CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-997

CHEMISTRY REVIEW(S)

NDA 21-997

Zolpidem Tartrate Sublingual Tablet

Orexo AB

Thomas M. Wong, Ph.D.
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

Division of Division of Neurology Drug Products
Review of Chemistry, Manufacturing, and Controls

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-997

2. REVIEW #: 1

3. REVIEW DATE: January 27, 2009

4. REVIEWER: Thomas M. Wong, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	09-May-2008
Amendment # 0001: Proposed Draft Labeling Text.	13-Jun-2008
Amendment # 0003: Responses to CMC Comments	19-Sep-2008
Amendment # 0004: Responses to CMC Comments	10-Oct-2008
Amendment # 0006: Responses to CMC Comments	12-Nov-2008
Amendment # 0007: Responses to CMC Comments	16-Dec-2008
Amendment # 0008: Responses to CMC Comments	18-Dec-2008
Amendment # 0009: Responses to CMC Comments	19-Dec-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Orexo AB
Address:	Virdings alle 32A, SE-754 50 Uppsala, Sweden
Representative:	DJA Globlal Pharma 115 Commons Court Chadds Ford, PA 19317
Telephone:	(610) 5584454

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: To be determined

Chemistry Review Data Sheet

b) Non-Proprietary Name (USAN): Zolpidem tartrate
c) Code Name/#: OX22
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2) Zolpidem tartrate sublingual tablets (5 mg and 10 mg strengths)

10. PHARMACOL. CATEGORY: For treatment of short-term insomnia

11. DOSAGE FORM: Sublingual tablet

12. STRENGTH/POTENCY: 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: Sublingual

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: Zolpidem tartrate

Chemical name: N,N,6-trimethyl-2-p-tolylimidazo(1,2-a)pyridine-3-acetamide L-(+)tartrate (2:1)

Other chemical name: bis[N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide] (2*R*,3*R*)-2,3-dihydroxybutanedioate

CAS registry number: 99294-93-6

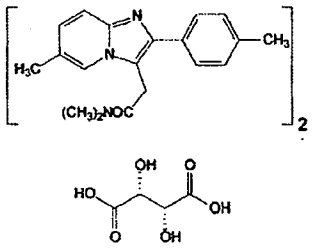
Company or lab code: OX22

Molecular Weight: 764.9

Structure:

Appears This Way
On Original

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
b(4)	II			3	Adequate	By Dr. Anil Pendse on February 9, 2008	LOA 04-Sep-2007
	III			4	N/A	N/A	LOA 22-Feb-2008

[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
IND	69,200	Commercial IND

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	18-Jun-2008	Office of Compliance
Pharm/Tox	N/A		No safety issue
Biopharm	N/A		
LNC	N/A		
Methods Validation	No validation request	As per this review	Thomas M. Wong, Ph.D.
DMFPA	Pending		Awaiting trade name approval
EA	Acceptable	As per this review	Thomas M. Wong, Ph.D.

Microbiology	N/A		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

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:

Executive Summary Section

The Chemistry Review for A/NDA ##-###

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product Zolpidem Tartrate Sublingual Tablets, 5 mg and 10 mg, is recommended as APPROVAL from a CMC perspective.

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

None at this time.

II. Summary of Chemistry Assessments

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

Drug Product

The applicant, Orexo, developed 5 mg and 10 mg strength zolpidem tartrate tablets for sublingual administration for treatment of short-term insomnia. There are several products containing the same drug substance on the market. These are Ambien® and oral controlled-release Ambien® CR and other generic products. The applicant's primary objective for development of this product is to provide a convenient, rapidly disintegrating tablet with mucoadhesive properties for sublingual administration to provide an earlier onset of sleep over Ambien® while maintaining a similar overall safety and efficacy profile for treatment of short term insomnia.

The drug product is a white, round, flat-faced, bevel-edged tablet 7.5 mm in diameter with V (5 mg tablets) or X (10 mg tablets) debossed on one side. Tablet weight is 120 mg and 130 mg for the 5 mg and 10 mg tablets, respectively. The tablets are packed in aluminum/aluminum Child Resistant Control (CRC) cold form blisters. Adequate information on the components and compositions of these two tablets is provided. Excipients in the formulation are common, compendial grades, and are widely used in the pharmaceutical industry. The manufacturing of zolpidem tartrate sublingual tablets consists of several common unit operations. The commercial batch size will be ——. The manufacturing process has been studied by the applicant at both pilot and commercial scales. This process has been optimized, critical process parameters at each step have been identified, and appropriate acceptance criteria for the critical process parameters have been implemented. b(4)

Since the drug substance has hypnotic effect and the sublingual tablet has faster disintegration and dissolution properties in water, the applicant has evaluated the potential abuse of zolpidem tartrate sublingual tablets. Several beverages were evaluated where a tablet was dissolved in each of the beverage evaluated. At the conclusion of the study, it was found that the appearance and the taste of the beverages tested are sufficient to detect the presence of the zolpidem tartrate sublingual tablet in the beverage.

The specifications for both zolpidem tartrate sublingual tablets 5 and 10 mg are adequate and are consistent between the two strengths. There is no ID test for the tartrate counter ion. The applicant justified the omission of the ID test for tartrate counter ion by saying that the manufacturing process for the drug product —— is reasonable to expect that the process will not affect the content and the identity of the tartrate salt. Identification and assay tests for tartrate with corresponding limits are applied for the drug substance. For dissolution, the applicant originally proposed an acceptance limit of —— at 10 minutes. The dissolution method, however, is not a discriminatory method and the applicant later excluded dissolution from the drug product specification. Due to the nature of the sublingual tablet and the route of administration, the tablet needs to disintegrate b(4)

and dissolve fast under the tongue. There is a good correlation between changes in dissolution profiles and changes in disintegration time. Tablets with disintegration time more than one minute (the acceptance limit for the disintegration time was not more than) have a slower dissolution rate. Thus, it is a good quality control method. The applicant revised the disintegration time acceptance limit as per the recommendation of the FDA. Analytical methods performed on the finished product are both compendial and non-compendial methods. The non-compendial methods have been fully validated. Batch analysis data on several batches of both 5 mg and 10 mg potency sublingual tablets were provided. All test results are well within the proposed specifications. one of the potential degradation products, was observed at a very low level in the tablets initially and in all stability samples. The levels of unidentified degradation products observed in all stability samples are also very low (. b(4)

The stability of four batches each of the two strengths of the final commercial product (FCP) formulation manufactured at pilot scale (3 batches) and commercial scale (1 batch of has been investigated. These batches are stored at long-term (25°C/60 % RH) and accelerated conditions (40°C/75 % RH). The tablets are packaged in aluminum/aluminum blisters. The results after 24 months of storage (FCP at pilot scale) at long-term (25°C/60 % RH) and 6 months at accelerated conditions (40°C/75 % RH) show no indication of chemical or physical deterioration of zolpidem tartrate in the FCP. Similar results after 18 months of storage (FCP at commercial scale) at long-term (25°C/60 % RH) and 6 months at accelerated conditions (40°C/75 % RH) have also been obtained. The available 24 months of primary stability data supports the 36 months shelf-life proposed by the applicant. b(4)

The applicant provided the post approval stability protocol for review. The applicant will place three commercial batches each of the two strengths made at the final commercial site at three different storage conditions for stability monitoring. Samples will be withdrawn at different time points. In addition, one batch each of the two strengths per year of future commercial batches will also be placed on stability and tested in accordance with the proposed protocol.

Drug substance

Zolpidem tartrate, Orexo company code OX22, is a non-benzodiazepine hypnotic of the imidazopyridine class. Chemically, zolpidem tartrate is N,N,6-trimethyl-2-p-tolylimidazo[1,2-a] pyridine-3-acetamide L-(+)-tartrate (2:1). It is a white to off-white crystalline powder and is sparingly soluble in water. The solubility in water is 23 mg/ml. The drug substance is manufactured . Zolpidem tartrate is listed in the Ph. Eur. Currently, there is no USP monograph for zolpidem tartrate. The drug substance is manufactured, tested and released by . Upon receipt of the released drug substance from . Orexo will test and released the drug substance according to Orexo's specification. Under the supervision of Orexo the analytical testing is outsourced to . b(4)

Orexo's proposed specification for zolpidem tartrate includes all test items listed in the Ph. Eur. monograph zolpidem tartrate. In addition, the proposed specification also includes testing and control for heavy metals, pH, tartaric acid, particle size, residual solvents and microbiological control. Test methods are either Ph. Eur. or USP. The applicant included batch analysis data for 11 batches of zolpidem tartrate. For each batch, two sets of results were included, one was generated by the manufacturer, , and the other was generated by the applicant. All results met the acceptance criteria and the results generated is very similar to those generated by the applicant.

impurity is listed in Ph. Eur. . This is an impurity resulting from one of the starting materials in the manufacturing process of zolpidem. An impurity/degradation product is identified which is the key starting material in the zolpidem process but it is also a primary degradation product of zolpidem, and it could be present due to hydrolysis. Impurities and degradation products are tested according to a validated procedure used by (supplier of drug substance) and Orexo. b(4)

The applicant refers to DMF —— for detailed information on the drug substance. This DMF has previously been reviewed by Dr. Anil Pendse on February 9, 2008 and the status of this DMF is adequate. b(4)

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

The applicant, Orexo, developed 5 mg and 10 mg strength of zolpidem tartrate tablets for sublingual administration for treatment of short-term insomnia. The dose should be individualized. The recommended dose for adults is 10 mg once daily taken immediately before bedtime and only when they are able to stay in bed a full night (7-8 hours) before being active again. The total daily dose should not exceed 10 mg. The tablet should be placed under the tongue, where it will rapidly disintegrate. The tablet should not be swallowed and the tablet should be taken without water. The effect of the tablet may be slowed by ingestion with or immediately after a meal. For earlier sleep onset the tablet should not be given with a meal.

The zolpidem tartrate sublingual tablet is available in 5 mg and 10 mg strength tablets for sublingual administration and the tablets are not scored. The tablet is classified as a Schedule IV controlled substance by federal regulation. Tablets are packaged into aluminium/aluminium Child Resistant Control (CRC) blisters. Three different blister packs are available, these are 10 tablets, 30 tablets, and 100 tablets per pack. Tablets are to be stored at controlled room temperature 20-25°C (68-77°F) and protect from light and moisture.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Orexo AB has submitted sufficient and appropriate information to support the approval of the drug product.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name:	Thomas M. Wong, Ph.D.
Branch Chief Name:	Ramesh Sood, Ph.D.
Project Manager Name:	

C. CC Block

See DFS.

98 Page(s) Withheld

8 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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/s/

Thomas M Wong
1/29/2009 01:45:12 PM
CHEMIST

Ramesh Sood
1/29/2009 02:33:11 PM
CHEMIST

CMC BRANCH CHIEF MEMORANDUM

To:	NDA 21-997
From:	Ramesh Sood, Ph.D., Branch Chief, ONDQA
Date:	27-Feb-2009
Drug:	Zolpidem Tartrate Sublingual Tablets
Route of administration:	Sublingual
Strength:	5 mg and 10 mg.
Subject:	**Approval** recommendation for NDA 21-997

Introduction: Zolpidem tartrate is currently marketed by Sanofi under the tradename Ambien. The current NDA is submitted as a 505(b)(2) application. The applicant developed 5 mg and 10 mg strength zolpidem tartrate tablets for sublingual administration for the treatment of short-term insomnia. The applicant's primary objective for development of this product is to provide a convenient, rapidly disintegrating tablet with mucoadhesive properties for sublingual administration to provide an earlier onset of sleep over Ambien® while maintaining a similar overall safety and efficacy profile for the treatment of short-term insomnia.

Drug Substance: Zolpidem tartrate is a non-benzodiazepine hypnotic of the imidazopyridine class. Chemically, zolpidem tartrate is N,N,6-trimethyl-2-p-tolylimidazo[1,2-a] pyridine-3-acetamide L-(+)-tartrate (2:1). It is a white to off-white crystalline powder and is sparingly soluble in water. The solubility in water is 23 mg/ml. The drug substance is manufactured [redacted]. Zolpidem tartrate is listed in the Ph. Eur. Currently, there is no USP monograph for zolpidem tartrate. Orexo's proposed specification for zolpidem tartrate includes all test items listed in the Ph. Eur. Monograph for zolpidem tartrate. In addition, the proposed specification also includes testing and control for heavy metals, pH, tartaric acid counter ion, particle size, residual solvents and microbiological control. The applicant refers to DMF [redacted] for detailed information on the drug substance. This DMF has previously been reviewed by Dr. Anil Pendse on February 9, 2008 and the current status of this DMF is adequate. b(4)

Drug product: The proposed product is a sublingual tablet available in 5 mg or 10 mg strengths. It is intended to disintegrate rapidly in saliva to 'small mucoadhesive units' to minimize swallowing of the active ingredient. [redacted] The drug product is a white, round, flat-faced, bevel-edged tablet 7.5 b(4)

mm in diameter with V (5 mg tablets) or X (10 mg tablets) debossed on one side. Tablet weight is 120 mg and 130 mg for the 5 mg and 10 mg tablets, respectively. Adequate information on the components and compositions of these two tablets is provided. Excipients in the formulation are common, compendial grades, and are widely used in the pharmaceutical industry. The manufacturing of zolpidem tartrate sublingual tablets consists of [redacted] tableting and packaging unit operations. The commercial batch size will be [redacted]. The manufacturing process has been optimized, critical process parameters at each step have been identified, and appropriate acceptance criteria for the critical process parameters have been implemented. The quality of the drug product is assured through well-controlled process, appropriate in-process and final drug product specification. The drug product specification includes test and an acceptable limits for appearance, identification (HPLC/UV), assay (HPLC), uniformity of dosage units (HPLC), related substances (HPLC), disintegration time, friability and microbiological control. All analytical methods have been adequately validated. b(4)

Since the drug substance has hypnotic effect and the sublingual tablet has faster disintegration and dissolution properties in water, the applicant has evaluated the potential abuse of zolpidem tartrate sublingual tablets. Several beverages were evaluated where a tablet was dissolved in each of the beverage evaluated. At the conclusion of the study, it was found that the appearance and the taste of the beverages tested are sufficient to detect the presence of the zolpidem tartrate sublingual tablet in the beverage.

The product is packaged in aluminum/aluminum blisters. Adequate stability data under long-term and accelerated storage conditions was submitted to support room temperature storage of the drug product for the proposed 36 month shelf-life.

The Office of Compliance has provided an overall acceptable recommendation for the manufacturing sites.

Recommendation: The application is recommended for "Approval" from CMC perspective.

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/s/

Ramesh Sood
2/27/2009 04:32:56 PM
CHEMIST