CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-726

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-726

Schwarz Pharma, Inc.
Attention: Gary M. Wieczorek
Manager, Regulatory Affairs
P.O. Box 2038
Milwaukee, WI 53201

Dear Mr. Wieczorek:

Please refer to your new drug application (NDA) dated December 19, 2003, received December 19, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Niravam™ (alprazolam) Orally Disintegrating Tablets.

We acknowledge receipt of your additional submissions dated:

March 19, 2004	May 21, 2004	August 17, 2004	October 22, 2004	December 23, 2004
March 25, 2004	June 7, 2004	September 3, 2004	November 18, 2004	January 14, 2005
March 30, 2004	July 15, 2004	September 14, 2004	November 22, 2004	
April 23, 2004	July 26, 2004	September 17, 2004	December 15, 2004	

The November 18, 2004 submission constituted a complete response to our October 19, 2004 action letter.

This new drug application provides for the use of Niravam (alprazolam) orally disintegrating tablets (ODTs) for Generalized Anxiety Disorder and Panic Disorder.

Labeling
We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and immediate container and carton labels submitted on January 14, 2005, received on January 19, 2005. Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-726.**" Approval of this submission by FDA is not required before the labeling is used.

Chemistry Manufacturing and Controls
We grant a 12 month expiry for the 0.25 mg and 0.5 mg alprazolam ODTs and a 24 month expiry for the 1 mg and 2 mg alprazolam ODTs.

Pediatric Research Equity Act (PREA)
Please refer to the Division's action letter dated October 19, 2004 in which the pediatric study requirement for this application was waived.

Postmarketing Commitment
We remind you of your postmarketing study commitment in your submission dated November 18, 2004. These commitments are listed below.

1. (b)(4)

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

Promotional Materials
In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Richardae C. Taylor, Pharm.D., Regulatory Project Manager, at (301) 594-2850.

Sincerely,
{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Russell Katz
1/19/05 03:46:59 PM

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Attention: Gary M. Wieczorek
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Dear Mr. Wieczorek:

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We acknowledge receipt of your additional submissions dated:

March 19, 2004	April 23, 2004	July 15, 2004	September 3, 2004
March 25, 2004	May 21, 2004	July 26, 2004	September 14, 2004
March 30, 2004	June 7, 2004	August 17, 2004	September 17, 2004

We have completed our review of this application, as amended, and have determined that it is approvable. Before the application may be approved, however, it will be necessary for you to respond to the following comments and requests.

Clinical

The safety database for this new formulation was quite limited, since data were available for only the 3 single-dose pharmacokinetic studies. We note that there were several laboratory abnormalities reported for ODT patients but not for Xanax IR 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

We ask that you provide the actual laboratory findings for these patients identified as having abnormalities, and any other relevant safety findings for these patients.

Office of Clinical Pharmacology and Biopharmaceutics

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

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

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. We recommend that drug interaction studies with drug classes that raise gastric pH, other than proton pump inhibitors (see later, Postmarketing Commitment), be conducted as these would provide useful information. The other classes include antacids and H2 antagonists. Please note that these studies are not being requested as a postmarketing commitment.

4. Since dry mouth due to concomitant drugs or other causes might effect the disintegration of the tablets — , a study to determine the effect of anticholinergic drugs on absorption rate both when administered with and without water is recommended. Please note that such a study is not being requested as a postmarketing commitment.

5. It is recommended that you perform a literature search examining what changes occur in esophogeal transit, saliva flow and composition, (i.e. pH and ionic composition) in healthy elderly patients 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. You should also propose labeling changes and/or studies as appropriate. Please note that these studies are not being requested as a postmarketing commitment.

Chemistry Manufacturing and Controls (CMC)

1. Provide a commitment that, if reprocessing is needed in the future, prior approval would be obtained from FDA before implementation.

2. Identification tests should be specific for drug substance (e.g. —). Identification solely by a — is not regarded as being specific. Provide a second identification test for alprazolam in drug product (e.g., —). Refer to ICH Guidance Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products.

3. You identified a peak — relative retention time (RRT that appeared in samples from batches of 0.25 mg, 0.5 mg, 1 mg, and 2 mg strengths stored in bottles at 40° C/75% RH. Provide the source of this impurity.

4. In a telecon dated October 8, 2003, between Mr. Gary Wieczorek (Regulatory Affairs Manager at Schwarz Pharma) and Thomas Oliver (Psychiatric Drug Chemistry TL), it was agreed that — would be added to the last five timepoints of the stability protocol — Provide — results for Niravam (alprazolam, USP) Orally Disintegrating Tablets, 0.25 mg, 0.5 mg, 1 mg, and 2 mg strengths collected as part of this stability program. Include an updated stability protocol, which includes —

5. In amendment 004, dated 15-JUL-04, you proposed to change the shape of the 0.25 mg and 0.5 mg tablets from a [redacted] tablet to a [redacted] tablet because the [redacted] . Only Comparative data for dissolution, [redacted], disintegration, [redacted], were provided. Provide full testing results (CoAs) of one batch (in each packaging configuration) of the 0.25 mg and 0.5 mg strength [redacted] tablets. What assurance do you have that these new 0.25 mg and 0.5 mg [redacted] tablets will remain within specifications over the proposed expiry?

6. Total impurities increased after [redacted] of storage under long term and accelerated conditions for all strengths packaged [redacted] bottles. Please indicate whether this increase was due to a single degradant or multiple degradants, and provide the respective relative retention times (RRT) or retention times (RT), and whether any of these degradants have been identified.

7. Revise the DESCRIPTION section of labeling to include the empirical formula and molecular weight of alprazolam.

Pharmacology/Toxicology

The total specification level of the [redacted] We consider this level high, and ask that you attempt to reduce [redacted], or justify the safety of these levels [redacted] In our review, the safety profile [redacted] is unknown except [redacted] where it was shown not be a carcinogen up to 1000ppm in rats and mice via inhalation. However, mutagenicity information was inconsistent, with some assays showing it to be a clastogen, whereas the results were negative in other mutagenicity assays.

Proprietary Name

The Division of Medication Errors and Technical Support (DMETS) find your proposed proprietary name, Niravam™, acceptable. However, they have the following requests.

1. Increase the font size of the established name so that it is at least ½ the size of the proprietary name. See 21 CFR 201.10(g)(2).

2. Decrease the prominence of the [redacted] since it is more prominent than the proprietary name.

3. DMETS notes that the strengths are differentiated using different colors. However, the colors for the 0.25 mg, 0.5 mg, and 2 mg strengths are very similar in appearance and may lead to confusion and selection errors. Therefore, DMETS recommends revising the color of the 0.25 mg, 0.5 mg, and 2 mg strengths so that they are distinctly different from each other.

4. Container label – 0.25 mg, 0.5 mg, 1 mg, and 2 mg (100 count): see comments 1-3 above.

5. [redacted]

6. [redacted]

b.

7.

Labeling
Accompanying this letter (Enclosure) is the Agency's proposal for the labeling of alprazolam. We have used, as our base labeling, the last approved labeling for Xanax (4/2/04). Brackets [] embedded within the text that follows include comments and explanations concerning our proposed labeling.

You must submit revised, draft labeling for alprazolam as part of your response to this letter. If you propose revisions to the attached labeling, we ask that you provide a highlighted or marked-up copy that shows all changes and identify which version of alprazolam labeling was used as the base document. This type of labeling document will facilitate the review.

In addition, we request that you provide a line-by-line comparison of your proposed labeling as compared to the approved Xanax Tablet labeling. We suggest that this labeling comparison be a highlighted or marked-up document where Xanax Tablet labeling is used as the base document. The goal of this comparison is to provide a document that permits us to easily identify (word for word) precisely how your alprazolam labeling differs from Xanax Tablet labeling.

Lastly, if additional information relating to the safety or effectiveness of this drug becomes available, further revision of the labeling may be required.

Postmarketing Commitment
We ask that you commit to the following postmarketing study commitment listed below. This commitment must be fulfilled within one year from the date of approval of this application.

Pediatric Research Equity Act (PREA)
All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

Safety Update
When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Promotional Materials
In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the

application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division/ the Division of Neuropharmacological Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Richardae Taylor, Pharm.D., Regulatory Project Manager, at (301) 594-5793.

Sincerely,

{See appended electronic signature page}
Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

-Enclosure