

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-726

ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE

PATENT INFORMATION
21 CFR § 314.54(v)

A signed patent declaration form FDA 3542a regarding patent information is herein submitted for each patent number (6,024,981 and 6,221,392), as required under section 505(b) of the Federal Food Drug & Cosmetic Act and 21 CFR § 314.53 and 314.54. The patents cover the composition and formulation of Alprazolam Orally Disintegrating Tablets, 0.25 mg, 0.5 mg, 1 mg, and 2 mg. Accordingly, Schwarz Pharma, Inc. requests that this information be published in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) upon approval of the application.

Also included are the following: a paragraph II certification for Patent No. 4,508,726; a paragraph IV certification for Patent No. 5,061,494; a statement concerning notice to patent holders and NDA holders, as required for paragraph IV certifications; and an exclusivity statement indicating there is no unexpired exclusivity for this product.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

NDA 21-726

NAME OF APPLICANT / NDA HOLDER

Schwarz Pharma, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ACTIVE INGREDIENT(S)

Alprazolam

STRENGTH(S)

0.25 mg, 0.5 mg, 1 mg, and 2 mg

DOSAGE FORM

Orally Disintegrating Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
6,024,981

b. Issue Date of Patent
2/15/2000

c. Expiration Date of Patent
4/9/2018

d. Name of Patent Owner

CIMA LABS INC.

Address (of Patent Owner)
7325 Aspen Lane

City/State
Brooklyn Park, MN

ZIP Code
55428

FAX Number (if available)
(763) 488-4770

Telephone Number
(763) 488-4700

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information Below)

Date Signed

11.18.03

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Steven R. Pollock, Vice President, Medical, Regulatory and Quality Assurance

Address

Schwarz Pharma, Inc.
6140 West Executive Drive

City/State

Mequon, WI

ZIP Code

53092-4467

Telephone Number

(262) 238-5206

FAX Number (if available)

(262) 238-0957

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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**PATENT INFORMATION SUBMITTED WITH THE
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*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

NDA 21-726

NAME OF APPLICANT / NDA HOLDER

Schwarz Pharma, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ACTIVE INGREDIENT(S)

Alprazolam

STRENGTH(S)

0.25 mg, 0.5 mg, 1 mg, and 2 mg

DOSAGE FORM

Orally Disintegrating Tablets

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1. GENERAL

a. United States Patent Number
6,221,392

b. Issue Date of Patent
4/24/2001

c. Expiration Date of Patent
4/9/2018

d. Name of Patent Owner

CIMA LABS INC.

Address (of Patent Owner)
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55428

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e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

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- 1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

11-18-03

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Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Steven R. Pollock, Vice President, Medical, Regulatory and Quality Assurance

Address

Schwarz Pharma, Inc.
6140 West Executive Drive

City/State

Mequon, WI

ZIP Code

53092-4467

Telephone Number

(262) 238-5206

FAX Number (if available)

(262) 238-0957

E-Mail Address (if available)

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Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SCHWARZ
P H A R M A**PATENT CERTIFICATION****PARAGRAPH II CERTIFICATION**

As required by 21 CFR § 314.50(i)(1)(i)(A)(2), Schwarz Pharma, Inc. hereby certifies that in its opinion and to the best of its knowledge, Patent No. 4,508,726 expired on September 16, 2002.



Steven R. Pollock
Vice President, Medical, Regulatory & Quality Assurance

11-22-03
Date

SCHWARZ
PHARMA**PATENT CERTIFICATION****PARAGRAPH IV CERTIFICATION**

As required by 21 CFR § 314.50(i)(1)(i)(A)(4), Schwarz Pharma, Inc. hereby certifies that in its opinion and to the best of its knowledge, Patent No. 5,061,494 (expiration date of October 29, 2008) will not be infringed upon by the manufacture, use, or sale of _____ (proposed trade name for Alprazolam Orally Disintegrating Tablets) for which this application is submitted.



Steven R. Pollock
Vice President, Medical, Regulatory & Quality Assurance

11.22.03
Date

SCHWARZ
P H A R M A

STATEMENT CONCERNING NOTICE
TO PATENT HOLDERS AND NDA HOLDERS

As required by 21 CFR § 314.52(a), Schwarz Pharma, Inc. hereby certifies that, upon receipt from FDA of an acknowledgment letter stating that this NDA is sufficiently complete to permit a substantive review, it will provide notice to the holder of Patent No. 5,061,494 and to the holder of the approved application for XANAX®. The notice shall meet the requirements of 21 CFR § 314.52(c). It will be sent by certified mail, return receipt requested.



Steven R. Pollock
Vice President, Medical, Regulatory & Quality Assurance

12.15.03
Date

SCHWARZ
P H A R M A**EXCLUSIVITY STATEMENT**

Schwarz Pharma, Inc. hereby certifies that in its opinion and to the best of its knowledge, there is no unexpired exclusivity for this product.



Steven R. Pollock
Vice President, Medical, Regulatory & Quality Assurance



Date

EXCLUSIVITY SUMMARY FOR NDA # 21-726 SUPPL # _____

Trade Name Niravam orally disintegrating tablets

Generic Name alprazolam

Applicant Name Schwarz Pharma, Inc. HFD # 120

Approval Date If Known January 19, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES / X / NO / ___ /

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / ___ / NO / X /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

This is a 505(b)(2) application

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 18-276 Xanax Tablets

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical

investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /__X_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally

know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____
_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____
_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____
_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	!	
IND # _____	!	NO /___/ Explain: _____
YES /___/	!	
	!	
Investigation #2	!	
IND # _____	!	NO /___/ Explain: _____
YES /___/	!	

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____
Investigation #2	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____

**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 03:55:03 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-726 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: December 19, 2003 Action Date: October 19, 2004

HFD- 120 Trade and generic names/dosage form: Niravam (alprazolam) orally disintegrating tablets

Applicant: Schwarz Pharma, Inc.

Therapeutic Class: triazolo analog of the 1,4 benzodiazepine class of central nervous system agents.

Indication(s) previously approved:

Each approved indication must have pediatric studies: **Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 2

Indication #1: Anxiety Disorder

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: studies impractical due to difficult enrollment

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Richardae Taylor, Pharm.D.
Regulatory Project Manager

cc: NDA
HFD-960/ Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Panic Disorder

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

**NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: studies impractical due to difficult enrollment

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

Richardae Taylor, Pharm.D.

{See appended electronic signature page}

Regulatory Project Manager



**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
10/19/04 11:52:38 AM

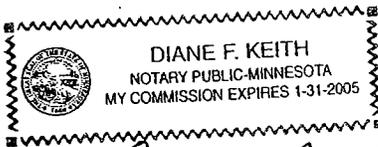


DEBARMENT STATEMENT
Certification Required by Generic Drug Enforcement Act of 1992

CIMA LABS INC.®, (the "Drug Product Manufacturer"), hereby certifies as follows:

- (i) The Drug Product Manufacturer hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application; and
- (ii) There are no convictions of the type described in section 306 (a) and (b) of the Federal Food, Drug and Cosmetic Act, which occurred within 5 years prior to the date of this Certificate, of the Drug Product Manufacturer or any affiliated person responsible for the development or submission of such application.

IN WITNESS WHEREOF, the undersigned has signed this certificate on behalf of CIMA LABS INC.®, on the 28th of February, 2003.



Diane F. Keith Feb. 28, 2003

By:

Jackie Torfin
 Jackie Torfin, Director Quality Assurance

CIMA LABS INC.®

Corporate Offices: 10000 Valley View Road, Eden Prairie, MN 55344 • 952-947-8700, Fax: 952-947-8770
 Research: 7325 Aspen Lane, Brooklyn Park, MN 55428 • 952-947-8950, Fax: 952-947-8970

SCHWARZ
PHARMA**CERTIFICATION STATEMENT****As Required By The****GENERIC DRUG ENFORCEMENT ACT OF 1992**

Pursuant to Section 306 (k) of the Federal Food, Drug and Cosmetic Act as amended by the Generic Drug Enforcement Act of 1992, Schwarz Pharma, Inc. hereby certifies that it did not, and will not use in any capacity, the services of any person debarred under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

Additionally, during the previous five years, neither the applicant nor any affiliated person responsible for the development or submission of this application, has been convicted of the offenses described in subsection (a) or (b) of the Generic Drug Enforcement Act of 1992.

Schwarz Pharma, Inc. further certifies that it will promptly amend this certification as necessary in light of new information.



Mary Cyrier
Vice President
Human Resources

12/2/03

Date



Ron Stratton, Ph.D.
President & COO

12-3-03

Date

A

5 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA	21776	Efficacy Supplement Type	SE-	Supplement Number
Drug:	Alparolan 005		Applicant:	Schwarz Pharma
RPM:		HFD-	120	Phone #
Application Type: () 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.			Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 21-18-276 Xanax [®] tab.	
<input checked="" type="checkbox"/> Confirmed and/or corrected				
❖ Application Classifications:				
<ul style="list-style-type: none"> • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC) 			<input checked="" type="checkbox"/> Standard () Priority	
User Fee Goal Dates			10/19/04	
❖ Special programs (indicate all that apply)				
			<input checked="" type="checkbox"/> None <input checked="" type="checkbox"/> Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2	
❖ User Fee Information				
<ul style="list-style-type: none"> • User Fee • User Fee waiver • User Fee exception 			<input checked="" type="checkbox"/> Paid UF ID number () Small business () Public health () Barrier-to-Innovation <input checked="" type="checkbox"/> Other (specify) 505(b)(2)	
			() Orphan designation <input checked="" type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify)	
Application Integrity Policy (AIP)				
<ul style="list-style-type: none"> • Applicant is on the AIP 			() Yes <input checked="" type="checkbox"/> No	

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? () Yes () No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? () Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	N/A
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ () No
Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	PM review

General Information

Actions	
<ul style="list-style-type: none"> Proposed action 	() AP () TA (X) AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	N/A
<ul style="list-style-type: none"> Status of advertising (approvals only) 	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	N/A
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	() Yes () Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	() None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	See AE pkg —
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	—
<ul style="list-style-type: none"> Original applicant-proposed labeling 	See AE pkg —
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 	N/A
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	N/A
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> Applicant proposed 	
<ul style="list-style-type: none"> Reviews 	
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	See AE ldr
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	—
❖ Memoranda and Telecons	—
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	
<ul style="list-style-type: none"> Pre-NDA meeting (indicate date) 	X
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) 	X
<ul style="list-style-type: none"> Other 	
❖ Advisory Committee Meeting	N/A
<ul style="list-style-type: none"> Date of Meeting 	
<ul style="list-style-type: none"> 48-hour alert 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Summary Application Review

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>		
Clinical Information		
❖ Clinical review(s) <i>(indicate date for each review)</i>		
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>		
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>		
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>		
❖ Pediatric Page (separate page for each indication addressing status of all age groups)		
❖ Demographic Worksheet <i>(NME approvals only)</i>		
❖ Statistical review(s) <i>(indicate date for each review)</i>		
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>		
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>		
❖ Clinical Inspection Review Summary (DSI)		
• Clinical studies		
• Bioequivalence studies		
CMC Information		
❖ CMC review(s) <i>(indicate date for each review)</i>		
❖ Environmental Assessment		
• Categorical Exclusion <i>(indicate review date)</i>		
• Review & FONSI <i>(indicate date of review)</i>		
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>		
❖ Facilities inspection (provide EER report)		Date completed: () Acceptable () Withhold recommendation
❖ Methods validation		() Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information		
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>		
❖ Nonclinical inspection review summary		
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>		
❖ CAC/ECAC report		

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Clearance for (b)(2) Approval

Taylor, Richardae

From: Colangelo, Kim M
Sent: Friday, January 14, 2005 2:04 PM
To: Taylor, Richardae
Cc: Peat, Raquel
Subject: NDA 21-726 is cleared for approval

Happy Action!

Kim

*Kim Colangelo
Associate Director for Regulatory Affairs
Office of New Drugs
CDER/FDA
301-594-3937
301-480-8329 (f)*

11 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED:

September 17, 2004

DESIRED COMPLETION DATE:

October 17, 2004

ODS CONSULT #: 04-0252

PDUFA DATE: October 19, 2004

TO:

Russell Katz, MD
Director, Division of Neuropharmacologic Drug Products
HFD-120

THROUGH:

Richardae Taylor, PharmD
Project Manager
HFD-120

PRODUCT NAME:

Niravam
(Alprazolam Orally Disintegrating
Tablets)
0.25 mg, 0.5 mg, 1 mg, and 2 mg

NDA SPONSOR: Schwarz Pharma

NDA#: 21-726

SAFETY EVALUATOR: Kristina C. Arnwine, PharmD

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Niravam. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in ODS Consult 03-0247-1 signed September 22, 2004.
3. DDMAC finds the proprietary name Niravam acceptable from a promotional perspective.

Denise P. Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 28, 2004

NDA#: 21-726

NAME OF DRUG: Niravam (Alprazolam Orally Disintegrating Tablets)
0.25 mg, 0.5 mg, 1 mg, and 2 mg

NDA HOLDER: Schwarz Pharma

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Neuropharmacologic Drug Products (HFD-120), for assessment of the proprietary name, Niravam, regarding potential name confusion with other proprietary or established drug names. Revised container labels, carton and insert labeling were not provided for review and comment at this time.

Schwarz Pharma submitted the proposed proprietary name _____ to DMETS for review and comment. DMETS had no objections to the proposed name, however, DDMAC objected to the name _____. Therefore, Schwarz Pharma has submitted the proposed proprietary name Niravam.

PRODUCT INFORMATION

Niravam is an orally disintegrating benzodiazepine anxiolytic indicated for the management of anxiety disorder (a condition corresponding most closely to the APA Diagnostic and Statistical Manual [DSM-III-R] diagnosis of generalized anxiety disorder) or the short-term relief of symptoms of anxiety. Niravam is also indicated for anxiety associated with depression and the treatment of panic disorder, with or without agoraphobia. The usual dose of Niravam is 0.25 mg by mouth three times daily to 10 mg daily in divided doses. Niravam is supplied in 0.25 mg, 0.5 mg, 1 mg, and 2 mg tablets in bottles of 100 tablets.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Niravam to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Niravam. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Niravam acceptable from a promotional perspective.
2. The Expert Panel identified six proprietary names that were thought to have the potential for confusion with Niravam. These products are listed in table 1 (see page 4), along with the dosage forms available and usual dosage.

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Niravam	Alprazolam Orally Disintegrating Tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg	0.25 mg three times daily to 5 mg daily in divided doses	
Viramune	Nevirapine Tablets: 200 mg Oral Suspension: 50 mg/5 mL	200 mg once daily for 14 days, then 200 mg twice daily	SA
Navane	Thiothixene Capsules 1 mg, 2 mg, 5 mg, 10 mg, 20 mg	2 mg by mouth three times daily to 60 mg once daily or in divided doses	LA
Mirena	Levonorgestrel Intrauterine Device 52 mg	Insert device into uterine within 7 days of onset of menstruation. Insert may be left in for no longer than 5 years.	LA
Narcan	Naloxone Injection 0.4 mg/mL and 1 mg/mL	Initial dose is 0.4 to 2 mg IV; may repeat IV at 2 to 3 minute intervals up to 10 mg.	SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike) ***Name pending approval. Not FOI releasable.			

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

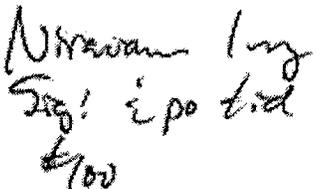
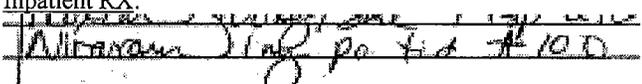
As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Niravam were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Niravam with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Niravam (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were

recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> 	<p>“Niravam 1 mg. One tablet by mouth tid. Quantity of 100.”</p>
<p>Inpatient RX:</p> 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Niravam, the primary concerns related to look-alike and sound-alike confusion with Viramune, Navane, Mirena, and Narcan. Upon further review of the names gathered from EPD and POCA, the names Mirena and Narcan were not reviewed further due to a lack of convincing look-alike/sound-alike similarities with Niravam in addition to numerous differentiating product characteristics such as the product strength, indication for use, frequency of administration, route of administration and dosage formulation. Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Niravam.

1. Niravam can look similar to Navane when scripted. Navane is a thioxanthene derivative antipsychotic agent indicated for the management of schizophrenia. Niravam and Navane both begin with the letter ‘N’ and contain the letters ‘ava’ in the middle of each name, which are the primary contributions to the look-alike characteristics of each name. However, the ‘ava’ is presented in the fourth through sixth positions in Niravam and in the second through fourth positions in Navane. In addition, Niravam has seven letters while Navane has six. Thus, Niravam is longer than Navane when scripted. Furthermore, the endings of each name are different (‘m’ vs. ‘ne’) and the letters ‘ir’ at the beginning of Niravam also help to distinguish the two names from each other. Despite an overlap in route of administration (oral), product strength (1 mg and 2 mg), and dosing frequency (once, twice, or three times daily), the orthographic differences differentiate Niravam from Navane. Overall, the

orthographic differences between the beginnings and endings of each name decrease the potential for medication errors due to name confusion between Niravam and Navane.

niravam *navane*

2. Niravam can look similar to Viramune when scripted. Viramune is a non-nucleoside reverse transcriptase inhibitor indicated for the treatment of HIV. The beginnings of each name ('nira' vs. vira') can look similar depending on how they are written. However, the endings of each name are different. Niravam and Viramune overlap in dosage form (tablets), route of administration (oral), and can overlap in dosing frequency (once or twice daily), and usual dose (one tablet). However, they do not overlap in product strengths (0.25 mg, 0.5 mg, 1 mg, and 2 mg vs. 200 mg and 50 mg/5mL). The availability of different strengths for Niravam negates the possibility of a prescription for "Niravam one tablet twice daily," that can be dispensed without the specification of a strength, which helps to distinguish Niravam from Viramune. However, both Niravam and Viramune can overlap in the numeral '5' being present in the usual dose (e.g. Niravam 5 mg vs. Viramune 5 mL). Therefore, a prescription written for Niravam 5 mg could be misinterpreted as Viramune 5 mL. However, even if Niravam 5 mg is misinterpreted as Viramune 5 mL, it would probably not be dispensed since Viramune 5 mL is a pediatric dose, and Niravam is not indicated for use in children. Overall, the endings of each name along with the differing product strengths decrease the potential for medication errors due to name confusion between Niravam and Viramune.

niravam *viramune*

- 3.

7

IV. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

DMETS recommends implementation of the label and labeling revisions outlined in ODS Consult 03-0247-1 signed September 22, 2004.

V. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name Niravam.. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions outlined in ODS Consult 03-0247-1 signed September 22, 2004.
- C. DDMAC finds the proprietary name Niravam acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Kristina C. Arnwine, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Attachment A

Outpatient Written	Inpatient Written	Verbal
Niravain	Niranam	Miravim
Niravam	Niraram	Nearavam
Niravam	Niraram	Neariva
Niravam	Niraram	Nearivim
Niravam	Niraram	Nearovam
Niravan	Niraram	Neerabam
Niravan	Niraram	Neravam
Niravan	Niraram	Neravam
Niravan	Niraram	Neravan
Niravan	Nirarom	Neravem
Niravan	Nirasan	Neravem
Niravan	Niravain	Neravem
Niravan	Niravam	Nerivam
Niravan	Niravam	Nerivim
Niravan	Niravam	Nerovam
Niravan	Niravam	Nerovam
Niravan	Niravam	Nerovam (or Nerovamp)
Niravan	Niravam	neuravam
Niravan	Niravam	Neurovam
Niravan	Niravam	Neurovam
Nirivan	Niravam	Neurovan
Nivarium	Niravan	Neurovan
	Niravarin	Neurovan
	Niravarir	Niravam
	Niravarir	Niravem
	Niraxam	Nirovam
	Niroxam	Nuravam
		Nuravamp

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

/s/

Kristina Arnwine
10/18/04 04:01:49 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
10/18/04 04:03:07 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/18/04 04:14:06 PM
DRUG SAFETY OFFICE REVIEWER

Taylor, Richardae

From: Tele, Chhagan
Sent: Thursday, October 14, 2004 1:09 PM
To: Taylor, Richardae
Cc: Oliver, Thomas F
Subject: NDA 21-726 CMC Review Comments

Hi Chardae,

Please see attached CMC review deficiencies and comments for NDA 21-726 for letter to be sent to the applicant. Please let me know if you need any additional information.

Thanks for your patience.



NDA 21-726
Review Deficie
Tele

The following CMC review deficiencies and comments should be sent accordingly to the applicant for additional information and response.

DEFICIENCIES:

- 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) The supplier of — has a specification limit of — monomers (—). Each 2 mg tablet consists of approximately — . With maximum daily dose of 10 mg of alprazolam per day, an individual could be exposed to approximately — per day. Provide justification for the safety of the ultimate monomer exposure level.
- 4) You identified a peak (— by 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.
- 5) 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 (9m, 12m, 18m, 24m, 36m). Provide — results for — (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 —
- 6) 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 — tablet to a — tablet because — Only Comparative data for dissolution, — disintegration, — were provided. Provide full testing results (CoAs) of one batch (in each packaging configuration) of the 0.25 mg and 0.5 mg strength — tablets. What assurance do you have that these new 0.25 mg and 0.5 mg — tablets will remain within specifications over the proposed expiry?
- 7) Total impurities increased after — of storage under long term and accelerate conditions for all strengths packaged in — bottles. Please indicate whether this increase was due to a single degradant or multiple, and provide the respective relative retention time (RRT) or retention time (RT), and whether any of these degradants have been identified.
- 8) Revise the DESCRIPTION section of labeling to include the empirical formula and molecular weight of the alprazolam.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
NDA 18-276 Xanax ® (alprazolam) Tablets

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

If "Yes," skip to question 6. Otherwise, answer part (c).

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? **YES** **NO**

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES **NO**

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

(b) Is the approved drug product cited as the listed drug? **YES** **NO**

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application provides for a change in dosage form, from tablets to orally disintegrating tablets.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). **YES** **NO**

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). **YES** **NO**

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). **YES** **NO**

10. Are there certifications for each of the patents listed for the listed drug(s)? **YES** **NO**

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent No. 4,508,726

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

Patent No. 5,061,494

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).)?

N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): **Sponsor did not request exclusivity.**

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER
The number of the applicant's IND under which the studies essential to approval were conducted.

IND # _____ NO

OR
A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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

/s/

Richardae Taylor
10/6/04 04:13:26 PM
CSO

Taylor, Richardae

From: Arnwine, Kristina
Sent: Wednesday, October 13, 2004 3:44 PM
To: Taylor, Richardae
Subject: RE: Niravam (NDA 21-726)

Chardae,

That's fine, you can let the sponsor know that we do not have any objections to Niravam.

Kristina

-----Original Message-----

From: Taylor, Richardae
Sent: Wednesday, October 13, 2004 11:07 AM
To: Arnwine, Kristina
Subject: RE: Niravam (NDA 21-726)

Thanks Kristina!

-----Original Message-----

From: Arnwine, Kristina
Sent: Wednesday, October 13, 2004 11:01 AM
To: Taylor, Richardae
Subject: RE: Niravam (NDA 21-726)

My review should be done by then. I am not sure about informing the sponsor yet. I will ask my Div Dir and let you know.

Kristina

-----Original Message-----

From: Taylor, Richardae
Sent: Wednesday, October 13, 2004 10:59 AM
To: Arnwine, Kristina
Subject: RE: Niravam (NDA 21-726)

Hi Kristina,

Does that mean that the name Niravam will be approved before 10/19? Also, can the sponsor be informed of this now?

Thanks,
Chardae

-----Original Message-----

From: Arnwine, Kristina
Sent: Wednesday, October 13, 2004 10:56 AM
To: Taylor, Richardae
Subject: RE: Niravam (NDA 21-726)

Chardae,

Right now it looks like we don't object to the name Niravam.

Kristina

-----Original Message-----

From: Taylor, Richardae
Sent: Thursday, October 07, 2004 9:42 AM
To: Arnwine, Kristina
Subject: RE: Niravam (NDA 21-726)

Thanks Kristina.
Chardae

-----Original Message-----

From: Arnwine, Kristina
Sent: Thursday, October 07, 2004 9:39 AM
To: Taylor, Richardae
Subject: RE: Niravam (NDA 21-726)

Chardae,

There are some issues that we have with both of the names, so I have forwarded those issues to my Division Director who is out on training this week. The plan is for her to read them this evening and get back to me tomorrow morning. So as soon as I hear from her, I will let you know what's going on.

Kristina

-----Original Message-----

From: Taylor, Richardae
Sent: Wednesday, October 06, 2004 4:02 PM
To: Arnwine, Kristina
Subject: RE: Niravam (NDA 21-726)

Hi Kristina,

I'm just checking in on the status of the tradename review for NDA 21-726 (alprazolam ODT). Do you know what name is going to be approved yet?

Many thanks!

Chardae

-----Original Message-----

From: Arnwine, Kristina
Sent: Thursday, September 30, 2004 2:08 PM
To: Taylor, Richardae
Subject: Niravam (NDA 21-726)

Chardae,

I am currently reviewing the proposed proprietary name Niravam. Although I have not completed my review, I think the name will be acceptable. However, we are currently doing a review on an ANDA with the name *_____* (name still pending, not FOI releasable). I believe that Niravam will probably be approved first since it has a PDUFA date of 10/19. So, if Niravam is approved, the name should not be a problem. However, if Niravam is not approved and *_____* is approved before Niravam, I may have to find the name unacceptable. I just wanted to give you a heads up with what's going on with the review.

Kristina

*Kristina C. Arnwine, PharmD
LT, USPHS
Safety Evaluator
Office of Drug Safety
Division of Medication Errors & Technical Support
Food & Drug Administration
Phone: 301-827-7848
Fax: 301-443-9664
E-mail: kristina.arnwine@fda.hhs.gov*

C

9 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN
SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office):
HFD- 860/Biopharm

FROM:
HFD-120/ Division of Neuropharmacological Drug Products

DATE
September 29, 2004

IND NO.

NDA NO.
21-726

TYPE OF DOCUMENT
New Drug Application

DATE OF DOCUMENT
September 14, 2004

NAME OF DRUG
Alprazolam Orally
Disintegrating Tablets

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
**User fee due date October
19, 2004**

NAME OF FIRM: Schwarz Pharma

REASON FOR REQUEST

COMMENTS/SPECIAL INSTRUCTIONS:

This submission contains the results of a study entitled, "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." The submission is located in the EDR at the following location:

^DSESUB1\N21726\N 000\2004-09-14

Thanks!

SIGNATURE OF REQUESTER
Richardae Taylor, Pharm.D.
Regulatory Project Manager
301-594-5793
taylorr@cderr.fda.gov

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

September 14, 2004

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 21-726
Alprazolam Orally Disintegrating Tablets, 0.25 mg, 0.5 mg, 1 mg and 2 mg
Amendment 006 – Addendum to Pharmacokinetic Report and Analytical Report

Dear Sir or Madam:

Reference is made to the above-mentioned new drug application, submitted December 19, 2003.

Schwarz Pharma, Inc. (SPInc) herein submits an addendum to Study 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*. The report has been amended/revised as a result of an August 16 – 20, 2004 district office inspection of _____ and as the result of a review of the report by _____, subsequent to the submission of the NDA. Though the report has been amended/revised, the conclusion is the same as that derived in the original submission of the NDA. The 1mg Alprazolam ODT administered as the test drug, either with or without water, has a similar safety profile and is bioequivalent to the 1 mg reference Xanax[®] Tablet.

A diskette of the bioequivalence study data is included. Only data pertaining to α -Hydroxyalprazolam has changed, as described in the addendum. Since this submission includes a diskette of the bioequivalence study data, it is being sent to the Central Document Room, as instructed in the *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – General Considerations*, dated January, 1999. The diskette is included only in the archival copy. The diskette is virus free as Symantec AntiVirus Corporate Edition, rev. 54, dated 9/12/2004, was used to check the files for viruses.

If there are any questions regarding this submission, please contact Gary M. Wiczorek, Regulatory Affairs Manager, at 262-238-5171 or by fax at 262-238-0957.

Sincerely,

SCHWARZ PHARMA, INC.

Donna K. Multhauf
Director
Regulatory Affairs

16 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN
SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

Division/Office):
HFD- 860/Biopharm

FROM:
HFD-120/ Division of Neuropharmacological Drug Products

DATE
July 22, 2004

IND NO.

NDA NO.
21-726

TYPE OF DOCUMENT
CMC Amendment: Tablet
Shape Change

DATE OF DOCUMENT
July 15, 2004

NAME OF DRUG

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE

Alprazolam Orally
Disintegrating Tablets

NAME OF FIRM: Schwarz Pharma

REASON FOR REQUEST

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the attached submission that contains a CMC amendment for a tablet shape change submitted to NDA 21-726 for Alprazolam Orally Disintegrating Tablets.

Thanks!



SIGNATURE OF REQUESTER
Richardae Taylor, Pharm.D.
Regulatory Project Manager
301-594-5793
taylora@cder.fda.gov

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

SCHWARZ
P H A R M A

FACSIMILE TRANSMISSION

CONFIDENTIAL

FAX NO. 301-594-2858

TO: Richardae Taylor
Regulatory Management Officer
Div. of Neuropharmacological Drug Products

FROM: Gary M. Wieczorek, Manager, Regulatory Affairs

DATE: July 8, 2004

RE: NDA 21-726 Alprazolam Orally Disintegrating Tablets

Number of Pages (Including This Page) Being Transmitted: 2

If Not Properly Received, Call 262/238-5171.
RETURN FAX: 262/238-0957

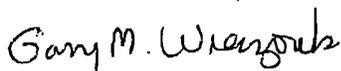
**RE: NDA 21-726 Alprazolam Orally Disintegrating Tablets
Additional Questions Related to the Tablet Change Filing Proposal**

Dear Richardae:

Per your request, I am sending you this fax to present the questions I raised in our July 8, 2004 telephone conversation about our tablet shape change filing proposal for the two lower strength (0.25 mg and 0.5 mg) Alprazolam Orally Disintegrating Tablets (ODT). I am sending a fax versus an e-mail for security reasons.

If you have any questions or require additional information, please do not hesitate to contact me at 262-238-5171.

Thank you,



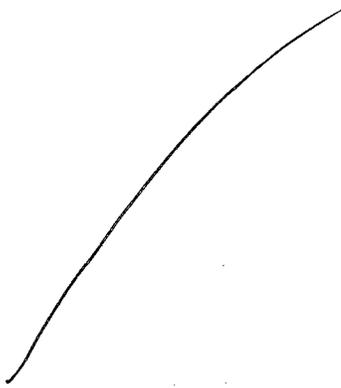
Gary M. Wieczorek
Manager, Regulatory Affairs

**ADDITIONAL QUESTIONS RELATED TO THE
ALPRAZOLAM ORALLY DISINTEGRATING TABLET FILING PROPOSAL
FOR A TABLET SHAPE CHANGE**

1. First, as I indicated, we plan to submit our amendment by the end of next week so that you will receive it on July 19, 2004, which is 90 days before the user fee date of October 19, 2004. This will enable us to have the changes incorporated without impacting the user fee date. Given that we have not received the concerns raised by the Division of Neurological Drug Products (DNNDP) chemistry team, in order to meet the July 19, 2004 deadline, we may have to submit our amendment only with the information we presented in our proposal. Any additional information required per the chemistry team would have to be submitted as an amendment to the amendment, after July 19, 2004.

To what extent would the DNNDP chemistry team be able to work with us to allow additional information to be submitted to this amendment after July 19, 2004 without impacting the October 19, 2004 user fee date?

2.



Does DNNDP agree that the change can be filed as a CBE-0 supplement if we choose to submit it post-approval?

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

Division/Office):
HFD- 860/Biopharm

FROM:
HFD-120/ Division of Neuropharmacological Drug Products

DATE
June 1, 2004

IND NO.

NDA NO.
21-726

TYPE OF DOCUMENT
Proposal for Tablet Shape
Change

DATE OF DOCUMENT
May 21, 2004

NAME OF DRUG

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE

Alprazolam Orally
Disintegrating Tablets

NAME OF FIRM: Schwarz Pharma

REASON FOR REQUEST

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the attached submission that contains a proposal for a tablet shape change submitted to NDA 21-726 for Alprazolam Orally Disintegrating Tablets. FYI...the user fee date on this application is October 19, 2004.

anks!

SIGNATURE OF REQUESTER
Richardae Taylor, Pharm.D.
Regulatory Project Manager
301-594-5793
taylorr@cder.fda.gov

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

Division/Office):
HFD- 860/Biopharm

FROM:
HFD-120/ Division of Neuropharmacological Drug Products

DATE 5/19/04	IND NO.	NDA NO. 21-726	TYPE OF DOCUMENT Response to Filing Letter	DATE OF DOCUMENT 3/25/04
NAME OF DRUG Alprazolam Orally Disintegrating Tablets		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE

NAME OF FIRM: Schwarz Pharma

REASON FOR REQUEST

COMMENTS/SPECIAL INSTRUCTIONS:

Hi Ray,

This was Schwarz's response to the biopharm issues raised in the filing letter. I gave a copy of this response to all of those reviewing this application back in March, including Ron. I wanted to follow-up with an official consult to ensure all information needed is officially received for review. Please let me know if you have any questions.

Thanks!

SIGNATURE OF REQUESTER
Richardae Taylor, Pharm.D.
Regulatory Project Manager
301-594-5793
taylorr@cderr.fda.gov

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

e

3 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

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 December 19, 2003 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for alprazolam orally disintegrating tablets (ODT).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b)(2) of the Act on February 17, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. 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 orally 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.
2. /

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

NDA 21-726

Page 2

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

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/s/

Russell Katz
2/18/04 07:45:40 AM

DSI CONSULT Request for Biopharmaceutical Inspections
--

DATE: February 4, 2004

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

FROM: Richardae C. Taylor, Pharm.D., Regulatory Health Project Manger, HFD-120 for
Ray Baweja, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader, HFD-
860

SUBJECT: Request for Biopharmaceutical Inspections
NDA 21-726 for Alprazolam Orally Disintegrating Tablets (ODT)

Study/Site Identification:

As discussed with you, the following study, pivotal to approval, has been identified for inspection:

NDA 21-726 **Alprazolam Orally Disintegrating Tablet (ODT)**

Sponsor: Schwarz Pharma, Inc.
6140 West Executive Dr.
Mequon, WI 53092

Contact Information: Donna K. Multhauf, Director of Regulatory Affairs
262-238-5171

Study Number: SP691

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

Contractor: _____

Clinical Investigator: _____

Clinical Study Site:

Project No.: AA03436

Contact Information:

Bioanalytic Site:

Principal Scientist:

Study Report Location: Volumes 12, 13, and 14
The bioanalytic report is located in appendix 4

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **September 1, 2004**. We intend to issue an action letter on this application by **October 19, 2004**.

Should you require any additional information, please contact Richardae C. Taylor, Pharm.D. at (301)594-5793 or email: taylorr@cderr.fda.gov.

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/s/

Richardae Taylor
2/4/04 01:31:18 PM

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

DATE: January 14, 2004

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

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

TO: File for NDA 21-726
[Note: Should be filed with 11-18-04 response to FDA's 10-19-04 approvable
letter.]

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.

We issued an approvable letter for this application on 10-19-04, and identified several issues to address prior to final approval:

Clinical Issues

We asked for more detailed information on 8 subjects in the PK studies who had laboratory abnormalities on alprazolam ODT.

Comment: It turns out there were 6 subjects with borderline and transient abnormalities. Dr. Levin concluded that these changes were of no consequence, and I agree.

Pharmacokinetic Issues

We asked the sponsor to consider doing several studies and a literature search, not as phase 4 commitments, but rather, just a recommendation:

-Drug interaction studies with drug classes that raise gastric pH (other than PPIs).

- A study to determine effect of anticholinergic drugs on absorption rate, with and without water.
- A literature search regarding changes that occur in esophageal transit, saliva flow, and composition in healthy elderly and elderly with common diseases.

We did ask for a _____ as a phase 4 commitment.

We also asked them to accept an alternative dissolution method and specs.

Comment:

- The sponsor has agreed to conduct the _____
- They will consider the studies with other drugs that raise gastric pH, pending the outcome of the PPI study.
- They will modify labeling as requested regarding dry mouth, and consider an in vivo study.
- They will consider a literature search as suggested.
- They have accepted our proposed dissolution specs.

CMC Issues

We asked that they address several issues and concerns, including minor revisions to labeling.

Comment: The CMC group was satisfied with the responses to the list of issues we asked the sponsor to address in the approvable letter.

Pharmacology/Toxicology Issues

_____ monomers, i.e. _____ We asked them to either try to reduce the levels or, alternatively, justify the safety of these levels.

Comment: The sponsor provided safety data for _____ and also lowered the spec to < _____. The pharm/tox group concluded there are sufficient safety data to justify this revised spec. Regarding the _____ the pharm/tox group is willing to accept the spec of < _____ and the relatively small amount of safety data, given the structural similarity of these to _____.

Packaging Issues

We asked them to address a number of issues pertinent to packaging and labeling of the packages.

Comment: The sponsor agreed to all the changes proposed by DMETS.

Labeling

OCPB recommended some modest changes to labeling.

Comment: We have obtained agreement on final labeling.

Conclusions/Recommendations

This application can now be approved, and I recommend that we issue the attached approval letter with the mutually agreed to final labeling.

cc:

Orig NDA 21-726/Alprazolam ODT

HFD-120/DivFile

HFD-120/TLaughren/RKatz/PAndreason/RLevin/RTaylor

DOC: Memo Alprazolam ODT AP1.doc

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/s/

Thomas Laughren
1/14/05 01:48:45 PM
MEDICAL OFFICER



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:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Alprazolam Orally Disintegrating Tablets

Review Priority Classification: Standard (S)

Date of Application: December 19, 2003

Date of Receipt: December 19, 2003

Our Reference Number: NDA 21-726

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 17, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 19, 2004.

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 note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

NDA 21-726

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, Rm. 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, Rm. 4008
1451 Rockville Pike
Rockville, Maryland 20852

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

Sincerely,

{See appended electronic signature page}

Robbin Nighswander, R.Ph., M.S.
Supervisory Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Robbin Nighswander
1/8/04 11:32:50 AM

DEPARTMENT OF HEALTH AND HUMAN
SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

Division/Office):
HFD- 860/Biopharm

FROM:
HFD-120/ Division of Neuropharmacological Drug Products

DATE
12/30/03

IND NO.

NDA NO.
21-726

TYPE OF DOCUMENT
New Drug Application

DATE OF DOCUMENT
12/19/03

NAME OF DRUG

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE

Alprazolam Orally
Disintegrating Tablets

**User fee due date October
19, 2004**

NAME OF FIRM: Schwarz Pharma

REASON FOR REQUEST

COMMENTS/SPECIAL INSTRUCTIONS:

This is a new 505 (b)(2) NDA# 21-726 for Alprazolam Orally Disintegrating Tablets. This NDA includes bioequivalence/bioavailability studies to support the application. It was submitted in both paper and electronic form. The EDR path is: \\CDSESUB1\N21726\N 000\2003-12-19. The user fee date on this application is October 19, 2004. The filing meeting for this NDA is on 2/3/04 from 2:30-3:30 pm (see attached meeting notice).

anks!

SIGNATURE OF REQUESTER
Richardae Taylor, Pharm.D.
Regulatory Project Manger
4-5793
taylorr@cder.fda.gov

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/s/

Anna-Marie Homonnay
9/25/03 04:56:51 PM

FOOD AND DRUG ADMINISTRATION
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
5600 FISHERS LANE [HFD-120]
ROCKVILLE, MARYLAND 20857
FAX: [301] 594-2858/594-2859
COVER SHEET

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DATE: 4/30/03

TIME: _____

PLEASE DELIVER THE FOLLOWING PAGES TO:

Mr. Gary Wilczek

FAX NUMBER: (202) 238-0957

FROM: Ms. Anna Marie H. Weikel

Total number of pages, including cover page: 5

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MESSAGE: FOA Meeting Minutes

FDA Teleconference Minutes

Drug: alprazolam orally disintegrating tablets
PIND #: 63,934
Indication: anxiety disorders
Firm: Schwarz Pharma
Meeting Type: Pre-NDA teleconference

Attendees:

FDA Division of Neuropharmacological Drugs

Russell Katz, MD, Division Director
Thomas Laughren, MD, Clinical Teamleader, Psychiatric Drugs
Paul Andreasson, MD, Clinical Teamleader, Psychiatric Drugs
Barry Rosloff, PhD, Pharmacology/Toxicology Teamleader
Elzbieta Chalecka-Franaszek, Pharm/Tox Reviewer
Ramana Uppoor, Ph.D. Clinical Pharmacology & Biopharmaceutics Teamleader
Wendy Chou, Pharm.D., PhD, Clinical Pharmacology & Biopharmaceutics Reviewer
Lorenzo Rocca, PhD, Chemistry Reviewer

Schwarz Pharma Inc (SPInc.)

Donna Multhaupt, Director, Regulatory Affairs and Quality Assurance
Steven Pollock, VP, Medical, Regulatory and Quality Assurance
Harald Steltzer, Project Manager
Gary Wieczorek, Regulatory Affairs Manager
Michelle Witt, Regulatory Affairs Associate
Patricia Witt, Clinical Trial Manager
Regulatory and Toxicology Consultant

Background:

Schwarz Pharma requested this pre-NDA teleconference in order to obtain FDA guidance regarding their plans for a 505(b)(2) NDA submission for alprazolam orally disintegrating tablets. A briefing package was submitted on May 22, 2003, which was the focus of the discussion.

Discussion

SPInc has evaluated the existing preclinical package, including the approval information for Xanax Tablets, the RLD, along with additional published literature. SPInc has determined that it is sufficient to support the new drug application. This information package includes a review of the existing data and provides the basis for SPInc's conclusion. SPInc seeks Agency concurrence on the acceptability of this preclinical package to support the 505(b)(2) application.

FDA Response: FDA agreed that the proposed package was acceptable.

- The proposed indications, strengths, and dosing for alprazolam orally disintegrating tablets are the same as those contained in the approved labeling for Xanax Tablets, the RLD. The indications are supported by clinical studies submitted to the Xanax Tablets application, NDA 18-276. It is SPInc's position that these studies are adequate to support the new drug application for the orally disintegrating tablets. To support this, a pharmacokinetic trial will demonstrate therapeutic equivalence of Xanax Tablets 1 mg, noted as the RLD dose in the Orange Book, and the 1 mg tablets of the proposed orally disintegrating tablets. At this time, the trial has been completed and preliminary results indicate that Xanax Tablets 1 mg and the 1 mg tablets of the proposed orally disintegrating tablet are bioequivalent. Biowaivers will be filed for the other strengths, based on the following justifications:*

3. SPInc intends to produce alprazolam orally disintegrating tablets in 0.25 mg, 0.5 mg, 1 mg and 2 mg strengths. Alprazolam is not a New Chemical Entity. The drug substance and conventional immediate release tablets are compendial items, and Xanax Tablets were approved prior to January 1, 1982. Several dosage forms of alprazolam have been approved since 1982. Thus, there is a great deal of CMC information available to the agency on both the drug substance and the current approved formulations. As noted above, the formulations proposed by SPInc

SPInc is proposing to produce _____ batches of each strength as support for the CMC portion of the application. In addition, SPInc proposes to file the application with _____ of accelerated and controlled room temperature stability data on the drug product, with stability updates provided to the application during the review process to support a 24-month expiration period. This stability proposal is consistent with the recommendations of the ICH Guidance for Industry: Q1C.

FDA Response: FDA agreed that _____ 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 is a review issue and will be decided based on the amount and quality of the stability data available at the time of review. FDA requested that _____ be added to the stability testing for this type of dosage form to be packaged in bottles. FDA also would like assurance that the tablet coating process is consistent*.

*Additional FDA Pre-NDA CMC Comments: On Wednesday July 16, 2003, Thomas F. Oliver, Ph.D. (HFD-120, Team Leader) contacted Schwarz Pharma, and spoke with Gary Wieczorek about additional Pre-NDA CMC comments. Mr. Wieczorek suggested the additional CMC comments be faxed to Schwarz. The additional pre-NDA CMC comments are listed below.

1. We recommend that you 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 to protect the drug product.
2. We recommend that you test for specific impurities in the drug product and list these known impurities in the drug product regulatory release specifications.
3. We recommend that you provide the statistical analysis results (per ICH Q1A) for the _____ stability data and subsequent stability data that you plan to submit.
4. The magnesium stearate used to manufacture the drug product needs to be from a plant source or, if from an animal source, you need to guarantee that the animals used are from a non-BSE country.

Post-Meeting Addendum:

SPInc provided a food-effect biostudy proposal on July 17, 2003; FDA comments are as follows:

We find that the proposed study design for the food effect study acceptable. However, it would be preferable to conduct the food-effect study with the highest strength, i.e. 2 mg, as recommended in the FDA Food-Effect Guidance. In addition, it would also be beneficial if additional PK data could be collected on the highest strength along with the food-effect PK data, which would otherwise be unavailable due to the biowaiver.

Minutes prepared by: Ms. Anna Marie H. Weikel
Project Manager

Concurred by: Chow/7.28.03/Uppoor/7.28.03/Oliver/Rocca/7.28.03
Finalized by: ahw/7.29.03

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/s/

**Thomas Laughren
7/30/03 01:30:51 PM**

FOOD AND DRUG ADMINISTRATION
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
5600 FISHERS LANE [HFD-120]
ROCKVILLE, MARYLAND 20857
FAX: [301] 594-2858-/594-2859
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DATE: 1/12/04

TIME: 9:20 am

PLEASE DELIVER THE FOLLOWING PAGES TO:

Gary M. Wiczorek

FAX NUMBER: 262-238-0957

FROM: Chardae Taylor

Total number of pages, including cover page: 2

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MESSAGE: Labeling negotiation

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Schwarz Pharma, Inc.
6140 W. Executive Drive
Mequon, WI 53092

Mailing Address:
P.O. Box 2038
Milwaukee, WI 53201

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
N021726

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(262) 238-5171

3. PRODUCT NAME

Alprazolam Orally Disintegrating Tablets, 0.25 mg, 0.5 mg, 1 mg, and 2 mg

6. USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

Gary M. Wiegand for

TITLE

Donna K. Multhauf
Director of Regulatory Affairs

DATE

12/19/03