

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-196

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

NDA 22-196

**ZOLPIMIST™
(Zolpidem Tartrate) Oral Spray**

NovaDel Pharmaceuticals

Division of Neurology Drug Products, HFD 120

**Shastri Bhamidipati,
Office of New Drug Quality Assessment,
Division of Pre-Marketing Assessment I**

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1. NDA 22-196
2. REVIEW #: 2
3. REVIEW DATE: 15-SEP-2008
4. REVIEWER: Shastri Bhamidipati, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA 22-196 Original Submission	20-NOV-2007
NDA 22-196 Amendment (BC)	01-JAN-2008
NDA 22-196 Amendment (BC)	20-MAR-2008
NDA 22-196 Amendment (BC)	30-APR-2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA 22-196 Amendment (BC)	15-AUG-2008
NDA 22-196 Amendment (BC)	29-AUG-2008
NDA 22-196 Amendment (BC)	12-SEP-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Novadel Pharmaceuticals, Inc.

Address: 25 Minneakoning Road,
Flemington, NJ 08822

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Representative: David H. Bergstrom, Ph.D.
Sr. Vice President, Chief Operating Officer
25 Minneakoning Road,
Flemington, NJ 08822

Telephone: (908) 782-3431 ext. 2150

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ZolpiMist
- b) Non-Proprietary Name (USAN): Zolpidem Tartrate
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.54 , 505(b)(2)

10. PHARMACOL. CATEGORY: Neurology, Insomnia

11. DOSAGE FORM: Oral Spray

12. STRENGTH/POTENCY: 5 mg/ 100 μ L spray (50 mg/mL)

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

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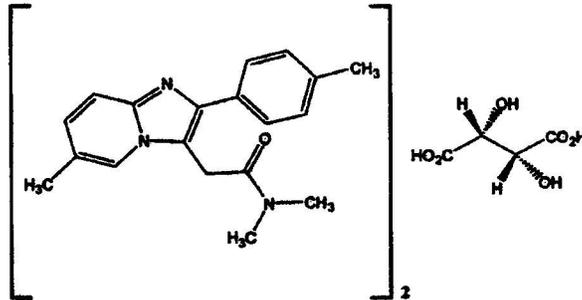
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

- Chemical Names: i) N,N,6-Trimethyl-2-*p*-tolylimidazo[1,2-*a*]pyridine-3-acetamide
L-(+)-tartrate (2:1)
ii) Bis[N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]acetamide] (2R,3R)-2,3-dihydroxybutanedioate
iii) N,N,6-Trimethyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-acetamide (2R,3R)-2,3-dihydroxybutanedioate (2:1)

Molecular Formula: C₄₂H₄₈N₆O₈

Molecular Weight: 764.89

CAS: [99294-93-6]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
					Adequate		Last reviewed in February 2008 by Dr. Anil Pandse
					Adequate		Last reviewed in August 2006 by Dr. Art Shaw
					Adequate	04-AUG-2008	
					Adequate		

¹ Action codes for DMF Table:
1 - DMF Reviewed.

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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	71,290	Zolpidem Tartrate oral spray

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics	Not applicable		
EES	Acceptable	20-JUN-2008	
Pharm/Tox	Not applicable		
Clinical Pharmacology	Approvable	18-AUG-2008	Dr. Jagan Parepally
Methods Validation	Not requested. The methods are conventional and do not qualify for internal validation by FDA labs		
DMETS	Approvable	31-AUG-2008	Tara Turner
EA	Categorical exclusion granted		
Microbiology	Not applicable as this is solid oral dosage form		

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 22-196

The Executive Summary

I. Recommendations

1. Recommendation and Conclusion on Approvability

This NDA for ZolpiMist™ (zolpidem tartrate) Oral Spray, 50 mg/mL is recommended for approval (AP) from CMC perspective. The responses provided by the sponsor to address the CMC deficiencies were evaluated and deemed adequate.

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

Not Applicable.

II. Summary of Chemistry Assessments

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

Drug Product:

ZolpiMist™, is a new oral formulation of Zolpidem Tartrate to be administered as a spray in to the mouth on the tongue for treatment of insomnia and submitted as a 505(b)(2) NDA application by NovaDel Pharmaceuticals based upon reference to Ambien (NDA 19-908). Zolpidem Tartrate formulated as immediate release (5 and 10 mg of Zolpidem Tartrate) and controlled release tablets of varying strengths (6.25 mg and 12.5 mg of Zolpidem Tartrate) was approved by the Agency and marketed under the trade names, Ambien and Ambien CR respectively for treating insomnia in adults. Zolpimist Oral spray, is a clear, slightly yellowish cherry flavored liquid containing 5.0% (w/v) of the drug substance Zolpidem tartrate as the active ingredient. The drug product will be available as multi-dose metered spray (60 sprays per unit) packaged in a _____ amber glass bottle (7.7 mL fill) equipped with a metered spray pump assembly to deliver 100 µL (containing 5 mg of the active) of drug product per spray. Each mL of the drug product consists of 50 mg of active along with _____ of inactive excipients, artificial Cherry flavor, benzoic acid, citric acid monohydrate, Neotame, propylene glycol, _____ hydrochloric acid and purified water.

b(4)

The pharmaceutical development of the formulation was adequately evaluated in terms of drug substance solubility, excipient compatibility and the choice of flavoring agents for taste masking. Additionally, the performance of spray pump assembly was evaluated for spray weight and content uniformity, droplet size distribution, spray angle and pattern in accordance with FDA guidance document: Nasal Spray and Inhalation

CHEMISTRY REVIEW

Executive Summary Section

Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing and Controls Documentation. (July 2002). The manufacturing process consists of making a _____ The drug product is also presented in the same container/closure configuration with smaller fill volume _____ as a Physician's sample. The stability of Zolpidem Tartrate Oral spray formulation manufactured at pilot and commercial scale and packaged in container /closure system intended for marketing (both commercial and Physician sample) was evaluated per ICH Q1A (R2) guidance document. Stability data for four registration batches and one process validation batch (commercial and Physician sample fill) up to a maximum of 12 months were provided and _____ expiration dating for the drug product was proposed. However, non-conformance results for spray weight and content uniformity were observed for stability samples stored under accelerated conditions. Additionally, two of the four registration batches were manufactured _____

b(4)

_____ Based on the evaluation of limited stability data for the registration batches and supporting stability data, a 12 month expiration date is recommended for the drug product stored at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature).

b(4)

Drug Substance:

Zolpidem tartrate, is a non-benzodiazepine hypnotic of the imidazopyridine class and its solubility is pH dependent. Chemically, zolpidem is N,N,6-trimethyl-2-p-tolylimidazo[1,2-a] pyridine-3-acetamide L-(+)-tartrate (2:1). There are no known polymorphic forms of the Zolpidem Tartrate. Drug substance, Zolpidem Tartrate was procured from _____, and the CMC information was referenced to type II DMF _____ through letter of authorization. At the manufacturing facility for the drug product (Rechon, AB), the incoming material was tested per Euro. Pharm. monograph for Zolpidem Tartrate.

b(4)

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

ZolpiMist™ (Zolpidem Tartrate) oral spray is supplied as a solution to be sprayed directly into the mouth over the tongue. Each metered actuation of ZolpiMist™ delivers 5 mg of zolpidem tartrate in 100 µL. The recommended dose for adults is 10 mg (two sprays) once daily immediately before bedtime and the dose is limited to 5 mg (one spray) for the elderly with hepatic insufficiency for rapid clearance. Zolpimist should not be taken with food as its effect may be slowed by ingestion with or immediately after meal. The drug product will be available as multi-dose metered spray (60 sprays per unit) packaged in a _____ amber glass bottle (7.7 mL fill) equipped with a metered spray pump assembly to deliver 100 µL (containing 5 mg of the active) of drug product per spray after initial priming with 5 actuations. A Physician sample of ZolpiMist™ packaged in the same primary container/closure configuration is targeted to deliver 8 sprays after initial priming. Zolpidem Tartrate is a Class IV controlled substance and its use is monitored as directed in Patient Counseling Information. The recommended storage conditions for the drug product are:

b(4)

CHEMISTRY REVIEW

Executive Summary Section

“Store at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature).

KEEP OUT OF REACH OF CHILDREN.”

C. Basis for Approvability or Not-Approval Recommendation

This NDA for ZolpiMist™ (zolpidem tartrate) Oral Spray, 50 mg/mL can be approved (AP) from CMC perspective. A shelf-life of 12 months is recommended for expiration dating of the product based on the 9 month long-term storage stability data submitted.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Shastri Bhamidipati, Ph.D./
Chemistry Team Leader Name/Date: Martha Heimann, Ph.D./
Project Manager Name: Cathleen Michaloski

C. CC Block

Original NDA 22-196
HFD-120/NDA Division File
HFD-120/CSO/C.Michaloski
ONDQA/DPAI/Chemist/S. Bhamidipati
ONDQA/DPAI//PAL/M. Heimann
ONDQA/DPAI RPM/S. Goldie
ONDQA/DPAI/R. Sood

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7 Page(s) Withheld

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/

Shastri P. Bhamidipati
9/16/2008 07:51:45 AM
CHEMIST

Ramesh Sood
9/16/2008 09:48:19 AM
CHEMIST

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