

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-774

CHEMISTRY REVIEW(S)



NDA 21-774

**AMBIEN CR™
(Zolpidem tartrate extended—release) tablets**

Sanofi-Synthelabo

**Danae D. Christodoulou
Chemistry for NDA 21-774, Division of Anesthetics, Critical
Care and Addiction Drug Products, HFD-170**



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Chemistry Review Data Sheet

1. NDA 21-774
2. REVIEW #: 3
3. REVIEW DATE: 22-AUG-05
4. REVIEWER: Danae D. Christodoulou, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	08-JUN-2004
Amendment (BZ)	27-AUG-2004
Amendment (BC)	05-OCT-2004
Amendment (BC)	22-FEB-2005
Amendment (BL)	18-MAR-2005
Amendment (BC)	01-APR-2005

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (AZ)	06-JUL-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Sanofi-Synthelabo Inc.
Address: 9, Great Valley Parkway, Malvern, PA 19355
Representative: Debra P. Gayda, Ph.D.,
Senior Director, Drug Regulatory Affairs
Telephone: 610-889-8645



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE: zolpidem tartrate / 3S

Proprietary Name: AMBIEN CR™

Non-Proprietary Name (USAN): Zolpidem tartrate extended-release tablets

a) Code Name/# (ONDC only):

b) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505 (b) (1)

10. PHARMACOL. CATEGORY: CNS depressant; treatment of insomnia

11. DOSAGE FORM: Extended-release tablets

12. STRENGTH/POTENCY: 12.5 mg (adults), 6.25 mg (elderly)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

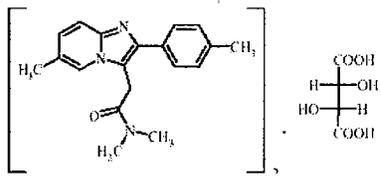
N,N,6-trimethyl-2-p-tolyl-imidazo[1,2- α]-pyridine-3-acetamide L-(+)-tartrate(2:1)

Molecular Formula: (C₁₄H₂₁N₃O)₂ · C₄H₆O₆

MW: 764.88

Structural Formula:

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS: NDA 19-908 (AMBIEN® tablets); IND 25,361

A. DMFs:

DMF #	TY PE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
-	II	-	/	1	Adequate	February 16, 2005	
-	IV	-	/	4	Adequate		
-	III	/	/	4, 3	Adequate		
-	III	/	/	4	Adequate		
-	III	/	/	4	Adequate		
-	III	/	/	4	Adequate		

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

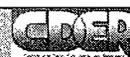
6 – DMF not available

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



The Chemistry Review for NDA 21-774

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is recommended for approval from CMC view point. All outstanding CMC issues have been addressed adequately by the sponsor. An "acceptable" recommendation has been made by the Office of Compliance for cGMP compliance. The firm addressed adequately the CMC comment included in the AE Letter of April 8, 2005, which pertained to the testing criteria for process validation and routine commercial manufacture.

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

None

II. Summary of Chemistry Assessments

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

AMBIEN CR™(zolpidem tartrate extended release)tablets are a new formulation of zolpidem tartrate for the treatment of insomnia. They are coated, round biconvex tablets debossed with A~ on one side. Strengths are 12.5 (blue coated) to be prescribed for the adults and 6.25 mg (pink coated)for the elderly. The drug product is a bi-layer tablet with an immediate release (layer 1) and an extended release (layer 2) component. The tablets are packaged in _____ bottles with CRC closures and in _____ blisters. This extended-release formulation is based on the marketed, immediate-release AMBIEN® 10-mg tablets.

The drug substance zolpidem tartrate is a non-benzodiazepine hypnotic of the imidazopyridine class and exhibits a _____ dissolution. This impacted the product's pharmaceutical development and hence a _____

_____ Retest date for the drug substance is _____

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

AMBIEN CR™ (zolpidem tartrate extended release) 12.5 and 6.25 mg tablets are administered once daily before bedtime, _____ the drug product is supplied in three count-size configurations: 30 tablets in a blister carton, (three cards of 10 tablets each) which represents one-month supply; 100 tablets in 100-ml bottles; 500 tablets in 175-ml bottles which represent pharmacy bulk package. Being

Executive Summary Section

a bi-layer tablets of an immediate release and an extended release layer, the tablet is not to be cut, broken or chewed before swallowing. Expiration dating period of 18 months may be granted based on the evaluation of the primary stability data. The recommended storage conditions are:

"Store between 15 and 25°C [59 -77°F] – limited excursions permissible up to 30°C [86°F]".

C. Basis for Approvability or Not-Approval Recommendation

Sanofi proposed a new indication for the extended-release zolpidem tartrate, i.e. decrease in sleep latency, improved sleep maintenance, Clinical and biopharmaceutical assessments do not seem to support the claim for AMBIEN CR™. Interestingly, the *in-vitro* drug release occurs rapidly, i.e., Q = after 30 minutes with completion (Q> at 4 hours. The immediate-release layer (1) of the tablet is based on AMBIEN®. Pharmaceutical development was aimed at developing an additional extended-release component, layer 2. Hypromellose in combination with (Potassium Bitartrate) were thus included

Coating of the tablet with blue or pink

Various formulation prototypes were tested in PK and PD studies. The 12.5-mg strength was selected from PD studies conducted for strengths in the mg range, and the formulation evolved to the final form 2C3 after addition of colloidal silicon dioxide, colorant to distinguish the two strengths. Formulation 2C3, the one proposed for marketing, was shown to be bioequivalent to the prototype 1A1.

The manufacturing process development included

The registration batches included two pilot scale and one production scale batches for each strength with longest stability data at 30°C/65% RH and 40°/75% RH. The intended production scale is and is based on

The primary stability data indicated no degradation of the drug product (degradants below LOQ, and the drug product dissolution performance remained robust throughout the study duration. Under accelerated storage in blisters,

Despite this, an

Executive Summary Section

expiration dating period of 18-months can be granted according to Q1E Guidelines and based on the recommendations from the reviewing statistician.

Responses to Deficiencies from Review #1: During pharmaceutical development, the applicant investigated physical properties of the drug substance and the excipients, such as _____, and provided data supporting no impact on the formulation's dissolution profile

_____ The drug substance is soluble in _____ Consistent dissolution kinetics for zolpidem tartrate _____ Therefore no additional controls of physical attributes were included in the specifications of the drug substance and the excipients. _____

_____ did not affect dissolution of the finished product.

stability was addressed by setting a specification for _____ that is adequate for tablet handling from the blisters. The firm provided adequate responses and clarifications to questions on process parameters, batch records, categorical exclusion from environmental assessment and purity factor for the analytical standard of zolpidem tartrate. The firm corrected an error pertaining to the proposed commercial packaging configurations for AMBIEN CR in bottles. The proposed commercial configurations "75 ml/100 tablets count-size and 150 ml/500 tablets count-size" are supported by the stability data on primary stability batches.

Additional justification was provided in the amendment of July 6, 2005 regarding the CMC comment in the Approvable Letter of April 8, 2005. The number of sampling locations for the _____ / have been specified for the validation batches. The proposed sampling plan for _____ testing of validation batches and routine commercial batches is consistent with the recommendations in the _____

_____ ' Based on the data provided on _____ production scale batches and _____ testing on the finished product is acceptable. Any limited variations in the _____ are not expected to impact significantly the quality, safety or efficacy of the drug product.

Based on the adequate resolution of the CMC deficiencies as amended on April 1, 2005, and adequate response to the CMC comment on _____ on July 6, 2005 and the overall "Acceptable" recommendation by the office of compliance, the NDA is recommended for Approval from CMC standpoint.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Danae D. Christodoulou, Ph.D./

ChemistryTeamLeaderName/Date: Ravi Harapanhalli, Ph.D./

ProjectManagerName/Date: Lisa Basham – Cruz/Gujral Renmeet (HFD-120)



Executive Summary Section

C. CC Block

cc: Orig. NDA 21-774
HFD-170/NDA Division File
HFD-170/Chemist/DChristodoulou
HFD-170/MO/DEMcNeil
HFD-170/Pharmacologist/AWasserman
HFD-120/CSO/ Gujral Renmeet
R/D Init by: R. Harapanhalli, Ph.D.
filename: c:/data/mydocs/21774Review3.doc

7 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/

Danae Christodoulou
8/22/2005 05:20:49 PM
CHEMIST

Eric Duffy
9/12/2005 10:00:54 AM
CHEMIST



NDA 21-774

AMBIEN CR™

(Zolpidem tartrate extended—release) tablets

Sanofi-Synthelabo

Danae D. Christodoulou

**Chemistry for NDA 21-774, Division of Anesthetics, Critical
Care and Addiction Drug Products, HFD-170**



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RESPONSES TO DEFICIENCIES	
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	30
A. Labeling & Package Insert	30
III. List Of Deficiencies To Be Communicated.....	32



Chemistry Review Data Sheet

1. NDA 21-774
2. REVIEW #: 2
3. REVIEW DATE: 08-APR-05
4. REVIEWER: Danae D. Christodoulou, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	08-JUN-2004
Amendment (BZ)	27-AUG-2004
Amendment (BC)	05-OCT-2004
Amendment (BC)	22-FEB-2005
Amendment (BL)	18-MAR-2005

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BC)	01-APR-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Sanofi-Synthelabo Inc.
Address: 9, Great Valley Parkway, Malvern, PA 19355
Representative: Debra P. Gayda, Ph.D.,
Senior Director, Drug Regulatory Affairs
Telephone: 610-889-8645



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE: zolpidem tartrate / 3S

Proprietary Name: AMBIEN CR™

Non-Proprietary Name (USAN): Zolpidem tartrate extended-release tablets

a) Code Name/# (ONDC only):

b) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505 (b) (1)

10. PHARMACOL. CATEGORY: CNS depressant; treatment of insomnia

11. DOSAGE FORM: Extended-release tablets

12. STRENGTH/POTENCY: 12.5 mg (adults), 6.25 mg (elderly)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

N,N,6-trimethyl-2-p-tolyl-imidazo[1,2- α]-pyridine-3-acetamide L-(+)-tartrate(2:1)

Molecular Formula: (C₁₄H₂₁N₃O)₂ · C₄H₆O₆

MW: 764.88

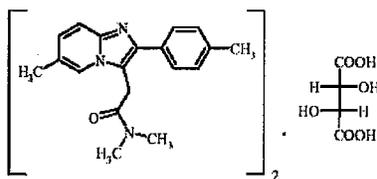
Structural Formula:



CHEMISTRY REVIEW



Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS: NDA 19-908 (AMBIEN® tablets); IND 25,361

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
✓	II	—	/	1	Adequate	February 16, 2005	
✓	IV	—	/	4	Adequate		
✓	III	/	/	4, 3	Adequate		
✓	III	/	/	4	Adequate		
✓	III	/	/	4	Adequate		
✓	III	/	/	4	Adequate		

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



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Stability Data (assay) support 18 month expiration dating	March 2, 2005	Dionne Price
EES	Inspections completed, recommendation pending		
Pharm/Tox	Not applicable		
Biopharm	Dr. David Lee agreed with the drug release specifications that were based on an acceptable IVIVC.		
LNC	Not consulted. The drug substance is not a NME and has USAN and international names. — was replaced by “extended-release” in the established name and LNC chair agreed.		
Methods Validation	Not requested; The Methods are conventional and do not qualify for any of the ONDC interim criteria for MV.		
DMETS	Carton and container labels Revisions recommended.	February 12, 2005 April 6, 2005	Felicia Duffy
EA	NA Categorical exclusion claimed but was insufficient. Calculations were requested.		
Microbiology	NA This is a solid oral form which does not promote microbial growth.		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:



The Chemistry Review for NDA 21-774

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is recommended for approval from CMC view point. All outstanding CMC issues have been addressed adequately by the sponsor. An "acceptable" recommendation has been made by the Office of Compliance for cGMP compliance. A comment pertaining to the testing criteria for process validation and routine commercial manufacture, attached at the end of the review, should be included in the action letter.

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

None

II. Summary of Chemistry Assessments

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

AMBIEN CR™(zolpidem tartrate extended release)tablets are a new formulation of zolpidem tartrate for the treatment of insomnia. They are coated, round biconvex tablets debossed with A~ on one side. Strengths are 12.5 (blue coated) to be prescribed for the adults and 6.25 mg (pink coated)for the ederyly. The drug product is a bi-layer tablet with an immediate release (layer 1) and an extended release (layer 2) component. The tablets are packaged in _____ bottles with CRC closures and in _____ blisters. This extended-release formulation is based on the marketed, immediate-release AMBIEN® 10-mg tablets.

The drug substance zolpidem tartrate is a non-benzodiazepine hypnotic of the imidazopyridine class and exhibits _____. This impacted the product's pharmaceutical development and hence a _____ for _____ substance is _____. Retest date for the drug

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

AMBIEN CR™ (zolpidem tartrate extended release) 12.5 and 6.25 mg tablets are administered once daily before bedtime, _____. The drug product is supplied in three count-size configurations: 30 tablets in a blister carton, (three cards of 10 tablets each) which represents one-month supply; 100 tablets in 100-ml bottles; 500 tablets in 175-ml bottles which represent pharmacy bulk package. Being



Executive Summary Section

a bi-layer tablets of an immediate release and an extended release layer, the tablet is not to be cut, broken or chewed before swallowing. Expiration dating period of 18 months may be granted based on the evaluation of the primary stability data. The recommended storage conditions are:

“Store between 15 and 25°C [59 -77°F] – limited excursions permissible up to 30°C [86°F]”.

C. Basis for Approvability or Not-Approval Recommendation

Sanofi proposed a new indication for the extended-release zolpidem tartrate, i.e. decrease in sleep latency improved sleep maintenance,

Clinical and biopharmaceutical assessments do not seem to support the claim for AMBIEN CR™. Interestingly, the in-vitro drug release occurs rapidly, i.e., Q = after 30 minutes with completion (Q> at 4 hours. The immediate-release layer (1) of the tablet is based on AMBIEN®. Pharmaceutical development was aimed at developing an additional extended-release component, layer 2. Hypromellose in combination with (Potassium Bitartrate) were thus included

Coating of the tablet with blue or pink

Various formulation prototypes were tested in PK and PD studies. The 12.5-mg strength was selected from PD studies conducted for strengths in the mg range, and the formulation evolved to the final form 2C3 after addition of colloidal silicon dioxide, colorant in to distinguish the two strengths. Formulation 2C3, the one proposed for marketing, was shown to be bioequivalent to the prototype 1A1.

The manufacturing process development included

The registration batches included two pilot scale and one production scale batches for each strength with longest stability data at 30°C/65% RH and at 40°/75% RH. The intended production scale is and is based on

The primary stability data indicated no degradation of the drug product (degradants below LOQ and the drug product dissolution performance remained robust throughout the study duration. Under accelerated storage in blisters, Despite this, an



Executive Summary Section

expiration dating period of 18-months can be granted according to Q1E Guidelines and based on the recommendations from the reviewing statistician.

Responses to Deficiencies from Review #1: During pharmaceutical development, the applicant investigated physical properties of the drug substance and the excipients, such as _____, and provided data supporting no impact on the formulation's dissolution profile and homogeneity. The drug substance is soluble _____

_____ Consistent dissolution kinetics for zolpidem tartrate. _____ Therefore no additional controls of physical attributes were included in the specifications of the drug substance and the excipients. _____

_____ ρ did not affect dissolution of the finished product. _____

stability was addressed by setting a specification for _____, that is adequate for tablet handling from the blisters. The firm provided adequate responses and clarifications to questions on process parameters, batch records, categorical exclusion from environmental assessment and purity factor for the analytical standard of zolpidem tartarte. The firm corrected an error pertaining to the proposed commercial packaging configurations for AMBIEN CR in bottles. The proposed commercial configurations "75ml/100 tablets count-size and 150ml/500 tabs count-size" are supported by the stability data on primary stability batches.

The proposed sampling plan for _____ testing of validation batches and routine commercial batches needs to be revised consistent with the recommendations in the _____

_____ This recommendation should be included in the action letter.

Based on the adequate resolution of the CMC deficiencies as amended on April 1, 2005, and the overall "Acceptable" recommendation by the office of compliance, the NDA is recommended for Approval from CMC standpoint.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Danae D. Christodoulou, Ph.D./

ChemistryTeamLeaderName/Date: Ravi Harapanhalli, Ph.D./

ProjectManagerName/Date: Lisa Basham – Cruz/

C. CC Block

- cc: Orig. NDA 21-774
HFD-170/NDA Division File
HFD-170/Chemist/DChristodoulou
HFD-170/MO/DEMcNeil



Executive Summary Section

HFD-170/Pharmacologist/A Wasserman

HFD-170/CSO/LBasham-Cruz

R/D Init by: R. Harapanhalli, Ph.D.

filename: c:/data/mydocs/21774Review2.doc

26 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/

Danae Christodoulou
4/8/05 03:02:28 PM
CHEMIST

Ravi Harapanhalli
4/8/05 03:11:07 PM
CHEMIST
AP with a comment



NDA 21-774

**AMBIEN CRTM
(Zolpidem tartrate extended—release) tablets**

Sanofi-Synthelabo

**Danae D. Christodoulou
Chemistry for NDA 21-774, Division of Anesthetics, Critical
Care and Addiction Drug Products, HFD-170**



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Chemistry Assessment	11
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	11
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Chemistry Review Data Sheet

1. NDA 21-774
2. REVIEW #: 1
3. REVIEW DATE: 29-MAR-05
4. REVIEWER: Danae D. Christodoulou, Ph.D.
5. PREVIOUS DOCUMENTS: None

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

08-JUN-2004

Amendment (BZ)

27-AUG-2004

Amendment (BC)

05-OCT-2004

Amendment (BC)

22-FEB-2005

Amendment (BL)

18-MAR-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Sanofi-Synthelabo Inc.

Address: 9, Great Valley Parkway, Malvern, PA 19355

Representative: Debra P. Gayda, Ph.D.,
Senior Director, Drug Regulatory Affairs

Telephone: 610-889-8645



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE: zolpidem tartrate / 3S

Proprietary Name: AMBIEN CR™

Non-Proprietary Name (USAN): Zolpidem tartrate extended-release tablets

a) Code Name/# (ONDC only):

b) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505 (b) (1)

10. PHARMACOL. CATEGORY: CNS depressant; treatment of insomnia

11. DOSAGE FORM: Extended-release tablets

12. STRENGTH/POTENCY: 12.5 mg (adults), 6.25 mg (elderly)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

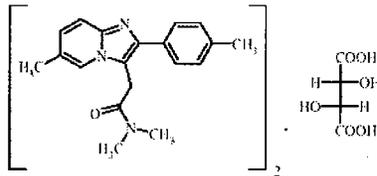
N,N,6-trimethyl-2-p-tolyl-imidazo[1,2- α]-pyridine-3-acetamide L-(+)-tartrate(2:1)

Molecular Formula: $(C_{14}H_{21}N_3O)_2 \cdot C_4H_6O_6$

MW: 764.88

Structural Formula:

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS: NDA 19-908 (AMBIEN® tablets); IND 25,361

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
✓	II	/	/	1	Adequate	February 16, 2005	
✓	IV			4	Adequate		
✓	III			4, 3	Adequate		
✓	III			4	Adequate		
✓	III			4	Adequate		
✓	III			4	Adequate		

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



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Stability Data (assay) support 18 month expiration dating	March 2, 2005	Dionne Price
EES	Inspections completed, recommendation pending		
Pharm/Tox	Not applicable		
Biopharm	Dr. David Lee agreed with the drug release specifications that were based on an acceptable IVIVC.		
LNC	Not consulted. The drug substance is not a NME and has USAN and international names. _____ was replaced by "extended-release" in the established name and LNC chair agreed.		
Methods Validation	Not requested; The Methods are conventional and do not qualify for any of the ONDC interim criteria for MV.		
DMETS	Carton and container labels Revisions recommended.	February 12, 2005	Felicia Duffy
EA	NA Categorical exclusion claimed but was insufficient. Calculations were requested.		
Microbiology	NA This is a solid oral form which does not promote microbial growth.		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:



The Chemistry Review for NDA 21-774

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable, pending satisfactory resolution of the deficiencies listed at the end of the review, and upon acceptable recommendations from the Office of Compliance. (See EER, Attachment 1)

Note that responses to the IR Letters were received on April 1 and seem to have adequately addressed all CMC Deficiencies. Review #2 (evaluation of the responses) will be filed in the DFS.

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

II. Summary of Chemistry Assessments

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

AMBIEN CR™ (zolpidem tartrate extended release) tablets are a new formulation of zolpidem tartrate for the treatment of insomnia. They are coated, round biconvex tablets debossed with A~ on one side. Strengths are 12.5 (blue coated) to be prescribed for the adults and 6.25 mg (pink coated) for the elderly. The drug product is a bi-layer tablet with an immediate release (layer 1) and an extended release (layer 2) component. The tablets are packaged in _____ bottles with CRC closures and in _____ blisters. This extended-release formulation is based on the marketed, immediate-release AMBIEN® 10-mg tablets.

The drug substance zolpidem tartrate is a non-benzodiazepine hypnotic of the imidazopyridine class and exhibits _____ this impacted the product's pharmaceutical development and hence a _____

_____. Retest date for the drug substance is _____

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

AMBIEN CR™ (zolpidem tartrate extended release) 12.5 and 6.25 mg tablets are administered once daily before bedtime, _____. The drug product is supplied in three count-size configurations: 30 tablets in a blister carton,

Executive Summary Section

(three cards of 10 tablets each) which represents one-month supply; 100 tablets in 100-ml bottles; 500 tablets in 175-ml bottles which represent pharmacy bulk package. Being a bi-layer tablets of an immediate release and an extended release layer, the tablet is not to be cut, broken or chewed before swallowing. Expiration dating period of 18 months may be granted based on the evaluation of the primary stability data. The recommended storage conditions are:

“Store between 15 and 25°C [59 -77°F] – limited excursions permissible up to 30°C [86°F]”.

C. Basis for Approvability or Not-Approval Recommendation

Sanofi proposed a new indication for the extended-release zolpidem tartrate, i.e. decrease in sleep latency, improved sleep maintenance,

Clinical and biopharmaceutical assessments do not seem to support the claim for AMBIEN CR™. Interestingly, the *in-vitro* drug release occurs rapidly, i.e., Q = — after 30 minutes with completion (Q> —, at 4 hours. The immediate-release layer (1) of the tablet is based on AMBIEN®. Pharmaceutical development was aimed at developing an additional extended-release component, layer 2. — Hypromellose — in combination with — Potassium Bitartrate) were thus included —

Coating of the tablet with — blue or pink —

Various formulation prototypes were tested in PK and PD studies. The 12.5-mg strength was selected from PD studies conducted for strengths in the — ng range, and the formulation evolved to the final form 2C3 after addition of — colloidal silicon dioxide, — colorant in — to distinguish the two strengths. Formulation 2C3, the one proposed for marketing, was shown to be bioequivalent to the prototype 1A1.

The manufacturing process development included —

The registration batches included two pilot scale — and one production — scale batches for each strength with longest stability data — at 30°C/65% RH and — at 40°/75% RH. The intended production scale is — and is based on —

The primary stability data indicated no degradation of the drug product (degradants below LOQ < —, and the drug product dissolution performance remained robust throughout the study duration. Under accelerated storage in blisters,

Executive Summary Section

Despite this, an expiration dating period of 18-months can be granted according to QIE Guidelines and based on the recommendations from the reviewing statistician.

Although the pharmaceutical development report covered several critical manufacturing issues, it did not adequately address the physical attributes of the drug substance and the excipients such as [redacted]. These are critical quality attributes for this low dose formulation, which contains only [redacted] % of the active on 260-mg tablets, both 6.25 and 12.5-mg. Although AMBIEN CR™ is manufactured by [redacted] and appears to be pharmaceutically robust with consistent dissolution performance, additional controls on the physical properties of the drug substance and the excipients are warranted as they are likely to impact the [redacted].

Alternatively, additional justification from pharmaceutical experience is needed to justify to the contrary. Zolpidem's [redacted] should be adequately assured through manufacturing so that this non-benzodiazepine hypnotic does not result in over-potency that may lead to residual hypnotic effects after sleep. In addition to compendial testing, functional testing of the excipients is needed to ensure quality is built into the product. It is not clear how the process parameters were optimized to achieve the [redacted] during the manufacture of the batches that were used in pivotal clinical and primary stability studies. The [redacted] is not identified. The sampling plans for both in-process and end testing are not identified. The master batch records need to be revised to include the batch numbers of the drug substance and the excipients for the purpose of tracking and tracing. trend on stability, the stability protocol needs to be revised to include monitoring of this parameter. Additional justification is needed to support the proposed marketing bottle configurations 100 count in 100-ml and 500 count in 175-ml relative to those used in the primary stability studies that formed the basis of the computation of expiration dating period.

Two information request letters were sent to the firm on March 22 and 28 in which the above CMC issues were enumerated and the responses are awaited. The nature of the CMC issues is such that a quick turn around response from the applicant is expected. From CMC perspective, the NDA is approvable pending satisfactory resolution of the CMC issues identified in these two IR letters and upon recommendation of satisfactory cGMP compliance from the Office of Compliance.

Responses to the IR Letters were received on April 1 and seem to have adequately addressed all CMC Deficiencies. Review #2 (evaluation of the responses) will be filed in the DFS.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Danae D. Christodoulou, Ph.D./

ChemistryTeamLeaderName/Date: Ravi Harapanhalli, Ph.D./



CHEMISTRY REVIEW



Executive Summary Section

ProjectManagerName/Date: Lisa Basham – Cruz/

C. CC Block

cc: Orig. NDA 21-774
HFD-170/NDA Division File
HFD-170/Chemist/DChristodoulou
HFD-170/MO/DEMcNeil
HFD-170/Pharmacologist/AWasserman
HFD-170/CSO/LBasham-Cruz
R/D Init by: R. Harapanhalli, Ph.D.
filename: c:/data/mydocs/N21774MAR29.doc

95 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/

Danae Christodoulou
4/1/05 02:36:26 PM
CHEMIST

Ravi Harapanhalli
4/1/05 03:15:27 PM
CHEMIST
Review # 2 provides the final recommendation