

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**

Table of Contents

Table of Contents2

Chemistry Review Data Sheet.....3

The Executive Summary7

I. Recommendations7

 A. Recommendation and Conclusion on Approvability7

 B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....7

II. Summary of Chemistry Assessments7

 A. Description of the Drug Product(s) and Drug Substance(s).....7

 B. Description of How the Drug Product is Intended to be Used.....8

 C. Basis for Approvability or Not-Approval Recommendation.....9

III. Administrative.....9

 A. Reviewer's Signature.....9

 B. Endorsement Block.....9

 C. CC Block9

Chemistry Assessment 10

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data.....10

 S DRUG SUBSTANCE [Zolpidem Tartrate, _____], 10

 P DRUG PRODUCT [ZOLPIDEM TARTRATE ORAL SPRAY, 5mg/100 µL] 19

 R REGIONAL INFORMATION 86

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 187

 A. Labeling & Package Insert..... 87

 B. Environmental Assessment Or Claim Of Categorical Exclusion 90

III. List Of Deficiencies To Be Communicated.....90

b(4)

Chemistry Review Data Sheet

1. NDA 22-196
2. REVIEW #: 1
3. REVIEW DATE: 03-AUG-2008
4. REVIEWER: Shastri Bhamidipati, Ph.D.

5. PREVIOUS DOCUMENTS:Previous DocumentsDocument Date**6. SUBMISSION(S) BEING REVIEWED:**Submission(s) ReviewedDocument Date

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

NDA 22-196 Amendment (BC)

20-JUN-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Novadel Pharmaceuticals, Inc.

Address: 25 Minneakoning Road,
Flemington, NJ 08822

CHEMISTRY REVIEW

Chemistry Review Data Sheet

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**

CHEMISTRY REVIEW

Chemistry Review Data Sheet

 X Not a SPOTS product

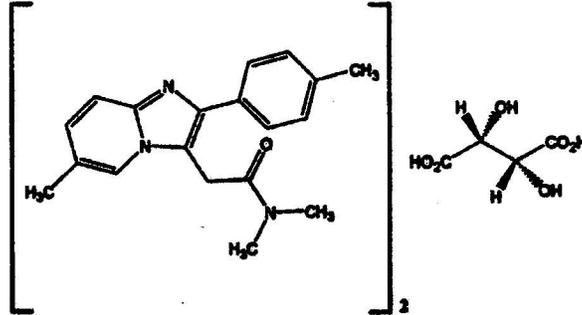
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

- 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
					Jequate		Last reviewed in February 2008 by Dr. Anil Pandse
					dequate		Last reviewed in August 2006 by Dr. Art Shaw
					Adequate		
					Adequate	04-AUG-2008	
					Adequate		

b(4)

CHEMISTRY REVIEW**Chemistry Review Data Sheet**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 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			
Methods Validation	Not requested. The methods are conventional and do not qualify for internal validation by FDA labs		
DMETS	Pending		
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 approvable (AE) from CMC perspective pending satisfactory responses from the sponsor to the deficiencies identified at the end of this review.

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.

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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 _____

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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).

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.

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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:

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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 is approvable (AE) from CMC perspective pending satisfactory responses from the sponsor to the deficiencies identified at the end of this review. 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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82 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
8/11/2008 04:14:54 PM
CHEMIST

Ramesh Sood
8/13/2008 07:47:42 AM
CHEMIST

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**Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I**

OND Division: Division of Neurology Products/
NDA: 22-196
Applicant: NovaDel Pharma
Stamp Date: 21-Nov-2007
PDUFA Date: 21-Sep-2008
Trademark: ZolpiMist
Established Name: Zolpidem Tartrate
Dosage Form: Spray
Route of Administration: Oral
Indication: Insomnia

PAL: Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues:

Summary

Zolpidem tartrate is currently marketed by Sanofi-aventis for treatment of insomnia as immediate release tablets (5 mg and 10 mg) and extended release tablets (6.25 mg and 12.5 mg), under the tradenames Ambien and Ambien CR, respectively. The current NDA is submitted by NovaDel Pharma as a 505(b)(2) application that references Sanofi-aventis' approved NDA 19-908 for Ambien Tablets. The proposed product, ZolpiMist (zolpidem tartrate) Oral Spray, is a metered dose pump that delivers 5 mg zolpidem tartrate in 100 µL solution per actuation. The recommended doses are 5 mg (1 actuation) or 10 mg (2 actuations).

Drug Substance

Zolpidem tartrate [chemical name: *N,N*,6-Trimethyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-acetamide (2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1)] is a white, or almost white, crystalline powder that is slightly soluble in water. The drug substance will be obtained from _____ DMF _____ is incorporated by cross-reference. The DMF has been reviewed and found adequate [A. Pendse review dated 09-Feb-2007].

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Zolpidem tartrate is tested on receipt by drug product manufacturer, Rechon Life Sciences AB, according to the European Pharmacopoeia (EP) monograph for zolpidem tartrate, with additional testing for residual solvents according to USP <467>. Copies of the EP monograph and EP test procedures are provided. The Rechon method qualification report for the EP HPLC related substances method is also provided in the NDA.

Drug Product

The proposed product, ZolpiMist (zolpidem tartrate) Oral Spray, is a clear, colorless to yellowish, cherry-flavored liquid containing 5.0% w/v of zolpidem tartrate as the active ingredient. The container closure is a _____ amber glass bottle with a metered-dose, snap-on, pump assembly which is manufactured by _____. The pump is designed to deliver 5.0 mg of zolpidem tartrate per metered spray (100 µL). The bottle for the commercial product is filled with a target amount of 8.22 g (7.7 mL) of the solution, intended to 60 metered sprays after initial priming. The physician sample will use the same container closure, but will contain _____, sufficient to deliver eight metered sprays after initial priming. The unit composition is summarized in the applicant's Table 3.2.P.1-1.

b(4)

Compound	Reference to Quality Standard	Function	Quantity per Unit		
			% w/w	% w/v	mg/100 µL
Zolpidem Tartrate	Ph. Eur.	Drug substance		3.00	5.00
Artificial Cherry Flavor	In-house	Flavoring agent			
Benzoic Acid	USP				
Citric Acid, Monohydrate	USP				
Hydrochloric Acid	NF				
Neotame	NF				
Propylene Glycol	USP				
Purified Water	USP				
Total					

Ph. Eur. = European Pharmacopoeia.
 NF = National Formulary.

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The drug product manufacturing process involves _____

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In addition to universal tests (assay, related substances, pH, etc) the proposed regulatory specification for ZolpiMist Spray includes physical/device functionality tests appropriate to the dosage form. A single gradient reverse HPLC method is used for assay, determination of related substances, spray content uniformity. A second, isocratic, method is used for determination of benzoic acid (_____ content. Physical tests for spray characteristics include droplet size distribution (by laser diffraction), spray angle and spray pattern.

The initial NDA submission contains a limited primary stability data package. Long-term stability data ranging between 6 months and 12 months are provided for a total of 4 finished product batches (3 commercial fill and 1 physician sample simple) filled from 3 lots of bulk solution. An additional 3 months of long-term and accelerated stability data are provided for one process validation batch split between commercial fill size and the physician sample fill. Further, it is noted that the first two primary stability batches (Lots AA0390 and AA0429) were manufactured using _____ Subsequently, the applicant discontinued use of the _____ for commercial production. Comparative stability data

b(4)

through 12 months are provided for one development batch to support _____
_____ from the commercial process; however, long-term data for the stability lots manufactured
according to the commercial process _____ are limited to 6 months.

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Critical issues for review

Drug Substance

No critical issues related to the bulk drug substance are identified.

Drug Product

The drug product is a homogeneous solution. Therefore, the primary critical issues are related to the performance of the spray pump assembly, suitability of product contact materials, and the chemical stability of the active solution. The following points are noted:

- Due to the change in manufacturing process, i.e., _____ there are limited stability data to support the final commercial process. The two stability lots that were manufactured _____ are not representative of the commercial process and would not be defined by the Agency as primary stability batches. The applicability of the data generated using these batches for assignment of product expiry is a matter for review.
- The applicant has submitted limited stability data to support the physician sample fill (i.e., 6 months long-term and accelerated data for one batch and 3 months data for a second batch). As both the commercial and sample products will be filled into the same size container; there are potential stability issues related to the difference in head space for the products. Thus, it is not clear whether the data for the commercial fill are applicable to support the sample fill.
- With respect to the container closure system, minor changes to the pump design may impact on spray characteristics. The reviewer should verify that there have been no changes to the spray pump assembly, or the individual components, subsequent to manufacture of the clinical batches.

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Additional issues

Administrative: A claim for categorical exclusion from environmental assessment is included in Module 1 of the application. It is however, that the applicant has claimed exclusion "in accordance with the criteria set forth in 21 CFR 25.31(a) through (c) and 25.15..." A claim under 25.31(b) is reasonable given the projected expected introduction concentration (EIC is _____ ppb). The applicant has not however, provided information to support a statement that approval of the application will not increase use of the active moiety [25.31(b)]. Further, 25.31(c) is not applicable as the active moiety does not occur naturally in the environment. The sponsor will be asked to revise the claim.

b(4)

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective. The drug substance is a well-characterized small molecule and the dosage form is relatively simple. No novel manufacturing processes are involved and the submission does not appear to require a review by the Manufacturing Sciences Branch.

Martha R. Heimann, Ph.D.
Pharmaceutical Assessment Lead

Date

Ramesh Sood, Ph.D.
Branch Chief

Date

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ATTACHMENT 1

Manufacturing Sites for ZolpiMist Oral Spray

Facility Information	Function
✓	✓
Rechon Life Science AB (formerly Ferring AB) P.O. Box 60043 SE-216 19 10 Limhamn Sweden Registration No.: 3006304750 Site Contact: Anders Ulfhielm Tel. No.: +46 40 361010 US Agent: Phone:	<u>Drug product manufacture.</u> #

b(4)

Need to verify Rechon address and registration number. Information provided by applicant does not correspond to any site listed for Ferring AB in EES or FACTS databases.

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**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR A NEW NDA/BLA**

NDA Numbers: 22-196

Applicant: NovaDel Pharma

Stamp Date: 21-Nov-2007

Drug Name: Zolpimist Oral Spray

NDA Type: Standard

Filing Meeting: TBD

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?		X	Need to confirm address and registration number for the drug product manufacturer.
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		Limited stability data for primary batches.
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	X		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?		X	The required methods validation package was not submitted.
12	If applicable, is documentation on the sterilization process validation included?	NA		

IS THE CMC SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant. NA

Martha R. Heimann, Ph.D.

12/7/07

Pharmaceutical Assessment Lead, DPA 1, ONDQA

Date

Ramesh Sood, Ph.D.

12/7/07

Branch Chief, DPA 1, ONDQA

Date

**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
12/7/2007 10:21:40 AM
CHEMIST

Ramesh Sood
12/7/2007 10:25:17 AM
CHEMIST

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