CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-412

CHEMISTRY REVIEW(S)

NDA 21-412

TRADENAME (zolpidem tartrate) Orally Disintegrating Tablets

Biovail Laboratories International SRL

Martha R. Heimann, Ph.D.
Office of New Drug Quality Assessment, DPA-1

For:

Division of Neurology Products

Table of Contents

Chemistry Review Data Sheet

1. **NDA 21-412**

2. **REVIEW #:** 6

3. **REVIEW DATE:** 06-SEP-2006

4. **REVIEWER:** Martha R. Heimann, Ph.D.

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
Original NDA	31-Dec-2001
D. Klein Review #1	29-Oct-2004
Approvable (AE) letter #1	31-Oct-2002
Resubmission, response to AE letter #1	20-Dec-2002
D. Klein Review #2	14-Feb-2003
AE letter #2	21-Feb-2003
Resubmission, response to AE letter #2	24-Nov-2004
D. Klein Review #3	18-May-2003
Tentative approval (TA) letter	26-May-2005
D. Klein Review #4 (2 Phase 4 Commitments)	31-Oct-2005
D. Klein Review #5 (Methods Validation)	10-May-2006
Resubmission, response to TA letter	20-Jul-2006

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Amendment (BL)	25-Mar-2006
Response to TA letter (AZ)	21-Jul-2006

7. **NAME AND ADDRESS OF APPLICANT:**

Name:	Biovail Laboratories Incorporated
Address:	Chelston Park, Building 2 Collymore Rock St. Micheal, BHI Barbados, West Indies
Representative:	Mr. John B. Dubeck (U.S. Agent) Keller and Heckman 1001 G Street, N.W. Suite 500 West Washington D.C. 20001
Telephone:	202-434-4100, Fax: 202-434-4646

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name (USAN): zolpidem tartrate
c) Code Name/#:
d) Chem. Type/Submission Priority:

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) submission.

10. PHARMACOLOGICAL CATEGORY: Insomnia

11. DOSAGE FORM: Orally Disintegrating Tablets

12. STRENGTH/POTENCY: 5 mg, 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ **Rx** ___ **OTC**

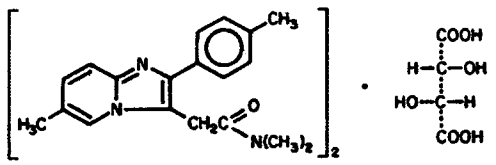
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ **SPOTS product – Form Completed**

__X__ Not a SPOTS product

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

N,*N*,6-Trimethyl-2-(4-methylphenyl)-imidazo[1,2-*a*]pyridine-3-acetamide, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (2:1); *N*,*N*,6-Trimethyl-2-*p*-tolylimidazo[1,2-*a*]pyridine-3-acetamide L-(+)-tartrate (2:1)



Molecular formula: $[C_{19}H_{21}N_3O]_2 \cdot C_4H_6O_6$

Molecular weight: 764.87

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Reviewed By/ Comments
				1	Adequate	25-Feb-2005	D. Klein
				1	Inadequate	13-May-2005	D. Klein DMF withdrawn 12-May-2005
				3	Adequate	20-Jun-2002	D. Klein
				3	Adequate	25-Aug-2004	A. Schroeder
				3, 4	Adequate	01-Apr-2003	S. Pagay
				4	N/A	N/A	N/A
				4	N/A	N/A	N/A
				4	N/A	N/A	N/A
				3, 4	Adequate	03-Apr-2001	J. Salemme
				4	N/A	N/A	N/A
				3, 4	Adequate	21-Apr-1998	M. Heimann
				3,4	Adequate	10-Oct-2002	D. Klein

b(4)

[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: None

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

18. STATUS:

Consults/CMC Related Reviews	Recommendation	Date	Reviewer
Biometrics	N/A	--	--
EES	Acceptable	31-Aug-2006	S. Ferguson
Pharmacology/Toxicology	N/A	--	--
Clinical Pharmacology	Phase 4 commitment for dissolution test requested.	--	T.-C. Wu
LNC	N/A	--	--
Methods Validation	Methods found suitable for control and regulatory purposes.	23-Mar-2006	T. Moore/D. Toler (DPA Laboratory)
DMETS	Tradename [redacted] unacceptable.	11-Jul-2006	K. Culley-Pedersen
Environmental Assessment	Categorical exclusion under 21 CFR 25.31(a) acceptable	18-May-2005	D. Klein
Microbiology	Approval	10-May-2005	J. McVey

b(4)

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-412

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls (CMC) perspective, approval of the application is recommended.

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

The following Phase 4 commitments were acknowledged in the Agency's May 26, 2005 tentative approval (TA) letter:

Commitment #1 (Requested by Clinical Pharmacology Reviewer)

Description:	Optimize the dissolution method and specifications using 50 rpm paddle speed and a different dissolution medium (e.g., pH 5.8 buffer).
Final Study Report:	The final study report should be submitted to the Agency within one year from the date of approval for the final selection of the dissolution specification.

Commitment #2

Description:	Generate data on biobatches and next 3 production batches for both 5 and 10 mg strengths using the selected more optimized dissolution method.
Final Study Report:	The final study report should be submitted to the Agency within one year from the date of approval for the final selection of the dissolution specification.

Commitment #3

Description:	Using the retained photostability testing samples (non-debossed 5 mg (2 Lots) and 10 mg (2 Lots) tablets), the dissolution and disintegration will be reported.
Final Study Report:	The final study report should be submitted to the Agency within three months of approval.

Commitment #4

Description:	Prior to commercial drug product manufacturing the applicant will provide a copy of the commercial Batch Record.
Final Study Report:	The final study report should be submitted to the Agency within two years of approval.

Commitment #5

Description:	Using the retained drug product release samples (Dublin (3 Lots of 5 mg and 3 Lots of 10 mg); and Chantilly (3 Lots of 5 mg), the Identification (UV) results will be reported.
Final Study Report:	The final study report should be submitted to the Agency within three months of approval.

The applicant subsequently addressed Commitment #3 and Commitment #5. [Refer to D. Klein Review # 4, dated October 31, 2005. The remaining commitments should be restated in the Agency action letter.

II. Summary of Chemistry Assessments

A. Description of the Drug Products and Drug Substances

Zolpidem tartrate was originally approved in 1992, under NDA 19-908, as conventional immediate-release oral tablets (Ambien® Tablets, 5 mg and 10 mg) for treatment of insomnia. Currently, the holder of NDA 19-908, Sanofi-Aventis, markets zolpidem tartrate as Ambien Tablets (immediate release) and as Ambien® CR (zolpidem tartrate extended release tablets).

NDA 21-412 provides for a new oral dosage form, which will be manufactured and marketed by Biovail Laboratories. The proposed products contain 5 mg or 10 mg zolpidem tartrate in a peppermint flavored, orally disintegrating tablet (ODT) formulation.

The active ingredient, zolpidem tartrate, will be obtained from ——— ——— All CMC information regarding the drug substance is incorporated by **cross-reference to — Drug Master File (DMF) No. —** b(4)

The zolpidem tartrate ODT formulation is manufactured by the sponsor using the firm's CEFORM® (Centrifugally Extruded & Formed Microspheres) technology. In this process, ⌜

b(4)

In addition to the ingredients listed previously, the zolpidem tartrate ODT formulations contain mannitol, sodium stearyl fumarate, silicon dioxide, acesulfame potassium, monoammonium glycyrrhizinate (———), FD&C Blue #2 (10 mg only) and natural peppermint flavor. All tablet excipients ——— b(4)

Zolpidem tartrate is relatively stable as the bulk drug substance under normal storage conditions. For the ODT tablet formulations, no degradation products were observed during stability studies performed under long-term (25°C/60% R.H.) or accelerated (40°C/75% R.H.) storage conditions. The physical integrity and physical properties of the ODT formulations are, however, susceptible to moisture. The tablets are, therefore, packaged in protective packaging, i.e., ——— blisters. b(4)

The proposed commercial products are identical to the formulations used in bioequivalence studies presented in the application. No efficacy studies were performed with this product.

Zolpidem Tartrate ODTs will be marketed in 28-count cartons containing four 7-count blister cards per carton.

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

The Zolpidem Tartrate Orally Disintegrating Tablets (5 mg and 10 mg) are intended for once-daily administration at bedtime. Once the tablet is placed in the mouth, exposure to saliva causes the tablets to disintegrate and release the TTMS. The microspheres can then be swallowed with or without water.

Based on stability data provided in the application, a tentative expiration dating period of 24 months, when stored at controlled room temperature (20 - 25°C), is established.

C. Basis for Approvability or Non-Approval Recommendation

Approval of NDA 21-412 was previously recommended by Donald Klein, Ph.D. after a series of CMC reviews. The current resubmission provides for some changes to controls for the drug substance and some tablet excipients. These changes, however, are relatively minor and do not impact on the approvability of the application from a CMC perspective. Finally, all facilities involved in the manufacture and control of the bulk drug substance and Zolpidem Tartrate Orally Disintegrating Tablets currently have acceptable compliance profiles based on the overall recommendation dated August 31, 2006. [Refer to Attachment 1 for detailed EER.] Minor corrections to the package insert are recommended. [Refer to Comments to Sponsor on pp. 18-19.] The requested corrections do not, however, affect approvability of the application from a CMC perspective.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

See electronic signatures in DFS.

C. CC Block

See DFS.

Chemistry Assessment

I. DRUG SUBSTANCE

1. Description and Characterization

No new information is provided in the 21-Jul-2006 resubmission.

2. Manufacturer

No new information is provided in the 21-Jul-2006 resubmission.

3. Synthesis/Method of Manufacture

No new information is provided in the 21-Jul-2006 resubmission.

4. Process Controls

No new information is provided in the 21-Jul-2006 resubmission.

5. Reference Standard

No new information is provided in the 21-Jul-2006 resubmission.

18 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Martha Heimann
9/6/2006 10:37:26 AM
CHEMIST

Ramesh Sood
9/6/2006 10:53:46 AM
CHEMIST

CHEMISTRY REVIEW

NDA 21-412

Zolpidem Tartrate Orally Disintegrating Tablets

Biovail Laboratories Incorporated

Chemistry Review

Donald N. Klein, Ph.D.
HFD-120

Table of Contents

CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 21-412 Zolpidem Tartrate Orally Disintegrating Tablets**

2. **CHEM. REVIEW: # 4**

3. **REVIEW DATE:** October 31, 2005.

4. **REVIEWER:** Donald N. Klein, Ph.D.

5. **PREVIOUS DOCUMENTS:**
N19-908 (Approved 12/16/92).
N21-412 Review # 1 (CMC Approvable, 10/31/02).
N21-412 Review # 2 (CMC Approved, 2/21/03).
N21-412 Review # 3 (CMC Approved, 5/19/05).
N21-412 Tentative Approval: 5/26/05.
N21-421 Review # 2 (CMC Approvable, 6/21/04).
N21-763 Review # 1 (CMC Approvable, 2/7/05).

6. **SUBMISSION BEING REVIEWED:**

Submissions Reviewed	Document Date
TA Letter	5/26/05
Amendment (BC)	5/26/05
Amendment (4M)	7/27/05

7. **NAME AND ADDRESS OF APPLICANT:**

Biovail Laboratories Incorporated
Chelston Park, Building 2
Collymore Rock
St. Micheal, BHI
Barbados, WI

APPEARS THIS WAY
ON ORIGINAL

U.S. Agent:
Mr. John Dubeck, Esq.
Agent for Biovail Laboratories Incorporated
Keller and Heckman
1001 G Street, N.W.
Suite 500 West Washington
D.C. 20001

8. **DRUG PRODUCT NAME:**
Proprietary: TRADENAME
Nonproprietary/USAN: zolpidem tartrate
Code Name/Number: N04F1
Chem. Type/Ther. Class: 3S

9. **LEGAL BASIS FOR SUBMISSION:** Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50.

10. **PHARMACOLOGICAL CATEGORY/INDICATION:** Insomnia

11. **DOSAGE FORM:** Orally Disintegrating Tablet.

12 **STRENGTHS:** 5.0 mg (white with off-white speckles) and 10.0 mg (blue with white speckles)

13. **ROUTE OF ADMINISTRATION:** Oral.

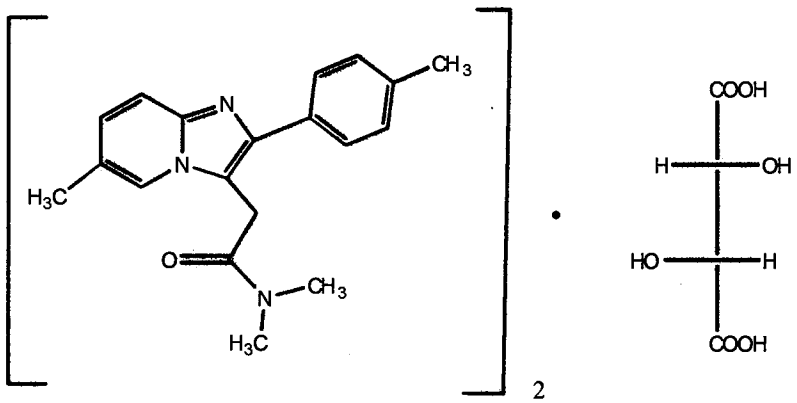
14. **DISPENSED:** XX RX ___OTC.

15. **SPOTS** (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): ___Yes XX NO.

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:**
N,N,6-trimethyl-2-*p*-toyl-imidazo[1,2-a]pyridine-3-acetamide L-(+)-tartrate (2:1).

Molecular formula: $C_{42}H_{48}N_6O_8$
Mol. Wt.: 764.87
CAS Registry: 99294-93-6

APPEARS THIS WAY
ON ORIGINAL



APPEARS THIS WAY
ON ORIGINAL

17. RELATED/ SUPPORTING DOCUMENTS:

A. DMF's:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
				1	Inadequate DEF Letter Adequate	02-FEB-2005 28-JAN-2005 01-MAR-2005	
				1	Inadequate DEF Letter IR Letter Inadequate DEF Letter Withdrawn	14-FEB-2005 09-FEB-2005 21-MAR-2005 13-MAY-2005 13-MAY-2005 12-MAY-2005	
				3	Adequate	03-NOV-2004	
				3	Adequate	25-AUG-2004	
				4, 7	Adequate	18-APR-2005	b(4)
				4, 7	Adequate	18-APR-2005	
				4, 7	Adequate	18-APR-2005	
				4, 7	Adequate	18-APR-2005	
				1, 4, 7	Adequate	06-APR-2001 18-APR-2005	
				4	Adequate	18-APR-2005	
				1, 4, 7	Adequate	21-APR-1998 18-APR-2005	
				3, 4	Adequate	09-OCT-2002 18-APR-2005	

[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:

b(4)

[2]Adequate, Inadequate

B. Other Documents: None

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
EES	Acceptable Acceptable	07-APR-2005 16-MAY-2005	Office of Compliance
Method Validation Updated method validation package received *Method Validation Package*	Acceptable *N/A* *To be submitted*	18-MAY-2005 26-AUG-2005 *N/A*	Donald Klein, Ph.D.
Medical	Approval	20-MAY-2005	Paul Andreason, M.D.
Microbiology	Approval	10-MAY-2005	Jim McVey, B.S.
OCPB	Approval	19-MAY-2005	Ta-Chen Wu, Ph.D.
Environmental Assessment	Acceptable	18-MAY-2005	Donald Klein, Ph.D.
Pharm/Tox	*Not applicable*	*N/A*	*Not applicable*

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Executive Summary

I. Recommendations:

A. Recommendations and Conclusions on Approvability.

Refer to CMC Review # 3 (5/18/05).

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

As stated in the May 26, 2005 TA Letter, the applicant should reply to these two Phase 4 CMC commitments within three months of approval. In the July 27, 2005 amendment, the applicant has adequately responded to the two CMC Commitments:

1. Using the retained [redacted] samples (non-debossed 5 mg [redacted] and 10 mg [redacted] tablets), the dissolution and distinegration results will be reported. b(4)

2. Using the retained drug product release samples (Dublin [redacted] of 50 mg and [redacted] of 10 mg); and Chantilly [redacted] of 5 mg), the Identification (UV) results will be reported.

II. Summary of Chemistry Assessments:

A. Description of Drug Product and Drug Substance

Refer to CMC Review # 3 (5/18/05).

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

Refer to CMC Review # 3 (5/18/05).

C. Basis for Approvable or Not-Approval Recommendation

N/A

D. Administrative:
Reviewer, HFD-130: Donald N. Klein, Ph.D.
Team Leader, HFD-130: Thomas F. Oliver, Ph.D.
Project Manager: Renmeet Gujral, Pharm. D.

8 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Donald Klein
10/31/2005 11:50:42 AM
CHEMIST
Copy of review along with the TA Letter and
the two amendments are in your mailbox.

Thomas Oliver
11/1/2005 03:32:59 PM
CHEMIST

CHEMISTRY REVIEW

NDA 21-412

Zolpidem Tartrate Orally Disintegrating Tablets

Biovail Laboratories Incorporated

Chemistry Review

Donald N. Klein, Ph.D.
HFD-120

Table of Contents

CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 21-412 Zolpidem Tartrate Orally Disintegrating Tablets**

2. **CHEM. REVIEW: # 3**

3. **REVIEW DATE:** May 18, 2005.

4. **REVIEWER:** Donald N. Klein, Ph.D.

5. **PREVIOUS DOCUMENTS:**
N19-908 (Approved 12/16/92);
N21-412 Review # 1 (CMC Approvable, 10/31/02);
N21-412 Review # 2 (CMC Approved, 2/21/03);
N21-763 Review # 1 (CMC Approvable, 2/7/05). b(4)

6. **SUBMISSION BEING REVIEWED:**

Submissions Reviewed	Document Date
Telecon	30-JUN-2003
Response (E-mail) for CMC guidance	02-NOV-2004
Complete Response (AZ)	24-NOV-2004
NDA Transfer Memo	01-DEC-2004
Request for Samples (E-mail)	09-DEC-2004
Information Request (E-mail)	20-DEC-2004
Response (E-mail)	20-DEC-2004
Information Request (E-mail)	21-DEC-2004
Response (E-mail)	21-DEC-2004
Amendment (BC)	22-DEC-2004
Information Request (E-mail)	29-DEC-2004
Information Request (E-mail)	30-DEC-2004
Microbiology Consult	04-JAN-2005
Information Request (E-mail)	10-JAN-2005
Information Request (E-mail)	12-JAN-2005
Desk Copies received	12-JAN-2005

SUBMISSION BEING REVIEWED (con't):

Submissions Reviewed

Response (E-mail)	14-JAN-2005
Amendment (BC)	17-JAN-2005
Amendment (BL)	17-JAN-2005
Information Request (E-mail)	18-JAN-2005
Response (E-mail)	25-JAN-2005
Memo to File	25-JAN-2005
Amendment (BC)	26-JAN-2005
Information Request (2 E-mails)	27-JAN-2005
Information Request (E-mail)	28-JAN-2005
Information Request (E-mail)	31-JAN-2005
Information Request Letter	02-FEB-2005
Information Request (2 E-mails)	03-FEB-2005
Information Request (E-mail)	09-FEB-2005
Information Request Letter	14-FEB-2005
Response (E-mail)	14-FEB-2005
Amendment (BC)	15-FEB-2005
Information Request (E-mail)	16-FEB-2005
Information Request (3 E-mails)	17-FEB-2005
Response (2 E-mails)	17-FEB-2005
Response (E-mail)	07-MAR-2005
Amendment (BC) (EDR and paper)	07-MAR-2005
Amendment (BC)	11-MAR-2005
Information Request (E-mail)	21-MAR-2005
Response (E-mail)	05-APR-2005
Amendment (BC)	05-APR-2005
Amendment (BC)	04-MAY-2005
Information Request (2 E-mails)	06-MAY-2005
Amendment (BC)	09-MAY-2005
Response (E-mail)	10-MAY-2005
Information Request (E-mail)	11-MAY-2005
Telecon (2x)	12-MAY-2005
Response (4 E-mails)	12-MAY-2005
Clarification from FDA (2 E-mails)	12-MAY-2005

SUBMISSION BEING REVIEWED (con't):

Submissions Reviewed	
Information Request (E-mail)	12-MAY-2005
Information Request (3 E-mails)	13-MAY-2005
Response (2 E-mails)	13-MAY-2005
Clarification from FDA (E-mail)	14-MAY-2005
Response (E-mail)	15-MAY-2005
Response (2 E-mails)	16-MAY-2005
Information Request (E-mail)	18-MAY-2005
Response (E-mail)	18-MAY-2005

7. NAME AND ADDRESS OF APPLICANT:

Biovail Laboratories Incorporated
Chelston Park, Building 2
Collymore Rock
St. Micheal, BHI
Barbados, WI

U.S. Agent:
Mr. John Dubeck, Esq.
Agent for Biovail Laboratories Incorporated
Keller and Heckman
1001 G Street, N.W.
Suite 500 West Washington
D.C. 20001

8. DRUG PRODUCT NAME:
Proprietary: TRADENAME
Nonproprietary/USAN: zolpidem tartrate
Code Name/Number: N04F1
Chem. Type/Ther. Class: 3S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50.

10. **PHARMACOLOGICAL CATEGORY/INDICATION:** Insomnia

11. **DOSAGE FORM:** Orally Disintegrating Tablet.

12 **STRENGTHS:** 5.0 mg (white with off-white speckles) and 10.0 mg (blue with white speckles)

13. **ROUTE OF ADMINISTRATION:** Oral.

14. **DISPENSED:** XX RX ___OTC.

15. **SPOTS** (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): ___Yes XX NO.

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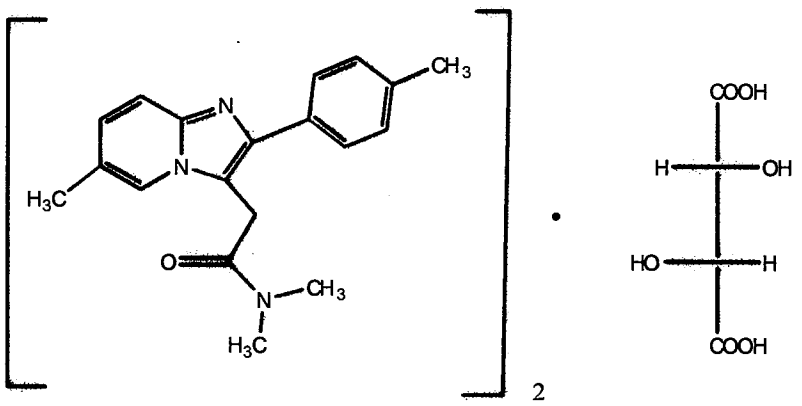
N,N,6-trimethyl-2-*p*-toyl-imidazo[1,2-a]pyridine-3-acetamide L-(+)-tartrate (2:1).

Molecular formula: $C_{42}H_{48}N_6O_8$
Mol. Wt.: 764.87
CAS Registry: 99294-93-6



17. RELATED/ SUPPORTING DOCUMENTS:

A. DMF's:

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				1	Inadequate DEF Letter IR Letter Inadequate DEF Letter Withdrawn	14-FEB-2005 09-FEB-2005 21-MAR-2005 13-MAY-2005 13-MAY-2005 12-MAY-2005	
				3	Adequate	03-NOV-2004	
				3	Adequate	25-AUG-2004	
				4, 7	Adequate	18-APR-2005	
				4, 7	Adequate	18-APR-2005	
				4, 7	Adequate	18-APR-2005	
				4, 7	Adequate	18-APR-2005	
				1, 4, 7	Adequate	06-APR-2001 18-APR-2005	
				4	Adequate	18-APR-2005	
				1, 4, 7	Adequate	21-APR-1998 18-APR-2005	
				3,4	Adequate	09-OCT-2002 18-APR-2005	

b(4)

[1]Action codes for DMF Table:
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4--Sufficient information in application
5--Authority to reference not granted
6--DMF not available
7--Other:

b(4)

[2]Adequate, Inadequate

B. Other Documents: None

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
EES	Acceptable Acceptable	07-APR-2005 16-MAY-2005	Office of Compliance
Methods Validation	Acceptable *To be validated*	18-MAY-2005	Donald Klein, Ph.D.
Medical	pending	pending	Paul Andreason, M.D.
Microbiology	Approval	10-MAY-2005	Jim McVey, B.S.
OCPB	pending	pending	Ta-Chen Wu, Ph.D.
Environmental Assessment	Acceptable	18-MAY-2005	Donald Klein, Ph.D.
Pharm/Tox	*Not applicable*	*N/A*	*Not applicable*

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Executive Summary

I. Recommendations:

A. Recommendations and Conclusions on Approvability.

NDA 21-412 (Zolpidem Tartrate Orally Disintegrating Tablets, Biovail Technologies, Ltd) is recommended approval from the CMC standpoint. During this 6 month review cycle the applicant has adequately addressed all the CMC deficiencies.

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

1. Using the retained ——— samples (non-debossed 5 mg ——— and 10 mg ———) tablets), the dissolution and disintegration results will be reported. b(4)
2. Prior to commercial drug product manufacturing the applicant will provide a copy of the commercial Batch Record.
3. Using the retained drug product release samples (Dublin ——— of 5 mg and ——— of 10 mg); and Chantilly ——— of 5 mg), the Identification (UV) results will be reported.
4. On May 12, 2005 the applicant withdrew DMF ——— zolpidem tartrate). b(4)

II. Summary of Chemistry Assessments:

A. Description of Drug Product and Drug Substance

Drug Product

The N21-412 (AZ) Review # 2 found the CMC of the 10 mg ——— orally disintegrating tablet acceptable. However, the N21-412 (AZ) Approvable Letter (2/21/03) proposed that Biovail manufacture a 5 mg strength tablet in addition to the 10 mg tablet. With this Resubmission (11/24/04) the applicant has reformulated the orally disintegrating tablet to be a ——— 5 mg and 10 mg. Prior to this submission the agency provided guidance (6/30/03 Telecon and 11/2/04 E-mail Response) to Biovail regarding their intent to reformulate in order to manufacture both the 5 mg and 10 mg tablets. The change in ——— .The following table delineates the components that have been either removed or added for this reformulation. b(4)

Reformulation to the Tablets (5 mg and 10 mg)

Component	Removed or Added
	Removed
	Added

b(4)

The primary delivery vehicle for the active component, the taste-masked microspheres (TMMS) remains consistent with both the original ((12/29/01)) and this Resubmission (11/24/04). The TMMS are packaged in bulk and are used within — days of manufacture. The applicant has generated 6 months of stability data for the TMMS. Prior to the incorporation of the TMMS in the drug product, the TMMS must meet the following specifications: Appearance; Identification; Assay; and Dissolution. b(4)

As in the ; the reformulated drug product

b(4)

The Zolpidem Tartrate Orally Disintegrating Tablets (5 mg and 10 mg) are intended for once-daily administration. For customer taste satisfaction both the 5 mg and 10 mg tablet are peppermint flavored. The tablets are dimpled on both sides and the tablets are differentiated by size (5 mg is smaller), color, and debossing:

> The 5 mg tablet is round, white with off-white speckles, and is dimpled on both sides. One side is debossed with "5" and the other side is debossed with a "ZT."

The 10 mg tablet is round, blue with white speckles, and is dimpled on both sides. One side is debossed with "10" and the other side is debossed with a "ZT."

In the original N21-412, there was only one manufacturing site, Chantilly, VA. However, with this Response, there are three manufacturing sites: Chantilly, VA ([redacted] Dublin, Ireland ([redacted] and Dorado, Puerto Rico ([redacted] b(4)

MANUFACTURING SITES' RESPONSIBILITIES

Processing Step	Chantilly,VA CFN 1125566	Dublin, Ireland FEI 3004159141	Dorado, Puerto Rico CFN 2650285
[redacted]	X	N/A	N/A
[redacted]	X	X	N/A
[redacted]	X	X	N/A
[redacted]	X	X	X
[redacted]	X	X	X
[redacted]	X	N/A	X

b(4)

Because there are different manufacturing sites, each of the test methods (drug product and drug substance) have corresponding ID codes. Thus the same test methods, Assay for example, have different ID codes, but the test methods are identical.

The 5 mg and 10 mg tablet manufacturing processes and batch formula (for each proposed Biovail manufacturing facility) reported in this submission are the same as each site's proposed commercial production process and batch size. The applicant provided a harmonized batch formula for both dosage strengths during the review cycle.

The drug product is proposed to be marketed in child resistant blisters.

With this Complete Response, the applicant submitted 6 months of stability data from the Dublin, Ireland site with the intent of submitting stability updates during the review cycle. In the March, 2005 and May, 2005 (2x) Biovail submitted the following stability data updates: Dublin (6 months); Chantilly (6 months); and Dorado (6 months).

Even though the DMF [redacted] was withdrawn on 5/12/05 (refer to drug substance section), the two Dublin drug product lots (5 mg and 10 mg) that contain [redacted] drug b(4)

substance, are viewed as supportive stability data. Also, the ——— stability data is considered supportive stability as the agency had discussed with Biovail prior to the 11/2004 Resubmission. It should be noted the ——— 10 mg tablet was granted an 18 month expiration date (N21-412 Review # 2 (2/19/03)). b(4)

Regarding the TMMS Dissolution test method chromatographic conditions (BD-SAM-003 (Dublin) and STM-125 (Chantilly)), the applicant has modified the method in order to improve the efficiency. Specifically, a ——— The improved method's validation data was submitted in this Resubmission. b(4)

The drug product test method used for Identification, Content Uniformity, Assay, and Degradants (BD-SAM-003 (Dublin), 06-155 (Dorado), and STM-124 (Chantilly)) has been revised from the original NDA 21-412 (——— . Specifically, the sample concentration ——— b(4)

The TMMS and drug product test methods have been adequately validated. Because this is a unique dosage form utilizing the TMMS, Dr. Klein recommends that the following TMMS and drug product test methods be validated: (1) TMMS: Dissolution; (2) Drug Product: (a) Assay and Degradant; and (b) Dissolution.

The drug product was subjected to forced degradation conditions per the Stability guidance (1998 *draft*) and the Analytical Procedures and Methods Validation guidance (2000 *draft*). The applicant had used the same drug substance lot in both the drug product and drug substance degradation study. However, for the drug product study a "worse case scenario" composition was subjected to the conditions instead of the 5 mg and 10 mg tablet. This study was conducted during the development stage of the ——— NDA. The "worse case scenario" composition utilizes the maximum drug substance along with the maximum amount of excipients. Refer to Table 63 in the Method Validation section. b(4)

The Microbiology review (5/10/05) recommended approval from a product quality Microbiology perspective.

The nine drug product manufacturing sites were submitted for inspection and all nine sites were found Acceptable (4/7/05) by the Office of Compliance.

Drug Substance

For the ——— tablet (original NDA 21-412) the applicant had referenced DMF———, zolpidem tartrate, Type II, which had been found adequate on 2/5/03 (N21-412 Review # 2). However, with this submission the applicant referenced two Type II drug substance DMFs, ——— and ——— During this review cycle DMF ——— was reviewed twice and the 2nd review (3/1/05) found the DMF ——adequate in support b(4)

of this NDA. However, DMF —— has been reviewed twice and is inadequate as of 5/13/05. On 5/12/05 Drs. Oliver and Klein discussed the status of DMF —— with Biovail and as a result, Biovail withdrew DMF ——from this application on 5/12/05. The DMF —— holder was sent a Deficiency Letter dated May 13, 2005.

b(4)

The majority of the primary stability batches were manufactured using —— (DMF —— drug substance: (1) 3 lots of 5 mg and 3 lots of 10 mg tablets manufactured at both the Dorado and Chantilly sites; (2) 2 lots of 5 mg and 2 lots of 10 mg tablets manufactured at the Dublin site; (3) the 2 biobatches (5 mg and 10 mg) manufactured at the Dublin site both contain the —— drug substance. With respect to the —— drug substance, the Dublin site manufactured one 5 mg lot and one 10 mg lot. For this reason it was recommended to Biovail that DMF —— be withdrawn in order to approve the CMC section.

Biovail has established a —— retest date for the reference standard.

For the drug substance the applicant validated the following two non-compendial test methods: (1) Related Substances (BD-SAM-026 (Dublin) and STM-074 (Chantilly); and (2) Residual Solvents (STM-129). The Related Substance HPLC method has been developed for the determination of related substances that may be found in the drug substance manufactured by either ——. Similarly, the Residual Solvent GC method has been developed for the determination of residual solvents present in the drug substance (———).

b(4)

The drug substance was subjected to forced degradation conditions per the Stability guidance (1998 *draft*) and the Analytical Procedures and Methods Validation guidance (2000 *draft*).

The two drug substance manufacturing sites were submitted for inspection and both sites were found Acceptable (4/7/05) by the Office of Compliance. However, the CFN —— site was withdrawn from the NDA on 5/16/05 because DMF —— was withdrawn by the applicant on 5/12/05. Subsequently, the Office of Compliance overall recommendation was acceptable on 5/16/05.

b(4)

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

The Zolpidem Tartrate Orally Disintegrating Tables (5 mg and 10 mg) are intended for once-daily administration. Biovail proposes to package the drug product in child-resistant blisters. Once the drug product is exposed to the oral cavity fluids, the tablet disintegrates. For customer taste satisfaction both the 5 mg and 10 mg tablet are peppermint flavored. The tablets are dimpled on both sides and the tablets are differentiated by size (5 mg is smaller), color, and debossing:

> The 5 mg tablet is round, white with off-white speckles, and is dimpled on both sides. One side is debossed with "5" and the other side is debossed with a "ZT."

The 10 mg tablet is round, blue with white speckles, and is dimpled on both sides. One side is debossed with "10" and the other side is debossed with a "ZT."

The blisters are to be marketed in a secondary package carton.

An 18 month expiration date is granted.

C. Basis for Approvable or Not-Approval Recommendation

NDA 21-412 (Zolpidem Tartrate Orally Disintegrating Tablets, Biovail Technologies, Ltd) is recommended approval. During this 6 month review cycle the applicant has adequately addressed the CMC deficiencies.

D. Administrative:
Reviewer, Neuropharm Team 2: Donald N. Klein, Ph.D.
Team Leader, Neuropharm Team 2: Thomas F. Oliver, Ph.D.
Project Manager: Renmeet Gujral, Pharm. D.

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_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Donald Klein
5/18/05 03:36:26 PM
CHEMIST
Converted WORD document to pdf on D.Klein's computer

Thomas Oliver
5/19/05 07:18:53 AM
CHEMIST

NDA 21-412

Zolpidem Tartrate Orally Disintegrating Tablets

Biovail Laboratories Incorporated

Chemistry Review

Donald N. Klein, Ph.D.
HFD-120

Table of Contents

CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 21-412 Zolpidem Tartrate Orally Disintegrating Tablets**

2. **CHEM. REVIEW #2**

3. **REVIEW DATE:** February 14, 2003

4. **REVIEWER:** Donald N. Klein, Ph.D.

5. **PREVIOUS DOCUMENTS:** CMC Review # 1 dated 29-OCT-02

6. **SUBMISSION BEING REVIEWED:**

Submission Reviewed	Document Date
Amendment (AZ)	20-DEC-02
Fax	04-FEB-03
Amendment (C)	06-FEB-03
Fax	10-FEB-03
EDR Amendment	10-FEB-03
BB Amendment	03-FEB-03

7. **NAME AND ADDRESS OF APPLICANT:**

Biovail Laboratories Incorporated
Chelston Park, Building 2
Collymore Rock
St. Micheal, BHI
Barbados, WI

Mr. John Dubeck, esq.
Agent for Biovail Laboratories
Keller and Heckman
1001 G Street, N.W.
Suite 500 West Washington D.C., 20001

8. **DRUG PRODUCT NAME:**

Proprietary:	Zolpidem Tartrate Orally Disintegrating Tablets
Nonproprietary/USAN:	zolpidem tartrate
Code Name/Number:	ZOL N05
Chem. Type/Ther. Class:	3S

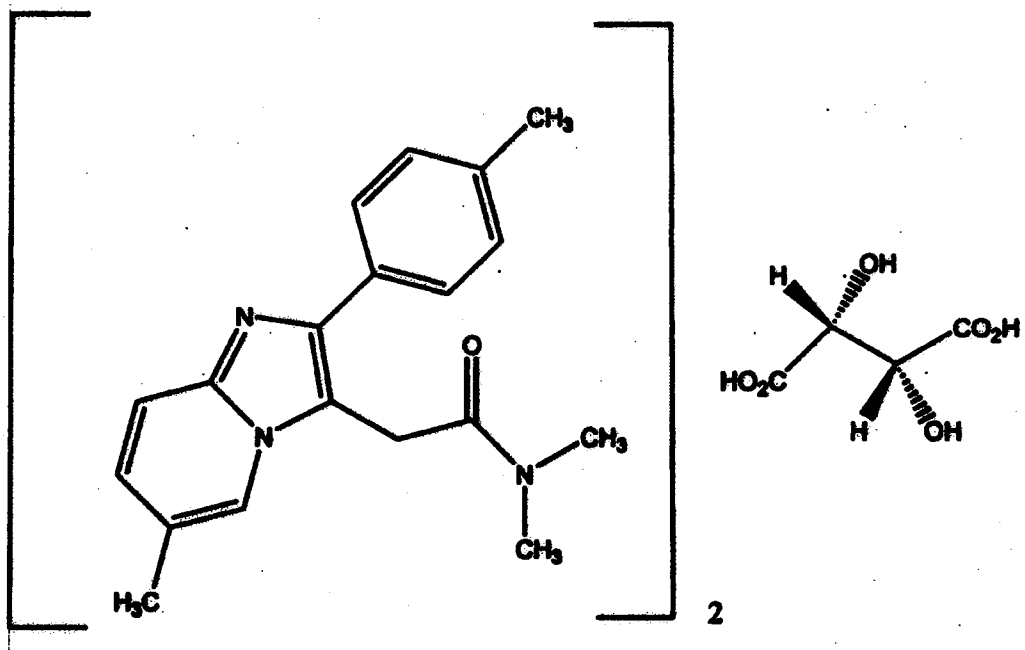
9. **LEGAL BASIS FOR SUBMISSION:** Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50

10. **PHARMACOLOGICAL CATEGORY/INDICATION:** Insomnia

11.	**DOSAGE FORM:**	**Disintegrating Tablet**
12	**STRENGTHS:**	**10mg (blue)**
13.	**ROUTE OF ADMINISTRATION:**	**Oral**
14.	**DISPENSED:**	**XX RX ___OTC**
15.	**SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**	**___ Yes XX NO**

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:**
N,N,6-trimethyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridine-3-acetamide L-(+)-tartrate (2:1)

Molecular formula: $C_{42}H_{48}N_6O_8$
Mol. Wt.: 764.87
CAS Registry #: 99294-93-6



[redacted]

17. **RELATED/ SUPPORTING DOCUMENTS:**

A. **DMF's:**

[redacted]	1	Adequate	05-FEB-2003
	1	Adequate	02-FEB-2002
	1	Adequate	20-JUNE-2002
	4	Adequate	18-OCT-2002
	4	Adequate	18-OCT-2002
	1,4	Adequate	06-APR-2002 18-OCT-2002
	1,4	Adequate	21-APR-1998 18-OCT-2002
	4	Adequate	18-OCT-2002
	4	Adequate	18-OCT-2002
	1	Inadequate Inadequate Inadequate Adequate	20-MAR-2002 14-MAY-2002 04-SEPT-2002 09-OCT-2002
	4	Adequate	18-OCT-2002
	1	Inadequate Adequate	21-MAR-2002 14-MAY-2002

b(4)

[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

B. OTHER DOCUMENTS:

[redacted]

b(4)

19-908, Ambien (zolpidem tartrate) Tablets	Lorex Pharmaceuticals	16-DEC-92 (Approval)

18. STATUS:

[redacted]

Medical	Approval	25-OCT-2002	Paul Andreason, M.D.
EES	Acceptable	04-OCT-2002	Office of Compliance
Methods Validation	To be submitted	14-FEB-2003	Donald Klein, Ph.D.
CDER Labeling & Nomenclature	Acceptable	11-FEB-2003	Daniel Boring, Ph.D.
Microbiology	Approval	17-JUNE-2002	James McVey, Ph.D.
OCPB/Bioequivalence	Approval	31-JAN-2003	Veneeta Tandon, Ph.D.
EA	Approval	29-OCT-2002	Donald Klein, Ph.D.
Pharm/Tox	*Not applicable*		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Executive Summary

I. Recommendations:

A. Recommendations and Conclusions on Approvability.

NDA 21-412 for Zolpidem Tartrate Orally Disintegrating Tablets (zolpidem tartrate) is recommended for Approval from the CMC standpoint.

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

II. Summary of Chemistry Assessments:

C. Description of Drug Product and Drug Substance

Drug Product

The applicant revised the specifications (Impurities and Moisture) as the Agency had requested in the October, 31, 2002 Approvable Letter.

The applicant had updated the 3 separate lots of stability data (25°C/60%RH and 30°C/60%RH) through 12 months. The applicant had requested a 24 month expiration but the stability data supports an 18 month expiration date.

The drug product manufacturing and testing sites were found Acceptable by Compliance.

Drug Substance

The applicant references DMF —, Type II, for the drug substance and the DMF Holder is — DMF — was found adequate on February 5, 2003 by D.Klein (HFD-120).

The drug substance manufacturing site was found Acceptable by Compliance.

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

Zolpidem Tartrate Orally Disintegrating Tablets (10mg) are intended for once-daily administration. The rapidly dissolving tablet disintegrates quickly when exposed to fluids, i.e., saliva when placed in the mouth.

The applicant proposes to market the drug product in — child resistant packaging. The labeling states that —. The labeling (carton and package insert) also states the — that is present in each 10mg tablet.

A. Basis for Approvable or Not-Approval Recommendation: N/A

B. Administrative:
Reviewer: Donald N. Klein, Ph.D.
Team Leader: Thomas F. Oliver, Ph.D.
Project Manager: Annie Marie Homonnay-Weikel, R.Ph.

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X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Donald Klein
2/14/03 04:50:25 PM
CHEMIST

revised as discussed on 2/14/03

Thomas Oliver
2/19/03 07:37:21 AM
CHEMIST

NDA 21-412

Zolpidem Tartrate Rapidly Dissolving Tablets

Biovail Laboratories Incorporated

Chemistry Review

Donald N. Klein, Ph.D.
HFD-120

Table of Contents

CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 21-412 Zolpidem Tartrate Rapidly Dissolving Tablets**

2. **CHEM. REVIEW #1**

3. **REVIEW DATE:** October 29, 2002

4. **REVIEWER:** Donald N. Klein, Ph.D.

5. **PREVIOUS DOCUMENTS:** None

6. **SUBMISSION BEING REVIEWED:**

Submission Reviewed	Document Date
ORIGINAL	29-DEC-01
Amendment (BC)	19-FEB-02
Amendment (BC)	27-MAR-02
Amendment (BC)	29-MAR-02
Amendment (BC)	28-JUNE-02
Amendment (BL)	19-JULY-02
Amendment (BC)	28-AUG-02
Amendment (BC)	02-OCT-02

7. **NAME AND ADDRESS OF APPLICANT:**

Biovail Laboratories Incorporated
Chelston Park, Building 2
Collymore Rock
St. Micheal, BHI
Barbados, WI

Mr. John Dubeck, esq.
Agent for Biovail Laboratories
Keller and Heckman
1001 G Street, N.W.
Suite 500 West Washington D.C., 20001

8. **DRUG PRODUCT NAME:**

Proprietary:	Zolpidem Tartrate Rapidly DissolvingTablets
Nonproprietary/USAN:	zolpidem tartrate
Code Name/Number:	ZOL N04
Chem. Type/Ther. Class:	3S

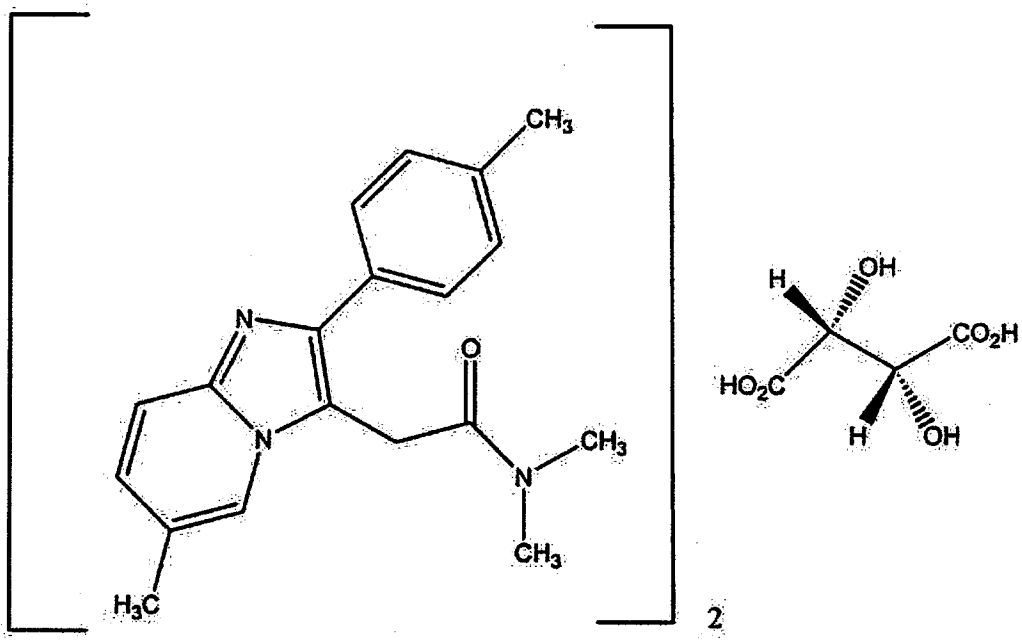
9. **LEGAL BASIS FOR SUBMISSION:** Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50

10. **PHARMACOLOGICAL CATEGORY/INDICATION:** Insomnia

11.	**DOSAGE FORM:**	Disintegrating Tablet
12	**STRENGTHS:**	10mg (blue)
13.	**ROUTE OF ADMINISTRATION:**	Oral
14.	**DISPENSED:**	XX RX ___OTC
15.	**SPOTS** (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):	___ Yes XX NO

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:** N,N,6-trimethyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridine-3-acetamide L-(+)-tartrate (2:1)

Molecular formula: $C_{42}H_{48}N_6O_8$
Mol. Wt.: 764.87
CAS Registry #: 99294-93-6



17. RELATED/ SUPPORTING DOCUMENTS:

A. DMF's:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
				1	Inadequate	04-SEPT-2002	
				1	Adequate	02-FEB-2002	
				1	Adequate	20-JUNE-2002	
				4	Adequate	18-OCT-2002	
				4	Adequate	18-OCT-2002	
				1,4	Adequate	06-APR-2002 18-OCT-2002	
				1,4	Adequate	21-APR-1998 18-OCT-2002	
				4	Adequate	18-OCT-2002	
				4	Adequate	18-OCT-2002	
				1	Inadequate Inadequate Inadequate Adequate	20-MAR-2002 14-MAY-2002 04-SEPT-2002 09-OCT-2002	
				4	Adequate	18-OCT-2002	
				1	Inadequate Adequate	21-MAR-2002 14-MAY-2002	

b(4)

[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

B. OTHER DOCUMENTS:

NDA	Applicant	Date
[redacted]	[redacted]	[redacted]
19-908, Ambien (zolpidem tartrate) Tablets	Lorex Pharmaceuticals	16-DEC-92 (Approval)

b(4)

18. STATUS:

Consults/CMC Related Reviews	Recommendation	Date	Reviewer
Medical	Approval	25-OCT-2002	Paul Andreason, M.D.
EES	Acceptable	04-OCT-2002	Office of Compliance
Methods Validation	In Preparation	29-OCT-2002	Donald Klein, Ph.D.
CDER Labeling & Nomenclature	Not Acceptable	16-OCT-2002	Daniel Boring, Ph.D.
Microbiology	Approval	17-JUNE-2002	James McVey, Ph.D.
OCPB/Bioequivalence	Approvable	25-JULY-2002	Maria Sunzel, Ph.D.
EA	Approval	29-OCT-2002	Donald Klein, Ph.D.
Pharm/Tox	*Not applicable*		

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Executive Summary

I. Recommendations:

A. Recommendations and Conclusions on Approvability.

NDA 21-412 for Zolpidem Tartrate Rapidly Dissolving Tablets is recommended Approvable from the CMC standpoint. The approval from the CMC standpoint is contingent on adequate responses to the CMC deficiencies related to the drug substance and the drug product as outlined in this review.

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

II. Summary of Chemistry Assessments:

A. Description of Drug Product and Drug Substance

Drug Product

The tablets are manufactured using both traditional manufacturing procedures (such as) and Biovail's proprietary drug delivery technologies known as **Ceform® (Centrifugally Extruded & Formed Microspheres)** b(4)

Below is a summary of the function of the components in the drug product.

b(4)

b(4)

4. Tablet Components

a.
b.
c.
d.
e.
f.

b(4)

The applicant has submitted 3 separate lots of stability data (25°C/60%RH, 30°C/60%RH and 40°C/75%RH) through 9 months.

Drug Substance

The applicant references DMF — Type II, for the drug substance and the DMF Holder is — DMF — as found Inadequate on September 4, 2002 by D.Klein (HFD-120).

b(4)

The drug substance manufacturing site was found Acceptable by Compliance.

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

Zolpidem tartrate Rapidly Dissolving Tablets (10mg) are intended for once-daily administration. The rapidly dissolving tablet disintegrates quickly when exposed to fluids, i.e., saliva when placed in the mouth.

The applicant proposes to market the drug product in — child resistant packaging.

b(4)

At this time, an expiration date cannot be determined due to outstanding stability and specification deficiencies.

C. Basis for Approvable or Not-Approval Recommendation

NDA 21-412 (Zolpidem Tartrate Rapidly Dissolving Tablets, Biovail Laboratories, Inc.) is recommended for approvable based on the following:

a. CMC concerns relate to both the drug substance and the drug product. The deficiencies are detailed in the draft deficiency letter at the end of this review.

D. Administrative:
Reviewer: Donald N. Klein, Ph.D.
Team Leader: Thomas F. Oliver, Ph.D.
Project Manager: Annie Marie Homonnay-Weikel, R.Ph.

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_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Donald Klein
10/29/02 11:13:49 AM
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Thomas Oliver
10/29/02 12:52:56 PM
CHEMIST