**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

# 022569Orig1s000

***Trade Name:*** Lazanda Nasal Spray

***Generic Name:*** fentanyl

***Sponsor:*** Archimedes Development Limited

***Approval Date:*** June 30, 2011

***Indications:*** Provides for the management of breakthrough pain in cancer patients, 18 years of age and older, who are already receiving and who are tolerant to regular opioid therapy for their underlying persistent cancer pain.

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**022569Orig1s000**

# APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022569

**NDA APPROVAL**

Archimedes Development Limited
c/o SciLucent, LLC
585 Grove St, Suite 300
Herndon, VA 20170

Attention: Ann Tunstall, PhD
Managing Consultant

Dear Dr. Tunstall:

Please refer to your New Drug Application (NDA) submitted August 30, 2009, received August 31, 2009, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lazanda (fentanyl) nasal spray, 100 and 400 mcg.

We acknowledge receipt of your amendments dated September 17, October 14 and 21, November 25, and December 4 and 18, 2009, and January 21, February 17 (2), March 11, April 1, 7, 19, and 29, and May 6, 14, 19, and 27, June 3, September 30, November 22 and 29, and December 10, and 22 (2), 2010, and January 12, 25, and 31, February 21, and 25, March 9, and 24, April 4, and June 1, 3, 27 and 29, 2011.

The September 30, 2010, submission constituted a complete response to our June 30, 2010, action letter.

This new drug application provides for the use of Lazanda (fentanyl) nasal spray for the management of breakthrough pain in cancer patients, 18 years of age and older, who are already receiving and who are tolerant to regular opioid therapy for their underlying persistent cancer pain.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text with the minor editorial revisions listed below.

We remind you of your June 22, 2011, commitment via email to update the images in the Medication Guide with the final artwork, enlarge Figure A, and to revise Figure B to show the location of the seal on the pouch.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

## CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your June 27, 2011, submission containing final printed carton and container labels.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth through 6 years because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients less than 7 years of age who could appropriately use this product is extremely small.

We are deferring submission of your pediatric study for ages 7 through 16 years for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1794-1 A safety and pharmacokinetic study of Lazanda (fentanyl) nasal spray for the management of breakthrough pain, including cancer pain and pain due to chronic medical conditions, in opioid-tolerant children 7 through 16 years of age.

| | |
|---|---|
| Final Protocol Submission: | December 2012 |
| Study Completion: | June 2015 |
| Final Report Submission: | December 2015 |

Submit clinical protocols to your IND 070854 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

## RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our complete response letter dated June 30, 2010.

Pursuant to 505-1(f)(1), we have determined that Lazanda (fentanyl) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risks of overdose, misuse, abuse, addiction, and serious complications due to medication errors that are listed in the labeling. The elements to assure safe use will provide for the education of prescribers and patients so that they are aware of the risks associated with the use of Lazanda (fentanyl) and about important information regarding how to use the product safely in order to help prevent the serious adverse effects noted above. The elements will also help assure proper patient selection and dispensing of Lazanda (fentanyl).

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on June 29, 2011, and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Lazanda (fentanyl) into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following.

1. For the assessment of enrollment and discontinuation statistics for prescribers, pharmacies, patients, and wholesalers/distributors, the following data will be tabulated
    a. The total numbers and geographic distribution of prescribers enrolled in the Lazanda REMS program, number of new prescribers enrolled during the current reporting period, and number of prescribers who were inactivated
    b. The total numbers and geographic distribution of pharmacies enrolled in the Lazanda REMS program, number of new pharmacies enrolled during the current reporting period, and number of pharmacies that were inactivated (reported by type of pharmacy, inpatient or outpatient)
    c. The total numbers and geographic distribution of patients enrolled in the Lazanda REMS program, new patients enrolled during the current reporting period, and number of patients who were inactivated
    d. The number of completed Knowledge Assessments for prescribers and authorized pharmacists, and a tabulation of the number of attempts required to successfully complete the Knowledge Assessment
    e. The total number of wholesalers/distributors enrolled in the Lazanda REMS program, number of new wholesalers/distributors enrolled during the current reporting period, and number of wholesalers/distributors that were inactivated
2. Dispensing activity for enrolled pharmacies (inpatient and outpatient); including authorization to dispense data from enrolled outpatient pharmacies
3. For the assessment of program infrastructure and performance
    a. A summary and root cause analysis of all unintended system interruptions (e.g., due to system failure, program failure, inaccurate training), including, but not limited to:
        (1) Barriers or delays in patient access due to:
            (a) False negatives: e.g., all entities are enrolled, but system generated a prescription rejection notice
            (b) Prescriber delay in submitting the completed *Patient-Prescriber Agreements* to the Lazanda REMS Program
            (c) Inadvertent enrollment deactivations, or failures to notify enrollees of forthcoming enrollment expirations
            (d) Prescriber who is not aware of Lazanda REMS program (i.e., not enrolled) prescribes Lazanda
            (e) Geographic barriers: lack of enrolled prescribers and/or pharmacies in a patient's local area
            (f) A report on the length of the delay (i.e., how long it took for patient to receive Lazanda after the original prescription was denied by the pharmacy)

(2) Inappropriate patient access:

(a) False positives: e.g., one or all entities were not enrolled but system verified dispensing/generated a unique authorization code

(b) Inpatient pharmacy dispensing for outpatient use

b. An assessment of the process for pharmacies to upgrade their pharmacy management systems, including a report on the time required for outpatient pharmacies to upgrade their pharmacy management systems (mean, maximum and minimum amount of time), and on the number of pharmacies that tried and were unable to modify their systems

c. An evaluation of the enrollment process for prescribers, pharmacists, and wholesalers/distributors, including a summary of the method used to enroll (e.g., online, fax), and a report on the quality of the data received (e.g., number of incomplete forms received)

d. Report of reasons for and the number of times a "back-up" system was used to validate a prescription, either due to problems at the pharmacy-level, Switch, or with the Lazanda REMS database

e. Call center report, including a summary of frequently asked questions and problems reported, and any needed program enhancements

f. A description of the corrective actions taken based on the programs/system tracking of these occurrences

4. Results of surveys conducted of prescribers' and pharmacists' (inpatient and outpatient) understanding and knowledge of the safe use and appropriate prescribing of Lazanda (fentanyl), as described in the Lazanda REMS educational materials and PI

5. Results of surveys conducted of patients' understanding and knowledge of the serious risks and safe use of Lazanda (fentanyl)

6. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

7. A report on the number of Dear Healthcare Professional letters mailed (prescriber and pharmacy), when the letters were mailed, what information was included in the mailings, and the number of returned mailings.

8. Results of any prescriber, pharmacy, wholesaler/distributor, and vendor audits conducted, and corrective actions taken during the reporting period

9. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

10. Results of surveillance and monitoring activities for abuse, misuse, and overdose including:

a. Signals that indicate misuse, abuse, overdose, or addiction

b. Signals that indicate serious adverse events or deaths related to inappropriate prescribing or other prescriber misuse of Lazanda (fentanyl), such as patients obtaining prescriptions

from multiple prescribers, prescriptions to non-opioid tolerant patients, and prescriptions for inappropriate doses.

11. Drug Utilization Data including the following information:

    a. The number of cumulative initial and continuing prescriptions to date and new initial prescriptions during the reporting period, as well as minimum, maximum, mean and median number of prescriptions per patient

    b. Lazanda (fentanyl) Month-to-Date Sales (Distribution) Report (by type of pharmacy, inpatient or outpatient)

    c. Data from flagged prescriptions from more than two prescribers to the same patient

    d. An analysis to evaluate Lazanda (fentanyl) REMS utilization patterns including use in non-opioid tolerant patients

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If you plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022569 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 022569**
**PROPOSED REMS MODIFICATION**
**REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)**
**FOR NDA 022569**
**REMS ASSESSMENT**
**PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

## EXPIRATION DATING PERIOD

A 24 month expiration date is granted for Lazanda (fentanyl) nasal spray when stored at 25° C (77° F) with excursions permitted from 15° to 30°C (59°-86°F).

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Matt Sullivan, Senior Regulatory Project Manager, at (301) 796-1245.

Sincerely,

*{See appended electronic signature page}*

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling
REMS

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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BOB A RAPPAPORT
06/30/2011