

NDA 22,196 ZolpiMist™ (zolpidem tartrate) Oral Spray

Teleconference to discuss Clinical Safety Literature Search

Feb 26, 2008

FDA Attendees:

June Cai, MD - Medical Officer

Elizabeth McNeal, MD - Team Leader

Cathleen Michaloski, BSN, MPH - Project Manager

NovaDel Attendees:

David Bergstrom, PhD – Senior VP and Chief Operating Officer

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Discussion:

In the original ZolpiMist NDA 22,196, relevant publications relating to zolpidem were summarized and provided in tabular format in the clinical sections of the NDA. Additional information including database used, search term “zolpidem”, search periods and responsible individuals was provided in SN0004 on 2/15/08; however upon review by the Division this was deemed to be insufficient. The teleconference was held to provide NovaDel with additional clarification regarding what FDA would consider complete information on the clinical literature search and safety assessment of zolpidem.

Dr. Cai explained that the following was requested:

- An expanded keyword search to include terms such as “suicidality” and “serious adverse events”, etc., in association with zolpidem.
- A description of the search strategy to assess the literature (databases, key search terms, search dates) and responsible individuals who carried out the search.
- A text summary of NovaDel overall conclusions drawn from the safety data contained in the relevant publications in relationship to the safety of zolpidem in the marketplace.
- A NovaDel warrant guaranteeing the accuracy of the review and safety conclusions in the ZolpiMist NDA.

NovaDel representatives stated that they understood the request and would provide a response as soon as possible to the NDA and thanked the NDA review team members for their assistance in clarifying the information requested.

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/s/

Cathleen Michaloski
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CSO

Cathleen Michaloski
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FILING COMMUNICATION

NDA 22-196

NovaDel Pharma, Inc.
25 Minneakoning Road
Suite 101
Flemington, NJ 08822

Attention: David H. Bergstrom, Ph.D.
Senior Vice President and Chief Operating Officer

Dear Dr. Bergstrom,

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for ZolpiMist (zolpidem tartrate) Oral Spray.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is Standard. Therefore, the user fee goal date is September 21, 2008.

We also acknowledge receipt of submissions dated January 1, 2008 and January 18, 2008.

We request that you submit the following information:

Chemistry, Manufacturing and Controls:

1. With regard to the registration stability package, we have determined that two of the batches presented as primary stability batches in the submission (i.e., Batches AA0390 and AA0429) do not meet the criteria for designation as primary stability batches. Specifically, the process used for manufacture of these batches included _____ Stability data generated using the batches will be reviewed as supportive stability data.
2. The NDA submission contains limited primary stability data, i.e., 6 months of long-term and accelerated data for one batch of bulk solution (Batch 07C01) that was manufactured according to the commercial process and filled into both commercial and physician sample presentation. Additionally, we acknowledge that initial data (through 3 months

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under long term and accelerated storage conditions) are provided for one process validation batch of the bulk solution (Batch IE0160) filled into both presentations. The expiration dating period assigned will be commensurate with the extent and quality of the available primary stability data. Submit additional available stability data to the Agency no later than the middle of the review cycle to permit timely completion of our review.

3. With regard to Environmental Assessment, you claim a categorical exclusion in accordance with the criteria set forth in 21 CFR 25.31(a) through (c) and 25.15. Although you have provided information to support a claim under 25.31(b); you have not provided any information to support the statement that "The requested action is not expected to increase the use of the active moiety." In the absence of such information a new dosage form would not meet the criteria for categorical exclusion under 25.31(a). Similarly, 25.31(c) is not applicable since, to the best of our knowledge, the active moiety does not occur naturally in the environment. Please submit a revised claim for categorical exclusion.
4. In regards to the Methods Validation Package, submitted under Regional Information, we have determined that you have to provide the following as required under 21 CFR §314.50(e):
 - i) Modify this package with links in the eCTD index backbone to allow us to send it to FDA testing laboratories as necessary.
 - ii) Include complete test results obtained at your testing facility for the drug substance and the drug product samples designated for submission as part of this package.
 - iii) Include Zolpidem Tartrate _____ and Benzoic acid reference standards in the list of samples designated to be sent to the FDA testing laboratory upon request.

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Clinical:

5. Please provide the following information on the literature search performed, include the database used, the search periods covered, the search terms, the individual(s) who is/are responsible for the search as well as your findings from the search. Finally, we need you to provide a statement that warrants that your conclusion is truthful based on your search.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We are granting your request for a waiver of pediatric studies for this application for pediatric patients in age birth up to 16 years.

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If you have any questions, call Cathleen Michaloski, BSN, MPH, Regulatory Project Manager, at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director, Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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Russell Katz
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-196

NDA ACKNOWLEDGMENT

NovaDel Pharma, Inc.
25 Minneakoning Road Suite 101
Flemington, NJ 08822

Attention: David H. Bergstrom, Ph.D.
Sr. Vice President, and Chief Operating Officer

Dear Dr. Bergstrom:

We have received your new drug application (NDA) submitted pursuant to section 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ZolpiMist (zolpidem tartrate) Oral Spray

Date of Application: November 20, 2007

Date of Receipt: November 21, 2007

Our Reference Number: NDA # 22-196

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 20, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(I)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above must be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, contact me at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

**Cathleen Michaloski, BSN, MPH
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research**

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