CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-726

CHEMISTRY REVIEW(S)

NDA 21-726

Niravam™ (alprazolam) Orally Disintegrating Tablets

Schwarz Pharma, Inc.

Chhagan G. Tele, Ph.D.
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-726

2. REVIEW #: 2

3. REVIEW DATE: December 03, 2004

4. REVIEWER: Chhagan G. Tele, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	19-DEC-2003
Amendment 000 N(C)	21-MAY-2004
Amendment 004 N(BZ)	15-JUL-2004
Amendment 000 N(BC)	26-JUL-2004
Amendment 005 N(BC)	17-AUG-2004
Amendment 000 N(BC)	03-SEP-2004
Amendment 007 N(BZ)	18-NOV-2004
CMC Review #1	15-OCT-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Response to Approvable Letter, Amendment 007 N(BZ)	18-NOV-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Schwarz Pharma, Inc.
Address:	P.O. box 2038, Milwaukee, WI 53201
Representative:	Gary M. Wieczorek, Manager, Regulatory Affairs
Telephone:	(262) 238-5171

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Niravam™
b) Non-Proprietary Name (USAN-1973): Alprazolam
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2); The RLD is Xanax® (alprazolam) Tablets, 0.25 mg, 0.5 mg, 1 mg, and 2 mg, Pharmacia and Upjohn NDA 18-276.

10. PHARMACOL. CATEGORY: For the management of anxiety disorder.

11. DOSAGE FORM: Orally Disintegrating Tablet

12. STRENGTH/POTENCY: 0.25 mg, 0.5 mg, 1 mg, and 2 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
___X_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN Name [1973]: 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3-a] [1,4] benzodiazepine

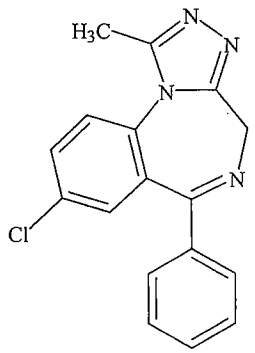
Non-Proprietary Name: Alprazolam

Chemical Formula: $C_{17}H_{13}ClN_4$

Molecular Weight: 308.76

CAS registry #: 28981-97-7

Structure:



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
	II			1	Adequate	Dr. Chhagan Tele
	II			3	Adequate	26-JUL-2000 Dr. S. McLamore
	III			3	Adequate	15-SEP-2000 Dr. D. Klein
	III			3	Adequate	26-FEB-2002 Dr. Arthur Shaw
	III			3	Adequate	24-AUG-2000 Dr. Alan Frankewich
	III			3	Adequate	06-AUG-2001 Dr. Prasad Peri
	III			3	Adequate	06-OCT-2003 Dr. M. Heimann

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	18-276	Xanax® Tablets
IND	63,934	Commercial IND (anxiety disorder)

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Overall Recommendation Acceptable	26-JUL-04	S. Ferguson (HFD-322)
Pharm/Tox	-	-	Aisar H. Atrakchi, Ph.D. (HFD-120)
Biopharm	Acceptable provided that satisfactory agreement is reached between FDA and the sponsor regarding the dissolution method, specifications, and labeling.	24-SEP-04	Ronald E. Kavanagh, Ph.D. (HFD-860)
LNC	USAN available	1973	USP Dictionary, 2002
Methods Validation	Pending		To be forwarded once specifications and methods finalized
DMETS	Evaluation of proposed trade name	01-APR-04	Linda Y. Kim-Jung, R.Ph. (HFD-420)
EA	Acceptable, categorical exclusion granted as per information from Schwarz in this NDA	As per this review	Chhagan G. Tele, Ph.D. (HFD-120)
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-726

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry, Manufacturing, and Controls (CMC) standpoint NDA 21-726 for Niravam™ (alprazolam) is recommended **APPROVAL**. The approval is based on the acceptable responses to the CMC deficiencies and acceptable recommendation from the Office of Compliance for all the drug substance and drug product manufacturing, packaging, labeling, and stability testing facilities.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Niravam™ (alprazolam, USP) Orally Disintegrating Tablets are indicated for the management of anxiety disorder or the short-term relief of symptoms of anxiety. It is also indicated in the treatment of panic disorder, with or without agoraphobia. Alprazolam is a potent anxiolytic triazolo analog of the 1,4-benzodiazepine class of central nervous system-active compounds, classified as an antipsychotic drug because its profile of binding at stereospecific receptors at several sites within the central nervous system. The exact mechanism of action is unknown.

Alprazolam was originally approved in 1981, under NDA 18-276, as conventional immediate-release oral tablets (Xanax® Tablets, 0.25 mg, 0.5 mg, 1 mg, and 2 mg) manufactured and distributed by Pharmacia Upjohn. The proposed product, Niravam™ (alprazolam, USP) Orally Disintegrating Tablets, manufactured by using CIMA's DuraSolve™ technology, is to be marketed as oral disintegrating tablets in strengths of 0.25 mg, 0.5 mg, 1 mg, and 2 mg. Each tablet contains 0.25 mg, 0.5 mg, 1 mg, and 2 mg of alprazolam. The maximum recommended total daily dose is 10 mg/day. The commercial manufacturing process for Alprazolam Orally Disintegrating Tablets

was used in the manufacture of all four strengths, 0.25 mg, 0.5 mg, 1 mg, and 2 mg Alprazolam Orally Disintegrating. The tablets also contain mannitol, microcrystalline cellulose, crospovidone, orange flavor, iron oxide (yellow), and magnesium stearate (The acceptable compatibility studies of Alprazolam, Iron Oxide Yellow, Mannitol (USP), Microcrystalline Cellulose, Magnesium Stearate (NF, , and orange flavor were provided by the applicant. No significant interactions between any of the Niravam™

(alprazolam, USP) ingredients were found after — at 60° C. Based on these results the applicant indicated that all excipients are compatible with the alprazolam present in the orally disintegrating tablets.

The registration batches were manufactured at the commercial drug product manufacturer, CIMA's, Eden Prairie, Minnesota facility. Adequate information was provided for the manufacturing and in-process controls of the drug product. However, no information was provided initially for re-processing of the drug product. In amendment 007 (BZ) dated November 18, 2004 to FDA's Approvable letter dated October 19, 2004, it is indicated by the applicant that the reprocessing is not intended to be performed with this drug product. Applicant also committed that if reprocessing is desired in the future, it will be communicated to the agency in the appropriate manner. The commercial-scale manufacturing and packaging process for Niravam™ (alprazolam, USP) involves

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blisters or bottles into final packages. —

— The proportions of components are the same for each strength, which differ only in tablet weight as noted in the components/composition section of drug product. In-process tests included — which are appropriate and characteristic of orally disintegrating tablets (ICH Q6A). Initially, the applicant proposed 0.25 mg and 0.5 mg tablets to be of — yellow, round — scored "SP321" and "SP322" once on one side and "0.25" and "0.5" on the other side, respectively. In amendment dated 15-JUL-04, the applicant wanted to change the shape of the 0.25 mg and 0.5 mg tablets from — because — . Given that the 1 mg and 2 mg tablets — , these tablets will remain as shaped tablets. The tablet weight is 100 mg each for both strengths. Certificate of Analysis and 3 — stability data (ambient conditions) of one batch of each strength, 0.25 mg and 0.5 mg — oulk tablets were provided. The updated specifications for Physical Appearance of both tablet strengths (0.25 mg and 0.5 mg) were changed from — ablets. The updated release and stability specifications for both strengths are similar except no tests will be performed during stability testing. The applicant committed that the first three production batches of 0.25 mg and 0.5 mg — tablets will be placed on stability to address the post-approval stability commitment noted in the original NDA.

The 1 mg and 2 mg tablets are — white, round — scored "SP323" and "SP324" once on one side and "1" and "2" on the other side, respectively. The tablet weights are 200 mg and 400 mg for 1 mg and 2 mg strengths, respectively. The specification for tablet included —

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— The batch analyses were provided for two batches of each strength of Alprazolam ODT. The release and stability specifications for the drug product are identical. Validated analytical methods were provided in the submission.

Alprazolam Orally Disintegrating Tablets will be marketed into bottles — The bottle sizes are 60 cc for 0.25 mg, 0.5 mg, and 1 mg tablets, and 100 cc for 2 mg tablets. —

— The applicant provided — ong term stability data for two registration batches of each strength, 0.25 mg,0.5 mg, 1 mg, and 2 mg of Niravam™ tablets in the response to approvable letter in addition of statistical analysis of the data through —. Based on this data, the applicant proposed an expiry date of 24 months for Niravam™ tablets. The applicant has requested

a 24 month expiration period (shelf life) for all strengths packaged in bottles — On the basis of acceptable stability data of — at long term and — at accelerated storage conditions for — shape Niravam™ tablets (0.25 mg, 0.5 mg, 1 mg, and 2 mg strengths) packaged bottles — tability data for 0.25 mg and 0.5 mg — bulk tablets stored at ambient conditions, we recommend expiry of 24 months for all strengths.

The drug substance, alprazolam, has a USP monograph (current USP 27, pp. 65). Alprazolam is a controlled substance under the Controlled Substance Act by the Drug Enforcement Administration, and Niravam™ (alprazolam, USP) Tablets have been assigned to Schedule IV. The drug substance, alprazolam, is manufactured and supplied to the applicant by — as according to the process and controls described in their DMF — A Letter of Authorization was provided for cross-reference. The DMF — was reviewed and found adequate by Dr. Chhagan Tele. Alprazolam is a white to off-white, crystalline powder. All the batches of alprazolam drug substance presented in the original NDA were manufactured at the — [1]. Batch analysis data of twelve batches were submitted. Validated analytical methods were provided in the DMF. A retest date of — has been established for the bulk alprazolam drug substance by — on the basis of — stability data for 3 commercial batches.

B. Description of How the Drug Product is Intended to be Used

Niravam™ (alprazolam, USP) drug product will be marketed in 100 count/60cc bottles for 0.25 mg, 0.5 mg, and 1 mg tablets, and 100 count/100cc bottles for 2 mg tablets. —

The maximum recommended total daily dose is 10 mg/day. Initial treatment with Niravam™ (alprazolam, USP) begins with a 0.25 or 0.5 mg orally disintegrating tablet three times daily and then continued with daily dosage increments of 0.25 mg/day, if well-tolerated, — . Subsequent dosage increments should be made at interval of 3 to 4 days, in increments not to exceed — Information concerning the remaining half tablet was not provided in the original package insert. The medical officer, Dr. Robert Levin was informed about this matter. Please refer to the medical review for any proposed changes in dosage and administration of Niravam™ (alprazolam, USP). The applicant has requested a 24 month expiration period (shelf life) for all strengths packaged in bottles — . On the basis of acceptable stability data of — at long term and — at accelerated storage conditions for — shape Niravam™ tablets (0.25 mg, 0.5 mg, 1 mg, and 2 mg strengths) packaged in bottles and/or blisters and — stability data for 0.25 mg and 0.5 mg — bulk tablets stored at ambient conditions, we recommend expiry of 24 months for 1 and 2 mg strengths and 12 months for 0.25 and 0.5 mg strengths on the basis of available data — at long term storage conditions).

The storage conditions for the drug product were recommended as "Store at 20° to 25° C (68° to 77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature]. Protect from moisture. The package insert instructs patients not to remove the orally-disintegrating tablet from the — bottle until the patient is ready to consume the tablet.

The applicant made the usual post-approval stability commitments with regards to stability studies, indicating that the first three production batches for each strength and each container/closure system will continue according to the approved stability protocols through the expiration dating period.

The Office of Compliance has found all manufacturing, testing, and packaging sites acceptable.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-726 for Niravam™ (alprazolam) is recommended to be granted **APPROVAL** from CMC standpoint. All CMC concerns related to the drug substance and drug product sections as outlined in the Chemistry review #1 by Dr. Chhagan G. Tele have been adequately addressed as of this review #2. There are no outstanding Chemistry, Manufacturing, and Controls issues related to this application.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name: Chhagan G. Tele, Ph.D.
Chemistry Team Leader Name: Thomas F. Oliver, Ph.D.
Project Manager Name: Richardae Taylor, Pharm.D.

C. CC Block

See DFS.

22 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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

/s/

Chhagan Tele
1/11/05 06:36:47 PM
CHEMIST

Thomas Oliver
1/11/05 06:40:36 PM
CHEMIST

NDA 21-726

— (Alprazolam)
Orally Disintegrating Tablets

Schwarz Pharma, Inc.

Review of Chemistry, Manufacturing, and Controls

Chhagan G. Tele, Ph.D.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-726

2. REVIEW #: 1

3. REVIEW DATE: July 28, 2004

4. REVIEWER: Chhagan G. Tele, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	19-DEC-2003
Amendment 000 N(C)	21-MAY-2004
Amendment 004 N(BZ)	15-JUL-2004
Amendment 000 N(BC)	26-JUL-2004
Amendment 005 N(BC)	17-AUG-2004
Amendment 000 N(BC)	03-SEP-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Schwarz Pharma, Inc.
Address:	P.O. box 2038, Milwaukee, WI 53201
Representative:	Gary M. Wieczorek, Manager, Regulatory Affairs
Telephone:	(262) 238-5171

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: —
b) Non-Proprietary Name (USAN-1973): Alprazolam
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2); The RLD is Xanax® (alprazolam) Tablets, 0.25 mg, 0.5 mg, 1 mg and 2 mg, Pharmacia and Upjohn NDA 18-276.

10. PHARMACOL. CATEGORY: For the management of anxiety disorder.

11. DOSAGE FORM: Orally Disintegrating Tablet

12. STRENGTH/POTENCY: 0.25 mg, 0.5 mg, 1 mg, and 2 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
___X_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN Name [1973]: 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3-a] [1,4] benzodiazepine

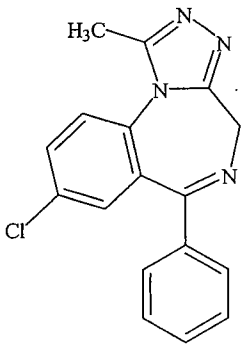
Non-Proprietary Name: Alprazolam

Chemical Formula: $C_{17}H_{13}ClN_4$

Molecular Weight: 308.76

CAS registry #: 28981-97-7

Structure:



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
	II			1	Adequate	Dr. Chhagan Tele
	II			3	Adequate	26-JUL-2000 Dr. S. McLamore
	III			3	Adequate	15-SEP-2000 Dr. D. Klein
	III			3	Adequate	26-FEB-2002 Dr. Arthur Shaw
	III			3	Adequate	24-AUG-2000 Dr. Alan Frankewich
	III			3	Adequate	06-AUG-2001 Dr. Prasad Peri
	III			3	Adequate	06-OCT-2003 Dr. M. Heimann

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	18-276	Xanax® Tablets
IND	63,934	Commercial IND (anxiety disorder)

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Overall Recommendation Acceptable	26-JUL-04	S. Ferguson (HFD-322)
Pharm/Tox	Pending	-	Aisar H. Atrakchi, Ph.D. (HFD-120)
Biopharm	Acceptable provided that satisfactory agreement is reached between FDA and the sponsor regarding the dissolution method, specifications, and labeling.	24-SEP-04	Ronald E. Kavanagh, Ph.D. (HFD-860)
LNC	USAN available	1973	USP Dictionary, 2002
Methods Validation	Pending		To be forwarded once specifications and methods finalized
DMETS	Evaluation of proposed trade name [redacted]	01-APR-04	Linda Y. Kim-Jung, R.Ph. (HFD-420)
EA	Acceptable, categorical exclusion granted as per information from Schwarz in this NDA	As per this review	Chhagan G. Tele, Ph.D. (HFD-120)
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-726

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

At this time NDA 21-726 for — (alprazolam) is recommended **APPROVABLE** from the CMC standpoint. CMC approval is contingent on adequate responses to the CMC deficiencies related to drug substance and drug product as noted in this review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

— (alprazolam, USP) Orally Disintegrating Tablets are indicated for the management of anxiety disorder or the short-term relief of symptoms of anxiety. It is also indicated in the treatment of panic disorder, with or without agoraphobia. Alprazolam is a potent anxiolytic triazolo analog of the 1,4-benzodiazepine class of central nervous system-active compound, classified as an antipsychotic drug because its profile of binding at stereospecific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown.

Alprazolam was originally approved in 1981, under NDA 18-276, as conventional immediate-release oral tablets (Xanax® Tablets, 0.25 mg, 0.5 mg, 1 mg, and 2 mg) manufactured and distributed by Pharmacia Upjohn. The proposed product, — (alprazolam, USP) Orally Disintegrating Tablets, manufactured by using CIMA's DuraSolve™ technology, is to be marketed as oral disintegrating tablets in strengths of 0.25 mg, 0.5 mg, 1 mg, and 2 mg. Each tablet contains 0.25 mg, 0.5 mg, 1 mg, and 2 mg of alprazolam. The maximum recommended total daily dose is 10 mg/day. The commercial manufacturing process for Alprazolam Orally Disintegrating Tablets

— was used in the manufacture of all four strengths, 0.25 mg, 0.5 mg, 1 mg, and 2 mg Alprazolam Orally Disintegrating. The tablets also contain mannitol, microcrystalline cellulose, crospovidone, orange flavor, iron oxide (yellow), and magnesium stearate (—). The acceptable compatibility studies of Alprazolam, Iron Oxide Yellow, Mannitol (USP), Microcrystalline Cellulose, Magnesium Stearate (NF, non-bovine), — and orange flavor were provided by the applicant. No significant interactions between any of the — (alprazolam, USP) ingredients were found after — at 60° C. Based on these results the

applicant indicated that all excipients are compatible with the alprazolam present in the orally disintegrating tablets.

The registration batches were manufactured at the commercial drug product manufacturer, CIMA's, Eden Prairie, Minnesota facility. Adequate information was provided for the manufacturing and in-process controls of the drug product. However, no information was provided for re-processing of the drug product. The commercial-scale manufacturing and packaging process for (alprazolam, USP) involves into tablets, packaging the tablets in bottles and placing bottles into final packages. The proportion of components are the same for each strength, which differ only in tablet weight as noted in the components/composition section of drug product. In-process tests included which are appropriate and characteristic of orally disintegrating tablets (ICH Q6A). Both, 0.25 mg and 0.5 mg tablets are **yellow**, round scored "SP321" and "SP322" once on one side and "0.25" and "0.5" on the other side, respectively. The tablet weight is 100 mg each for both strengths. The 1 mg and 2 mg tablets are **white**, round scored "SP323" and "SP324" once on one side and "1" and "2" on the other side, respectively. The tablet weights are 200 mg and 400 mg for 1 mg and 2 mg strengths, respectively. The specification for tablet included The batch analyses were provided for two batches of each strength of Alprazolam ODT. The release and stability specifications for the drug product are identical. Validated analytical methods were provided in the submission.

The applicant submitted amendment dated 15-JUL-04 to change the shape of the 0.25 mg and 0.5 mg tablets from tablet to a tablet because Given that the 1 mg and 2 mg tablets will , these tablets will remain as tablets. No release and stability data was provided for these tablets. It was stated that tablet diameter, scoring, , will not be affected by this change. This amendment included the tooling drawings for both the tablets, comparative data for dissolution, disintegration, , and updated specifications for Alprazolam 0.25 mg and 0.5 mg Tablets. The tablet diameters, scoring, and remained the same. The tablet thickness, however, was changed from inches for the 0.25 mg tablet and from inches for the 0.5 mg tablet. Dissolution , disintegration, results of both, tablets were comparable except slight increase in and disintegration rate at higher end of the range for 0.25 mg tablets [convex Tablets (seconds), tablets (seconds)] and 0.5 mg tablets [Tablets (seconds), . Tablets (seconds)]. The updated specifications for Physical Appearance of both tablet strengths (0.25 mg and 0.5 mg) were changed from tablets. The updated release and stability specifications for both strengths are similar except no tests will be performed during stability testing. Schwarz Pharma should provide CoAs of one batch (in each packaging configuration) of Alprazoalm 0.25 mg and 0.5 mg orally disintegrating tablets. The applicant indicated that the first three production batches of 0.25 mg and 0.5 mg tablets will be placed on stability to address the post-approval stability commitment noted in the original NDA.

Alprazolam Orally Disintegrating Tablets will be marketed into bottles — The bottle sizes are 60 cc for 0.25 mg, 0.5 mg, and 1 mg tablets, and 100 cc for 2 mg tablets. —

— The original NDA provided — long term and accelerated stability data for two registration batches of each strength, 0.25 mg,0.5 mg, 1 mg, and 2 mg of — tablets. The August amendment updated this stability data to — which also provided statistical analysis of the data through — Based on this data, the applicant proposed an expiry date of 24 months for — tablets. A recommended expiry will be determined in Review #2.

The drug substance, alprazolam, has a USP monograph (current USP 27, pp. 65). Alprazolam is a controlled substance under the Controlled Substance Act by the Drug Enforcement Administration, and — (alprazolam, USP) Tablets have been assigned to Schedule IV. The drug substance, alprazolam, is manufactured and supplied to the applicant by as according to the process and controls described in their DMF — and Letter of Authorization was provided for cross-reference. The DMF — was reviewed and found adequate by Dr. Chhagan Tele. Alprazolam is a white to off white, crystalline powder with no chiral centers. All the batches of alprazolam drug substance presented in the original NDA were manufactured at the ... Batch analysis data of — batches was submitted. Validated analytical methods were provided in the DMF. A retest date of — s has been established for the bulk alprazolam drug substance by — — on the basis of — stability data for 3 commercial batches.

B. Description of How the Drug Product is Intended to be Used

— alprazolam, USP) drug product will be marketed in 100 count/60cc bottles for 0.25 mg, 0.5 mg, and 1 mg tablets, and 100 count/100cc bottles for 2 mg tablets. —

The maximum recommended total daily dose is 10 mg/day. Initial treatment with (alprazolam, USP) begins with a 0.25 or 0.5 mg orally disintegrating tablet three times daily and then continued with daily dosage increments of 0.25 mg/day, if well-tolerated, to achieve a target — Subsequent dosage increments should be made at interval of 3 to 4 days, in increments not to exceed — nformation concerning the remaining half tablet was not provided in the original package insert. The medical officer, Dr. Robert Levin was informed about this matter. Please refer to the medical review for any proposed changes in dosage and administration of — (alprazolam, USP). Schwarz Pharma initially provided — of stability data at both, 25° C/60% RH and 40° C/75% RH for registration batches of each strength, 0.25 mg, 0.5 mg, 1 mg, and 2 mg alprazolam orally disintegrating tablets. In NDA amendment 005(BC) dated 17-AUG-04 the applicant provided — stability data for coated alprazolam at 30 C/60%RH storage condition and — s long term stability data for the — (alprazolam, USP) drug product, 0.25 mg, 0.5 mg, 1 mg, and 2 mg tablets. The applicant has requested a 24 month expiration period (shelf life) for all strengths packaged in bottles — A recommended expiry will be determined in Review #2.

The storage conditions for the drug product were recommended as "Store at 20° to 25° C (68° to 77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature]. Protect from moisture. The package insert instructs patients not to remove the orally-disintegrating tablet from the — bottle until the patient is ready to consume the tablet.

The applicant makes the usual post-approval stability commitments with regards to stability studies, indicating that the first three production batches for each strength and each container/closure system will continue according to the approved stability protocols through the expiration dating period.

The Office of Compliance has found all manufacturing, testing, and packaging sites acceptable.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-726 for [redacted] (alprazolam) is recommended to be granted **Approvable** status from CMC standpoint based on the following:

- CMC concerns related to the drug substance and drug product sections as outlined in the review.
- The deficiencies are detailed at the end of this review to be forwarded to Schwarz Pharma.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name: Chhagan G. Tele, Ph.D.
Chemistry Team Leader Name: Thomas F. Oliver, Ph.D.
Project Manager Name: Richardae Taylor, Pharm.D.

C. CC Block

See DFS.

84 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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/s/

Chhagan Tele
10/15/04 02:52:33 PM
CHEMIST

Thomas Oliver
10/15/04 04:03:55 PM
CHEMIST