Alprazolam Orally Disintegrating Tablets in the treatment of adult patients with a diagnosis of Panic Disorder (with or without Agoraphobia) or Generalized Anxiety Disorder. The sponsor has demonstrated the bioequivalence of NIRAVAM (orally disintegrating alprazolam tablets) and the conventional alprazolam formulation.

**1.2 Recommendation on Postmarketing Actions**

Currently, I do not recommend any specific risk management or Phase 4 commitments.

**1.3 Summary of Clinical Findings**

**1.3.1 Brief Overview of Clinical Program**

Alprazolam Orally Disintegrating Tablets contains alprazolam, a benzodiazepine anxiolytic drug. Alprazolam ODT is an orally administered formulation of alprazolam that rapidly disintegrates on the tongue and does not require water to aid dissolution or swallowing. Based on previously established indications for the reference drug Xanax (alprazolam), the sponsor seeks indications for Alprazolam ODT in the treatment of: 1) Panic Disorder with or without Agoraphobia; and 2) Generalized Anxiety Disorder. The sponsor also proposes indications for the management of Anxiety Disorder (a condition corresponding most closely to the DSM-III-R diagnosis of Generalized Anxiety Disorder) or the short-term relief of symptoms of anxiety, since these are indications for Xanax. The drug would be indicated for the treatment of adult patients with the above diagnoses.

The clinical program under review consisted of three bioequivalence studies in healthy subjects. The primary objective was to establish the bioequivalence of Alprazolam ODT 0.5 mg and 1 mg tablets with the reference compound Xanax (conventional immediate-release 0.5 mg and 1 mg alprazolam tablets). No efficacy studies were conducted with the drug; however, safety data were collected in each bioequivalence study. The bioequivalence studies involved a total of 52 healthy adult male and female subjects. Subjects were exposed to either one or two doses of either the 0.5 mg or 1 mg orally disintegrating tablet. The drug was given either in the fasting or fed state with or without water. In the bioequivalence program, the total exposure to Alprazolam Orally Disintegrating Tablets was 125 person-days (0.337). In addition, 35 healthy subjects were exposed to the conventional immediate-release formulation of alprazolam 0.5 or 1 mg tablet for a total exposure of 35 person-days.

### 1.3.2 Bioequivalence

In three studies, the sponsor demonstrated the bioequivalence of Alprazolam Orally Disintegrating Tablets (0.5 mg and 1 mg) and the conventional immediate-release alprazolam tablet (0.5 and 1 mg). The sponsor conducted two fasting bioequivalence studies to assess the bioequivalence of test drug, Alprazolam Orally Disintegrating Tablet (ODT) with the reference drug, Xanax® Tablet. The first study (SP691) compared the pharmacokinetic profiles of the 1mg tablets of the two alprazolam formulations. The second study (SP765) compared the PK profiles of the 0.5 mg tablets of each formulation. In both 3-period crossover studies, healthy subjects received a single dose of the reference drug, a single dose of the test drug administered with water, and a single dose of the test drug administered without water. Alprazolam ODT was placed on the tongue for oral disintegration, with or without water. Each treatment was separated by a one-week washout period.

The results indicate that Alprazolam ODT tablets (0.5 mg and 1 mg) are bioequivalent to the reference drug, Xanax® tablets (0.5 mg and 1.0 mg) when Alprazolam ODT is administered either with or without water. In both cases, the 90% confidence intervals for the comparison of ln-transformed C<sub>max</sub>, AUC(0-t), and AUC(0-inf) were within the acceptable range of 80% to 125%, indicating that Alprazolam ODT administration results in a similar rate and extent of alprazolam exposure when compared to the reference Xanax® Tablet. When analyzed by gender, the results for the 1mg tablet study indicate that there were no significant or consistent differences in C<sub>max</sub> between gender groups. However, female subjects tended to have marginally lower AUC values for all three drug treatments (Alprazolam ODT +/- water and Xanax®). These differences consisted of approximately one standard deviation. The sponsor expects that these differences would not be clinically significant. In the 0.5 mg tablet study, only 20% (3/15) of subjects were female subjects. As a result, the sponsor did not perform a formal subgroup analysis by gender.

The sponsor conducted **Study SP766** to evaluate the effect of food intake on the bioavailability of the Alprazolam ODT 1mg tablet. The presence of food decreased the rate of absorption of alprazolam, resulting in a decrease in C<sub>max</sub> of 23% and an increase in T<sub>max</sub> from 2.2 to 4.4 hours after ingestion of a high-fat meal. However, food intake did not affect the overall extent of alprazolam absorption (AUC) or the elimination half-life (12.5 hours). Results of the analysis by gender indicated that there were no significant differences between male and female subjects in the pharmacokinetic profile of Alprazolam ODT when administered with food.

### **1.3.3 Safety**

Safety data were gathered and submitted for all of the 52 healthy subjects enrolled in the bioequivalence studies. The extent of safety data are relatively limited, since the studies involved a small number of subjects, and each subject received only one or two doses of the study drug. Moreover, the study drug was not evaluated in the target populations (patients with Panic Disorder or Generalized Anxiety Disorder). Nevertheless, the safety assessment was adequate and appropriate, given the objectives of the clinical program. The total exposure to alprazolam ODT was 125 person-days for a total of 52 healthy adult male and female subjects. Generally, the drug was reasonably safe and well tolerated. There were no deaths or other serious adverse events in any of the 3 studies. Only one subject discontinued from the study due to an adverse event. The event was not related to study drug treatment. The most commonly reported drug-related adverse events were the types that would be expected with treatment with alprazolam. Fatigue, somnolence, dizziness, and lightheadedness were the most commonly reported adverse events. It appeared that these adverse events were dose-related, as would be expected. There were no new or unexpected findings with alprazolam treatment in these studies.

### **1.3.4 Dosing Regimen and Administration**

With ~~the~~ the sponsor proposes a new formulation and route of administration for alprazolam. Patients would be instructed to place the orally disintegrating alprazolam tablet on the tongue. The patient would swallow the resultant mixture without water.

~~the~~ (alprazolam orally disintegrating tablet) would be dosed in a manner similar to conventional alprazolam tablets in the treatment of Panic Disorder and Generalized Anxiety Disorder. Treatment should be initiated with a dose of 0.25 to 0.5 mg given three times daily. The dose may be increased, as needed for adequate response, at intervals of 3 to 4 days, to a maximum daily dose of approximately 4 mg, given in divided doses. However, successful treatment of Panic Disorder may require daily doses greater than 4 mg. In controlled trials in Panic Disorder, doses ranged from 1 to 10 mg per day. The mean daily dose was approximately 5 to 6 mg. For patients treated with doses greater than 4 mg/day, periodic reassessment and consideration of dosage reduction is advised. Proposed labeling includes additional appropriate details regarding dosage and administration. The sponsor's proposed dosing regimen is reasonable, based on previous experience with alprazolam dosing and based on the bioequivalence results.

### 1.3.5 Drug-Drug Interactions

Drug interaction studies have not been conducted specifically with Alprazolam ODT. However, drug interaction studies have been conducted with conventional alprazolam tablets.

Alprazolam is primarily metabolized via the CYP3A4 enzyme system. Thus, drugs which are potent inhibitors of CYP3A4 would be expected to increase plasma alprazolam concentrations in vivo. The following drugs have been studied in vivo, and the extent of increases in alprazolam AUC are indicated: itraconazole (2.7 fold); nefazodone (1.98 fold); ketoconazole (3.98 fold); erythromycin (1.61 fold); and fluvoxamine (1.96 fold). Fluoxetine resulted in a modest (30%) increase in alprazolam concentrations. The use of alprazolam is contraindicated with ketoconazole and itraconazole.

CYP3A4 inducers would be expected to decrease plasma alprazolam concentrations. Following administration of carbamazepine 300 mg/day for 10 days, oral clearance of alprazolam was increased from 0.90 mL/min/kg to 2.13 mL/min/kg.

Alprazolam can produce additive CNS depressant effects when co-administered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression. The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20% by the concomitant administration of XANAX.

Based on clinical drug interaction studies, caution is recommended for co-administration of alprazolam with the following medications: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from *in vitro* studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. Co-administration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.

### 1.3.6 Special Populations

#### 1.3.1 Pediatric Population

Pediatric subjects were not studied in the Alprazolam Orally Disintegrating Tablet clinical program. The safety and effectiveness of conventional alprazolam tablets has not been studied in subjects below the age of 18 years.

#### **Pregnant or Nursing Women, Labor and Delivery, Oral Contraceptive Use**

Teratogenic Effects:

XANAX XR has been placed in Pregnancy Category D.

The sponsor directs readers: "(See WARNINGS section)."

Nonteratogenic Effects:

The sponsor states: "It should be considered that the child born of a mother

who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines.”

**Labor and Delivery:**

XANAX has no established use in labor or delivery.

**Nursing Mothers:**

Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use XANAX.

**Women Using Oral Contraceptive Medications**

Co-administration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.”

**Geriatric Population**

The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. The sponsor states that the smallest effective dose of alprazolam should be used in the elderly to preclude the development of adverse effects such as ataxia and oversedation.

**Hepatic Impairment**

For patients with clinically significant hepatic impairment, lower doses should be used than those used in patients with normal hepatic function.

**APPEARS THIS WAY  
ON ORIGINAL**

## **2 INTRODUCTION AND BACKGROUND**

### **2.1 Product Information**

— (alprazolam orally disintegrating tablet) contains alprazolam, which is a triazolo analog of the 1,4 benzodiazepine class of CNS-active compounds. — is an orally administered formulation of alprazolam that rapidly disintegrates on the tongue and does not require water to aid dissolution or swallowing.

Each orally disintegrating tablet contains either 0.25, 0.5, 1 or 2 mg of alprazolam and the following inactive ingredients: colloidal silicon dioxide, corn starch, crospovidone, magnesium stearate, mannitol, methacrylic acid copolymer, microcrystalline cellulose, natural and artificial orange flavor, sucralose and sucrose. The 0.25 mg and 0.5 mg tablets also contain yellow iron oxide.

The sponsor seeks approval of — for the treatment of adult patients with a diagnosis of either Panic Disorder (with or without Agoraphobia) or Generalized Anxiety Disorder. The indications sought are based on the established efficacy and safety of the reference drug, Xanax (alprazolam) in the treatment of Panic Disorder and Generalized Anxiety Disorder. Xanax also has an indication for Anxiety Disorder, which closely resembles Generalized Anxiety Disorder. In addition, Xanax is indicated for the short-term relief of symptoms of anxiety.

The proposed dosing regimen for — is similar to the regimen for conventional alprazolam tablets. However, — tablets should be placed on the tongue to allow for disintegration. Treatment should be initiated with a dose of 0.25 to 0.5 mg given three times daily. The dose may be increased, as needed for adequate response, at intervals of 3 to 4 days, to a maximum daily dose of approximately 4 mg, given in

divided doses. However, successful treatment of Panic Disorder may require daily doses greater than 4 mg. In controlled trials in Panic Disorder, doses ranged from 1 to 10 mg per day. The mean daily dose was approximately 5 to 6 mg. For patients treated with doses greater than 4 mg/day, periodic reassessment and consideration of dosage reduction is advised. Proposed labeling includes additional appropriate details regarding dosage and administration.

## **2.2 Currently Available Treatment for Indications**

A number of medications have been approved to treat Panic Disorder. These include two benzodiazepines (alprazolam and clonazepam) and three SSRI antidepressants (fluoxetine, sertraline, and paroxetine). Several drugs have been approved for the treatment of Generalized Anxiety Disorder (alprazolam, buspirone, paroxetine, and venlafaxine extended-release). A number of benzodiazepine drugs have been approved for short-term management of symptoms of anxiety (alprazolam, clorazepate, diazepam, lorazepam, and oxazepam).

## **2.3 Availability of Proposed Active Ingredient in the United States**

The active ingredient of Alprazolam Orally Disintegrating Tablet would be readily available in the U.S.

## **2.4 Presubmission Regulatory Activity**

### **DNDP Discussions with the Sponsor About the Alprazolam ODT Submission**

On June 26, 2003, a Type B (pre-NDA) meeting was held between the Division of Neuropharmacological Drug Products and Schwarz Pharma, Inc. to discuss the submission of the application. The FDA meeting minutes, dated July 30, 2003, summarize the important discussion points. The Division agreed that the proposed package would be acceptable. In addition to the bioequivalence data, the NDA submission would include the existing alprazolam preclinical package, the approval information for Xanax tablets, the RLD, and additional published literature. The proposed indications, strengths, and dosing for alprazolam orally disintegrating tablets would be the same as those approved for Xanax Tablets, the RLD. The indications would be supported by the clinical studies submitted to the Xanax Tablets application, NDA 18,276.

In pharmacokinetic trials, the sponsor planned to demonstrate the bioequivalence of Xanax Tablets (0.5 and 1 mg) and alprazolam ODT (0.5 and 1 mg). The sponsor requested biowaivers for the other strengths (0.25 and 2 mg), stating that the formulations of all strengths are therefore dose-proportional. Furthermore, in discussion with the bioequivalence division of OGD (February 2, 2002) the Agency determined that a waiver could be submitted for the 2 mg tablet. The Division stated that biowaivers would be granted for the 0.25 mg and 2 mg tablets, based on the proportional similarity in composition, as long as the 0.5 and 1 mg tablets were

studied adequately. However, the biowaiver for the 0.5 mg tablet might be problematic, since the sponsor did not justify the total changes in each individual excipient.

A full report on the justification for the selection of the dissolution method and specification including, but not limited to, different apparatus, different media, and different speeds should be submitted. From the preliminary dissolution profiles presented in the stability data, the sponsor was encouraged to re-evaluate whether the dissolution specification of  $Q = \text{---}$  at 30 minutes or  $Q = \text{---}$  at 15 minutes is appropriate. In order to facilitate the future NDA review, the above justification and dissolution profiles, including those from 3 media, should be submitted to the Clinical Pharmacology & biopharmaceutics section.

The Division advised that if a labeling claim for taking the orally disintegrating tablet with or without water is intended, a study to evaluate this issue should be conducted, or a justification should be provided for not doing so. The sponsor responded that the bioequivalence study with the 1 mg tablet demonstrated bioequivalence with or without water. The Division also recommended that the sponsor conduct a food-effect study for the new formulation of alprazolam, preferably with the highest strength (2 mg). If the sponsor does not plan to conduct a food-effect study, they should provide a justification for not doing so. The Division encouraged the sponsor to demonstrate, with dissolution data (by an appropriate dissolution method), that halving the scored tablets does not affect the release profile of the tablet. If such a study were not conducted, the sponsor would need to provide a rationale for not doing so.

The Division agreed that  $Q = \text{---}$  of stability data would be acceptable for filing the NDA but cautioned against submitting stability updates in the final three months of the review cycle. The approved expiration period would be a review issue and will be decided based on the quantity and quality of the stability data available at the time of the review. The Division requested that a  $Q = \text{---}$  test be added to the stability testing for the dosage form to be packaged in bottles. The Division also requested assurance that the  $Q = \text{---}$  is consistent.

On July 16, 2003, the Division provided additional comments and recommendations regarding the CMC portion of the NDA submission. The sponsor must include ICH photostability testing of the drug substance and the drug product. The drug product stability protocol should demonstrate the photostability of all strengths of the drug product, as well as the adequacy of the proposed commercial container closure systems used to protect the drug product. It would be necessary to test for specific impurities in the drug product and list these known impurities in the drug product regulatory release specifications. The sponsor must also provide the statistical analysis results (per ICH Q1A) for the  $Q = \text{---}$  stability data and subsequent stability data planned for the submission. Finally, the magnesium stearate used to manufacture the drug product must derive from a plant source; if it derives from an animal source, the sponsor would need to guarantee that the animals used are from a country determined to be "non-BS".

### **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

#### **3.1 Biopharmaceutics**

Based on the presented data the Office of Clinical Pharmacology and Biopharmaceutics concludes that the NDA for Alprazolam Orally Disintegrating Tablets is acceptable. For details, please refer to Dr. Ron Kavanaugh's review.

#### **3.2 Division of Scientific Investigation**

The final draft of the DSI review is currently not available.

#### **3.3 Chemistry**

The final draft of the chemistry review is currently unavailable. However, the chemistry reviewer has concerns about whether product qualifies as an orally disintegrating tablet, based on the wide range of disintegration times observed in study subjects. The chemistry reviewer also strongly recommends that patients should immediately dispose the portion of the unused tablet, if they are taking only a split portion of the tablet.

#### **3.4 DMETS**

The DMETS reviewers did not object to the sponsor's originally proposed proprietary name, QIETAL. DMETS has drawn this conclusion, based on an analysis of potential name confusion with other proprietary and established drug names.

#### **3.5 DDMAC**

DDMAC and their regulatory counsel state that the name \_\_\_\_\_ does not follow the regulations and that they strongly object to our approving this name. DDMAC objects to the trade name ' \_\_\_\_\_ because " \_\_\_\_\_

The Division has discussed the potential problem with the proposed name, \_\_\_\_\_. The sponsor will submit an application for two potential alternative proprietary names for the drug: 1) NIRAVAM; and 2) \_\_\_\_\_

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

Sources of clinical data included the biopharmaceutical data, safety data, data tables, and data summaries provided by the sponsor. There were data from two bioequivalence studies (SP691 and SP765) and one bioavailability food effect study (SP766).

### 4.2 Table of Clinical Studies

Table 4.2. Bioequivalence Studies

STUDY	SP691	SP765	SP766
Type	Bioequivalence- fasting	Bioequivalence- fasting	Food Effect- Bioavailability
Subjects	21 healthy subjects	15 healthy subjects	16 healthy subjects
Study Drug	1 mg Alp ODT & 1 mg Alprazolam Tablet	0.5 mg Alp ODT & 0.5 mg Alprazolam Tablet	1 mg Alprazolam ODT
Design	Single-dose, randomized, open-label, 3-treatment crossover study to demonstrate bioequivalence of Alp ODT 1 mg & Alprazolam Tablet 1 mg (in fasted state)  Treatments: 1. Alp ODT without water 2. Alp ODT with water 3. Conventional Alp tablet (Doses of 1 mg)  7-day washout period	Single-dose, randomized, open-label, 3-treatment crossover study to demonstrate bioequivalence of Alp ODT 0.5 mg and Alprazolam Tablet 0.5 mg (in fasted state)  Treatments: 1. Alp ODT without water 2. Alp ODT with water 3. Conventional Alp tablet (Doses of 0.5 mg)  7-day washout period	Single-dose, randomized, open-label, 2-treatment crossover food-effect study of Alp ODT 1 mg  Treatments: 1. Alp ODT 1 mg in fasted state 2. Alp ODT 1 mg in fed state, after a high fat meal
Results	Demonstrated bioequivalence for 1 mg Alprazolam ODT- (AUCs within acceptable range)	Demonstrated bioequivalence for 0.5 mg Alprazolam ODT- (AUCs within acceptable range)	Food effect: Decreased C <sub>max</sub> Increased T <sub>max</sub> None on overall absorption

### 4.3 Review Strategy

I reviewed the data, data tables, and summaries for the three studies. The safety data and biopharmaceutical data were reviewed in detail. Dr. Ron Kavanaugh provided considerable consultation regarding the biopharmaceutical data.

#### **4.4 Data Quality and Integrity**

The data quality and integrity are adequate in this submission.

#### **4.5 Compliance with Good Clinical Practices**

It appears that the studies were conducted in compliance with good clinical practices.

#### **4.6 Financial Disclosures**

The sponsor submitted appropriate and sufficient documentation regarding potential financial interests and arrangements of clinical investigators (Form FDA 3454 2/03). The financial disclosure is adequate. It appears that there is no significant conflict of interest on the part of investigators involved in the studies.

### **5 INTEGRATED REVIEW OF BIOEQUIVALENCE**

The sponsor conducted three studies for the — bioequivalence program. Two of the studies assessed the bioequivalence of either the 1 mg or the 0.5 mg orally disintegrating tablet with the 1 mg or 0.5 mg conventional alprazolam tablet. A third study was a bioavailability food effect study using the 1 mg — orally disintegrating. Table above 4.2 illustrates some of the features of the studies.

#### **5.1 Protocol SP691**

**5.1.1 Study Dates:** February 21, 2003 to March 11, 2003

#### **5.1.2 Objective**

The study objective was to evaluate the single dose bioequivalence of a 1 mg Alprazolam ODT formulation administered with and without water, compared with the reference product, Xanax (alprazolam), when administered with water following a single 1 mg dose in the fasted state.

#### **5.1.3 Subject Selection**

##### **5.1.3.1 Inclusion Criteria**

A total of 21 healthy adult subjects between the ages of 19 and 50 (13 male and 8 female) completed the study. Subjects must have been non-smokers. Women were of non-

childbearing potential or used a medically acceptable barrier method of contraception. Women must not have been pregnant or nursing.

### 5.1.3.2 Exclusion Criteria

Exclusion criteria included numerous appropriately specified organ system diseases, such as hepatic, renal, GI, pulmonary, endocrine, oncologic, or psychiatric illnesses. Subjects must not have had a history of allergic or adverse response to alprazolam or related drugs (benzodiazepines). Subjects could not have a history of or current evidence of narrow angle glaucoma. Subjects could not have been receiving treatment with particular enzymes that might alter hepatic enzyme functioning. Women could not have used a hormonal method of contraception with appropriately specified time periods before the study. Other medications were appropriately prohibited.

### 5.1.3.3 Screening Procedures

Subjects were screened within 21 days before enrollment. Assessments included medical history, physical examination, measurement of height and weight, vital signs, ECG, pregnancy testing, and standard clinical laboratory tests, as well as HIV antibody and hepatitis antibody screening.

### 5.1.4 Design of Study SP691

This was a randomized, open-label, single dose, 3-treatment crossover study assessing the bioequivalence of — orally disintegrating 1mg tablets with conventional alprazolam 1 mg tablets. Subjects were randomized to one of three sequences of treatments. Each subject received all three treatments after a 10-hour fast. Each treatment was separated by a 7-day washout period. For each study period, subjects were confined to the clinic during the 48-hour post-dose assessment, and they returned to the clinic for the 72-hour sample collection. Blood samples were collected frequently (pre-dosing and up to 72 hours), in order to measure PK parameters.

#### Study Treatments:

##### A. — 1 mg + water

Single oral 1mg dose of — was placed on the tongue until there was total disintegration of the tablet. Subjects then swallowed the drug mixture followed by 240 mL of water.

##### B. — 1 mg without water

Single oral 1mg dose of — was placed on the tongue until there was total disintegration of the tablet. Subjects then swallowed the drug mixture without administration of water.

##### C. Xanax (alprazolam) 1 mg with water

Single oral 1 mg dose of alprazolam tablet administered with 240 mL of water.

### 5.1.4 Results of Study SP691

The tables below summarize the arithmetic means and standard deviations of plasma PK parameters and statistical comparisons of ln-transformed C<sub>max</sub>, AUC(0-t), and AUC(0-inf) following Treatments A, B, C. These are the sponsor's results.

**Table 5.1.5.A. Study SP691 Bioequivalence Results (with water)**

PK Parameter	TREATMENT A ODT 1 MG WITH WATER		TREATMENT B XANAX 1 MG WITH WATER		90% CI	% mean ratio
	Mean	SD	Mean	SD		
C <sub>max</sub> (ng/mL)	14.39	2.12	15.48	2.19		
T <sub>max</sub> (hr)	1.91	0.87	1.71	0.85		
AUC(0-t) ng*hr/mL	241.5	64.23	259	66.8		
AUC(0-inf) ng*hr/mL	249	69.73	267.66	75.96		
T <sub>1/2</sub> (hr)	12.4	3.11	12.8	3.28		
K <sub>el</sub> (1/hr)	0.059	0.014	0.057	0.012		
AUCR	0.973	0.018	0.973	0.023		
ln(C <sub>max</sub> )	2.656	0.151	2.731	0.134	87.85- 97.4	92.5
ln(AUC(0-t))	5.452	0.273	5.527	0.25	89.61- 95.92	92.7
ln(AUC(0-inf))	5.48	0.283	5.555	0.267	89.55- 95.98	92.7

**Table 5.1.5.B. Study SP691 Bioequivalence Results (without water)**

PK Parameter	TREATMENT B ODT 1 MG W/OUT WATER		TREATMENT C XANAX 1 MG + WATER		90% CI	% mean ratio
	Mean	SD	Mean	SD		
C <sub>max</sub> (ng/mL)	14.497	2.598	15.48	2.19		
T <sub>max</sub> (hr)	2.1	1.06	1.71	0.845		
AUC(0-t) ng*hr/mL	246.6	69.08	259.01	66.79		
AUC(0-inf) ng*hr/mL	254.68	76.098	267.66	75.956		
T <sub>1/2</sub> (hr)	12.5	3.05	12.8	3.28		
K <sub>el</sub> (1/hr)	0.06	0.01	0.057	0.0123		
AUCR	0.972	0.02	0.973	0.023		
ln(C <sub>max</sub> )	2.659	0.176	2.731	0.1339	88.4- 98.0	93.1
ln(AUC(0-t))	5.472	0.2738	5.527	0.2499	91.64- 98.1	94.8
ln(AUC(0-inf))	5.5	0.287	5.555	0.2673	91.62- 98.19	94.8

For alprazolam, the mean ratios of ln-transformed C<sub>max</sub>, AUC(0-t), and AUC(0-inf) for the comparison of ODT 1 mg with water versus Xanax 1 mg with water were 92.5%, 92.7%, and 92.7%, respectively. The 90% CI were 87.85%- 97.4%, 89.61%- 95.92%, and 89.55% - 95.98%, respectively. Since the 90% CI did not encompass 100%, the

results indicate a small but statistically significant difference in the rate and extent of alprazolam when the test ODT formulation is administered with water compared to when Xanax is administered with water. Nevertheless, the 90% CI for the comparison of these two treatments were still within the 80% to 125% range required for the demonstration of bioequivalence. The sponsor concludes that the differences, although statistically significant, are too small to have any clinical relevance.

Comparison of alprazolam ln-transformed C<sub>max</sub>, AUC(0-t), and AUC(0-inf) between ODT 1 mg without water and Xanax 1 mg with water yielded similar results. The mean ratios were 93.1%, 94.8%, and 94.8%, respectively. The 90% CI were 88.4%- 98%, 91.64%- 98.1%, and 96.62%- 98.19%, respectively. The results indicate a small but statistically significant difference in the rate and extent of alprazolam when the test ODT formulation was administered without water compared to when Xanax was administered with water. Nevertheless, the 90% CI for the comparison of these two treatments were still within the 80% to 125% range required for the demonstration of bioequivalence. The sponsor concludes that the differences, although statistically significant, are too small to have any clinical relevance.

During Treatment A (ODT 1 mg with water), the mean  $\pm$  disintegration time was 63.9  $\pm$  37.96 seconds, ranging from 21 to 146 seconds. During Treatment B (ODT 1 mg without water), the mean  $\pm$  disintegration time was 55.86  $\pm$  23.57 seconds, ranging from 23 to 134 seconds.

## **5.2 Protocol SP765**

5.2.1 **Study Dates:** August 22, 2003 to September 9, 2003

### **5.2.2 Objective**

The study objective was to evaluate the single dose bioequivalence of a 0.5 mg Alprazolam ODT formulation administered with and without water, compared with the reference product, Xanax (alprazolam), when administered with water following a single 0.5 mg dose in the fasted state.

### **5.2.3 Subject Selection**

Fifteen (15) healthy male (12) and female (3) subjects were enrolled and completed the study. The inclusion and exclusion criteria were identical to those used in Study SP691 (Section 6.1.3).

### **5.2.3 Design of the Study**

The design was essentially identical to that of AP691, except that 0.5 mg tablets were administered instead of 1 mg tablets. This was a randomized, open-label, single dose, 3-treatment crossover study assessing the bioequivalence of — orally disintegrating 0.5 mg tablets with conventional alprazolam 0.5 mg tablets. Subjects were

randomized to one of three sequences of treatments. Each subject received all three treatments after a 10-hour fast. Each treatment was separated by a 7-day washout period. For each study period, subjects were confined to the clinic during the 48-hour post-dose assessment, and they returned to the clinic for the 72-hour sample collection. Blood samples were collected frequently (pre-dosing and up to 72 hours), in order to measure PK parameters.

**Study Treatments:**

**A. — 0.5 mg + water**

Single oral 0.5 mg dose of — was placed on the tongue until there was total disintegration of the tablet. Subjects then swallowed the drug mixture followed by 240 mL of water.

**B. — 0.5 mg without water**

Single oral 0.5 mg dose of — was placed on the tongue until there was total disintegration of the tablet. Subjects then swallowed the drug mixture without administration of water.

**C. Xanax (alprazolam) 0.5 mg with water**

Single oral 0.5 mg dose of alprazolam tablet administered with 240 mL of water.

**5.2.5 Results of SP765**

The tables below summarize the arithmetic means and standard deviations of plasma PK parameters and statistical comparisons of ln-transformed Cmax, AUC(0-t), and AUC(0-inf) following Treatments A, B, C. These are the sponsor's results.

**Table 5.2.5.A. Study SP765 Bioequivalence Results (with water)**

PK Parameter	TREATMENT A ODT 0.5 MG WITH WATER		TREATMENT C XANAX 0.5 MG WITH WATER		90% CI	% mean ratio
	Mean	SD	Mean	SD		
Cmax (ng/mL)	7.73	1.78	8.63	1.62		
Tmax (hr)	1.63	0.8	1.1	0.69		
AUC(0-t) ng*hr/mL	127.1	46.8	132.6	39		
AUC(0-inf) ng*hr/mL	133.2	49.48	137.6	40.34		
T1/2 (hr)	12.6	2.8	12.6	2.3		
Kel(1/hr)	0.058	0.012	0.057	0.01		
AUCR	0.96	0.012	0.963	0.015		
ln(Cmax)	2.021	0.2214	2.138	0.198	81.58- 97.07	89
ln(AUC(0-t))	4.786	0.3537	4.845	0.3068	89.01- 99.81	94.3
ln(AUC(0-inf))	4.832	0.3570	4.882	0.3030	89.65- 100.86	95.1

**Table 5.2.5.B. Study SP765 Bioequivalence Results (without water)**

	TREATMENT B ODT 0.5 MG W/OUT WATER	TREATMENT C XANAX 0.5 MG + WATER		

PK Parameter	Mean	SD	Mean	SD	90% CI	% mean ratio
Cmax (ng/mL)	8.34	1.8	8.63	1.62		
Tmax (hr)	1.95	0.97	1.07	0.697		
AUC(0-t) ng*hr/mL	122.2	43.6	132.6	39		
AUC(0-inf) ng*hr/mL	127.7	46.4	137.6	40.34		
T1/2 (hr)	12.5	2.68	12.6	2.32		
Kel(1/hr)	0.058	0.012	0.057	0.01		
AUCR	0.96	0.015	0.963	0.015		
ln(Cmax)	2.097	0.2307	2.138	0.1979	88.01- 104.73	96
ln(AUC(0-t))	4.746	0.3631	4.845	0.3068	85.52- 95.9	90.6
ln(AUC(0-inf))	4.789	0.3668	4.882	0.3030	85.84- 96.57	91

For alprazolam, the mean ratios of ln-transformed Cmax, AUC(0-t), and AUC(0-inf) for the comparison of the ODT formulation 0.5 mg with versus Xanax 0.5 mg with water were 89%, 94.3%, and 95.1%, respectively. The 90% CI were 81.58%- 97.07%, 89.01%- 99.81%, and 89.65% - 100.86%, respectively. Since the 90% CI did not encompass 100%, the results indicate a small but statistically significant difference in the rate and extent of alprazolam when the test ODT formulation is administered with water compared to when Xanax is administered with water. Nevertheless, the 90% CI for the comparison of these two treatments were still within the 80% to 125% range required for the demonstration of bioequivalence.

Comparison of alprazolam ln-transformed Cmax, AUC(0-t), and AUC(0-inf) between the ODT formulation 0.5 mg without water and Xanax 0.5 mg with water yielded similar results. The mean ratios were 96%, 90.6%, and 91%, respectively. The 90% CI were 88.01%- 104.73%, 85.52%- 95.9%, and 85.84%- 96.57%, respectively. The results indicate a small but statistically significant difference in the rate and extent of alprazolam when the test ODT formulation (0.5 mg) was administered without water compared to when Xanax (0.5 mg) was administered with water. Nevertheless, the 90% CI for the comparison of these two treatments were still within the 80% to 125% range required for the demonstration of bioequivalence. The sponsor concludes that the differences, although statistically significant, are too small to have any clinical relevance.

During Treatment A, the mean  $\pm$  disintegration time was  $63.9 \pm 37.96$  seconds, ranging from 21 to 146 seconds. During Treatment B, the mean  $\pm$  disintegration time was  $55.86 \pm 23.57$  seconds, ranging from —  $\dagger$  seconds.

### 5.3 Study SP766

5.3.1. Study dates: August 22, 2003 to September 2, 2003

#### 5.3.2 Objective

The objective of the study was to assess the effect of food on the single-dose bioavailability of a 1 mg dose of Alprazolam Orally Disintegrating Tablet.

### **5.3.3. Subject Selection**

Sixteen healthy male (7) and female (9) subjects were enrolled and completed the study. The inclusion and exclusion criteria were identical to those used in Protocols SP691 and SP765 (refer to Section 6.1.3).

### **5.3.4. Design of the Study**

This was a single-dose, randomized, open-label, two-period crossover study. Subjects received two treatments in a randomized sequence.

### **5.3.5 Results**

There was a food effect on Tmax and Cmax; however, total absorption was not changed. The biopharmaceutics reviewer concludes that the food effect would not be clinically significant.

## **6 INDICATIONS**

The sponsor seeks indications for Panic Disorder (with or without Agoraphobia) and Generalized Anxiety Disorder.

## **7 INTEGRATED REVIEW OF SAFETY**

### **7.1 Methods and Findings**

The sponsor's Summary of Safety and safety tables were reviewed.

#### **7.1.1 Deaths**

There were no deaths in the bioequivalence studies.

#### **7.1.2 Other Serious Adverse Events**

There were no serious adverse events reported in the bioequivalence studies.

#### **7.1.3 Discontinuations Due to Adverse Events**

One subject in one of the studies discontinued due to an adverse event. The subject discontinued due to difficulty with venipuncture as well as pain and bruising after venipuncture attempts. The events were not serious and were not related to study drug.

#### **7.1.4 Common Adverse Events**

Subjects included in the safety analysis were treated with either alprazolam ODT or conventional alprazolam tablets. There was no placebo group for comparison. In the

alprazolam ODT group, 94% of subjects reported adverse events. In the alprazolam tablet group, 89% of subjects reported adverse events. The most commonly reported AE in the ODT group were fatigue (63%), somnolence (31%), and dizziness or lightheadedness (31%). In the alprazolam tablet group, the AE profile was similar. Fatigue was reported by 54%, 23% reported somnolence, and 26% reported dizziness. These commonly reported AE are expected with alprazolam treatment. Furthermore, the rates for these commonly reported AE are similar to the rates previously reported for alprazolam tablets. In controlled trials in patients with anxiety or panic disorder (NDA 18,276), the most commonly reported AEs were drowsiness (41-77%), fatigue or tiredness (49%), impaired coordination (40%), lightheadedness or dizziness (23-30%), insomnia (29%), headache (13-29%), and diarrhea (10-21%). In the alprazolam ODT studies, there appeared to be a dose-related increased risk for developing fatigue and dizziness.

**Table. Commonly Reported Adverse Events by Dose**

ADVERSE EVENT	ALPRAZOLAM ODT (N=52) (%)	ALPRAZOLAM TABLETS (N=35) (%)
Fatigue	63	54
Somnolence	31	23
Dizziness/lightheaded	31	26

In the table below, the AE data are presented for Alprazolam ODT when administered with and without water following disintegration on the tongue. The safety and tolerability profiles appear to be similar; although, there appears to be a trend toward higher risk of developing these AE when the drug was administered with water compared to administration without water.

**Table. Commonly Reported Adverse Events (ODT administered with vs. without water)**

ADVERSE EVENT	ODT WITH WATER	ODT WITHOUT WATER
Fatigue	55	45
Somnolence	52	48
Dizziness/lightheaded	64	36

### 7.1.5 Less Common Adverse Events

There were few adverse events reported at proportions of > 2% in either the alprazolam ODT or alprazolam tablet groups. Elevated SGPT was reported for 6% of the ODT group. In contrast, no subjects in the alprazolam tablet group had elevated SGPT. Currently, no details are available about the cases in which SGPT was elevated. For example, the timing between dosing and LFT testing is unclear, as is the degree of elevation and the subsequent course. Thus it is difficult to determine whether elevated SGPT cases were related to treatment with alprazolam ODT. Although elevated SGPT

has not been specifically associated with treatment with conventional alprazolam tablets, unspecified “liver enzyme elevations” (<1% of subjects in clinical trials) and elevated SGOT (3.2% of subjects in clinical trials) have been reported with Xanax in prescribing information.

It is possible that several types of gastrointestinal adverse events were associated with alprazolam ODT treatment, since they occurred in 2-4% of the ODT group and not in the conventional tablet group. These AE were abdominal pain, nausea, diarrhea, anorexia, flatulence, and dyspepsia.

In the subjects exposed to Alprazolam ODT, 4% of subjects had anemia, and 2% of subjects reported taste perversion. No subjects in the conventional alprazolam group had reports of either of these adverse events.

Generally, it is difficult to attribute any of the less commonly reported AE to ODT treatment because: 1) the number of subjects studied was small; 2) there was no placebo group for comparison; and 3) the proportion of subjects reporting most AE was relatively low. Please refer to the table below for details about less commonly reported adverse events.

**Table. Less Commonly Reported Adverse Events**

ADVERSE EVENT	ALPRAZ ODT N=52 (%)	ALPRAZ TAB N=35 (%)
SGPT elevation	6	0
Ataxia	2	3
Amnesia	2	0
Insomnia	0	3
Abdominal pain	4	0
Nausea	4	0
Diarrhea	4	0
Anorexia	2	0
Flatulence	2	0
Dyspepsia	2	0
Hyperglycemia	2	0
Back pain	2	0
Anemia	4	0
Rash maculopapular	0	3
Pruritus	0	3
Taste perversion	2	0
Albuminuria	0	3
Hematuria	0	3
Urine abnormal	0	3

### **7.1.6 Electrocardiogram Findings**

There are no electrocardiogram data in the submission. The sponsor states that ECG recordings were conducted at screening, before dosing during each treatment period, and upon completion of the study. The results were not submitted.

### **7.1.7 Vital Signs Findings**

There are no vital sign data in the submission. Vital signs were monitored upon screening and before each dose on the days of dosing.

### **7.1.8 Laboratory Findings**

Clinical laboratory parameters were measured at screening and upon completion of the study. The sponsor has provided information about individual abnormal clinical laboratory results. However, the sponsor did not provide a full data set of laboratory results. In the alprazolam ODT treatment group, 3 subjects (5.8%) had elevated SGPT levels. There was no placebo group for comparison. None of the subjects in the alprazolam tablet group had elevated SGPT levels. Apparently, there were no other cases of liver function abnormalities. Other than the number of subjects with SGPT abnormalities, there is no other information available. Two subjects (4%) in the alprazolam ODT group had hyperglycemia. None in the alprazolam tablet group had hyperglycemia. Four subjects (8%) in the ODT group had anemia, compared to none in the conventional tablet group. No other details are available. There were no reports of any other clinical laboratory abnormalities in the alprazolam ODT group.

### **7.1.9 Withdrawal/Drug Discontinuation Phenomena**

Potential drug discontinuation phenomena were not specifically assessed in these single dose studies. However, it is well known that clinically significant withdrawal or discontinuation symptoms can occur when alprazolam is discontinued abruptly or tapered. The nature and risk of discontinuation signs and symptoms are specified in labeling for alprazolam. These symptoms include: nervousness, anxiety, tremor, dizziness, headache, insomnia, diarrhea, depression, anorexia, hyperventilation, derealization, hypoesthesia, muscle twitching, paresthesia, depersonalization, hot flushes, and seizures. It is extremely important to avoid abrupt discontinuation or rapid tapering of alprazolam, due to the relatively high risk of developing discontinuation symptoms. When considering discontinuation of treatment with alprazolam, the clinician and the patient must be aware of the need to carefully taper alprazolam. This point is included in current labeling.

## **7.2 Adequacy of Patient Exposure and Safety Assessments**

### 7.2.1 Exposure- Populations Exposed and Extent of Exposure

Overall, 52 healthy subjects were treated with one or two doses of Alprazolam ODT 0.5 mg or 1 mg for a total exposure of 125 person-days, or 0.337 person-years. There were 37 subjects exposed to the 1 mg tablet for an exposure of 93 person-days. There were 15 subjects exposed to the 0.5 mg tablet for an exposure of 32 person-days. In addition, 35 subjects were exposed to single doses of the reference drug, Alprazolam Tablets (0.5 or 1 mg) for a total of 35 person-days, or 0.096 person-years.

**Table. Exposures to Alprazolam ODT & Alprazolam Tablet**

	Number of Subjects	Exposure
<b>Alprazolam ODT Total (0.5 or 1 mg)</b>	<b>52</b>	<b>Total exposure: 125 person-days</b>
Alprazolam ODT 1 mg	37	93 person-days
Alprazolam ODT 0.5 mg	15	32 person-days
Alprazolam Tablet (0.5 or 1.0 mg)	35	35 person-days

In **Study SP691**, 21 subjects were exposed to Alprazolam ODT 1 mg. Twenty (20) subjects were exposed to two doses, and 21 subjects were exposed to one dose. Twenty (20) subjects were exposed to a single dose of reference drug, Alprazolam Tablet 1 mg. One subject did not complete the trial. In **SP765**, 15 subjects were exposed to two doses of Alprazolam ODT 0.5 mg, and 15 subjects were exposed to single doses of reference drug, Alprazolam Tablet 0.5 mg. In **Study SP766**, 16 subjects were exposed to two doses of Alprazolam ODT 1 mg.

### 7.2.2 Adequacy of Overall Clinical Experience

The clinical program was adequate to determine the bioequivalence and safety of the drug.

### 7.2.3 Adequacy of Routine Clinical Testing

It appears that the clinical safety assessments were adequate. It would have been helpful to have more complete reports for the electrocardiogram and clinical laboratory results.

### 7.2.4 Adequacy of Evaluation for Potential Adverse Events

The assessment for potential adverse events in these bioequivalence studies was adequate.

### 7.2.5 Assessment of Quality and Completeness of Data

## 7.3 Safety Conclusions

Safety data were gathered and submitted for all of the 52 healthy subjects enrolled in the bioequivalence studies. The extent of safety data are relatively limited, since the studies involved a small number of subjects, and each subject received only one or two doses of the study drug. Moreover, the study drug was not evaluated in the target populations (patients with Panic Disorder or Generalized Anxiety Disorder). Nevertheless, the safety assessment was adequate and appropriate, given the objectives of the clinical program. The total exposure to alprazolam ODT was 125 person-days for a total of 52 healthy adult male and female subjects. Generally, the drug was reasonably safe and well tolerated. There were no deaths or other serious adverse events in any of the 3 studies. Only one subject discontinued from the study due to an adverse event. The event was not related to study drug treatment. The most commonly reported drug-related adverse events were the types that would be expected with treatment with alprazolam. Fatigue, somnolence, dizziness, and lightheadedness were the most commonly reported adverse events. It appeared that these adverse events were dose-related, as would be expected. There were no new or unexpected findings with alprazolam treatment in these studies.

## **8 ADDITIONAL CLINICAL ISSUES**

### **8.1 Dosing Regimen and Administration**

The sponsor recommends that the patient place Alprazolam Orally Disintegrating Tablet on the tongue to allow for rapid disintegration of the tablet. It is not necessary to take the tablet with water. The recommended stable dosing of Alprazolam Orally Disintegrating Tablet is identical to the established recommended dosing for conventional alprazolam tablets.

Treatment should be initiated with a dose of 0.25 to 0.5 mg given three times daily. The dose may be increased, as needed for adequate response, at intervals of 3 to 4 days, to a maximum daily dose of approximately 4 mg, given in divided doses. However, successful treatment of Panic Disorder may require daily doses greater than 4 mg. In controlled trials in Panic Disorder, doses ranged from 1 to 10 mg per day. The mean daily dose was approximately 5 to 6 mg. For patients treated with doses greater than 4 mg/day, periodic reassessment and consideration of dosage reduction is advised. Proposed labeling includes additional appropriate details regarding dosage and administration.

### **8.2 Drug-Drug Interactions**

Drug interaction studies have not been conducted specifically with Alprazolam ODT. However, drug interaction studies have been conducted with conventional alprazolam tablets.

Alprazolam is primarily metabolized via the CYP3A4 enzyme system. Thus, drugs which are potent inhibitors of CYP3A4 would be expected to increase plasma alprazolam concentrations in vivo. The following drugs have been studied in vivo, and the extent of increases in alprazolam AUC are indicated: itraconazole (2.7 fold); nefazodone (1.98 fold); ketoconazole (3.98 fold); erythromycin (1.61 fold); and fluvoxamine (1.96 fold). Fluoxetine resulted in a modest (30%) increase in alprazolam concentrations. The use of alprazolam is contraindicated with ketoconazole and itraconazole.

CYP3A4 inducers would be expected to decrease plasma alprazolam concentrations. Following administration of carbamazepine 300 mg/day for 10 days, oral clearance of alprazolam was increased from 0.90 mL/min/kg to 2.13 mL/min/kg.

Alprazolam can produce additive CNS depressant effects when co-administered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression. The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20% by the concomitant administration of XANAX.

Based on clinical drug interaction studies, caution is recommended for co-administration of alprazolam with the following medications: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from *in vitro* studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. Co-administration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.

### **8.3 Special Populations**

#### **8.3.1 Pediatric Population**

Pediatric subjects were not studied in the Alprazolam Orally Disintegrating Tablet clinical program. The safety and effectiveness of conventional alprazolam tablets has not been studied in subjects below the age of 18 years.

#### **Pregnant or Nursing Women, Labor and Delivery, Oral Contraceptive Use**

Teratogenic Effects:

XANAX XR has been placed in Pregnancy Category D.

The sponsor directs readers: "(See WARNINGS section)."

Nonteratogenic Effects:

The sponsor states: "It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines."

**Labor and Delivery:**

XANAX has no established use in labor or delivery.

**Nursing Mothers:**

Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use XANAX.

**Women Using Oral Contraceptive Medications**

Co-administration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.”

**Geriatric Population**

The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. The sponsor states that the smallest effective dose of alprazolam should be used in the elderly to preclude the development of adverse effects such as ataxia and oversedation.

**Hepatic Impairment**

For patients with clinically significant hepatic impairment, lower doses should be used than those used in patients with normal hepatic function.

**8.4 Postmarketing Risk Management Plan**

Currently, I do not have specific recommendations for a risk management plan.

**9 OVERALL ASSESSMENT**

**9.1 Conclusions**

- A. The sponsor has demonstrated the bioequivalence of Alprazolam ODT (0.25 and 1.0 mg) with conventional alprazolam tablets (0.25 and 1.0 mg).
- B. Alprazolam ODT was reasonably safe and tolerable. The safety and tolerability of the drug is quite similar to those of conventional alprazolam tablets.

**9.2 Recommendation on Regulatory Action**

I recommend that the Division take an approvable action for NDA 21,726 for Alprazolam Orally Disintegrating Tablets in the treatment of adult patients with a diagnosis of Panic Disorder (with or without Agoraphobia) or Generalized Anxiety Disorder. The sponsor has demonstrated the bioequivalence of NIRAIVAM (orally disintegrating alprazolam tablets) and the conventional alprazolam formulation.

**9.3 Recommendation on Postmarketing Actions**

Currently, I do not recommend any specific risk management or Phase 4 commitments.

#### **9.4 Labeling Review**

A review of the sponsor's proposed labeling will be presented in a separate document.

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ON ORIGINAL**

#### **10 APPENDICES**

##### **10.1 List of Investigators and Study Sites**

##### **Clinical Investigator and Subinvestigators for Alprazolam Orally Disintegrating Tablet Bioequivalence Studies.**

Name and Address of Clinical Investigator:

/

Name and Address of Subinvestigators:

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ON ORIGINAL**

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Robert Levin, M.D., September 20, 2004  
Medical Reviewer,  
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C Taylor  
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Robert Levin  
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MEDICAL OFFICER

Thomas Laughren  
10/15/04 10:45:59 AM  
MEDICAL OFFICER

I agree that this application is approvable, however, we  
will need to request additional information on several  
patients with laboratory abnormalities; see memo to file  
for more detailed comments--TPL