CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210793Orig1s000
207318Orig1s003

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABELS AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 21, 2018
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 210793 and NDA 207318/S-003
Product Name and Strength:	Nuplazid (pimavanserin) capsules, 34 mg Nuplazid (pimavanserin) tablets, 10 mg
Applicant/Sponsor Name:	ACADIA Pharmaceuticals, Inc.
FDA Received Date:	May 24, 2018
OSE RCM #:	2017-2069-1 and 2017-2454-1
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Psychiatry Products requested that we review the revised commercial container labels, and professional sample carton and blister pack labeling for Nuplazid (pimavanserin) 34 mg capsules (NDA 210793) and Nuplazid (pimavanserin) 10 mg tablets (NDA 207318/S-003), (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review.[a]

2 CONCLUSION

The revised commercial container labels, and professional sample carton and blister pack labeling for Nuplazid (pimavanserin) 34 mg capsules (NDA 210793) and Nuplazid (pimavanserin) 10 mg tablets (NDA 207318/S-003) are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Holmes, L. Label and Labeling Review for Nuplazid (NDA 210793 and NDA 207318/S-003). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Apr 30. RCM No.: 2017-2069 and 2017-2454.

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/s/

LORETTA HOLMES
06/21/2018

LOLITA G WHITE
06/21/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: **May 9, 2018**

To: Bernard A. Fischer M.D., Clinical Reviewer
Division of Psychiatry Products (DPP)

Mona Kalsi, Pharm.D., Regulatory Project Manager, (DPP)

Brendan Muoio, Pharm.D., Regulatory Project Manager, (DPP)

Kimberly Updegraff, Pharm.D., Associate Director for Labeling, (DPP)

From: Domenic D'Alessandro, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Acting Team Leader, OPDP

Subject: OPDP Labeling Comments for NUPLAZID (pimavanserin) capsules, for oral use & NUPLAZID (pimavanserin) tablets, for oral use (Nuplazid)

NDA: 210793 & 207318/S-003

In response to DPP consult requests dated October 10, 2017 and December 12, 2017, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for Nuplazid. The purpose of the original application (NDA 210793) is to provide for a 34 mg immediate release capsule, allowing patients to take a single 34 mg capsule once daily, and the supplemental application (NDA 207318, S-003) proposes the addition of a new dosing regimen to support a 10 mg tablet for use in patients on concomitant CYP3A4 inhibitors.

PI: OPDP's comments on the proposed labeling are based on the draft PI accessed from the DPP SharePoint on May 7, 2018, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 31, 2017, and October 27, 2017, and the April 30, 2018, Division of Medication Error and Prevention and Analysis' (DMEPA's) review. We concur with DMEPA's review regarding the proposed carton and container labeling, and have no additional comments.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

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/s/

DOMENIC G DALESSANDRO
05/09/2018

LABELS LABELING AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 30, 2018
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 210793 and NDA 207318/S-003
Product Name and Strength:	Nuplazid (pimavanserin) capsules, 34 mg Nuplazid (pimavanserin) tablets, 10 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	ACADIA Pharmaceuticals, Inc.
FDA Received Date:	August 31, 2017 (NDA 210793) October 27, 2017 (NDA 207318/S-003)
OSE RCM #:	2017-2069 and 2017-2454
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

The Division of Psychiatry Products (DPP) consulted the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate the labels, labeling and packaging submitted for NDA 210793 and NDA 207318/S-003 to determine if they are acceptable from a medication error perspective.

NDA 210793 proposes a new 34 mg strength immediate release capsule, allowing patients to be able to take a single 34 mg capsule, rather than taking two of the currently marketed 17 mg tablets.

NDA 207318/S-003 provides for a new 10 mg strength tablet for use in patients who are concomitantly administered strong CYP3A4 inhibitors.

2 REGULATORY HISTORY

Nuplazid (pimavanserin) tablets 17 mg, NDA 207318, was approved on April 29, 2016. The recommended dose is 34 mg (taken orally as two 17 mg tablets) once daily. Upon approval of NDA 210793 for the 34 mg capsules, the Applicant will discontinue marketing the 17 mg tablets.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed commercial container labels, professional sample carton and blister pack labeling, and prescribing information for Nuplazid to determine if there are any areas of concern or needed improvement from a medication safety perspective. We identified the following:

1. The proprietary name and established name lack sufficient prominence relative to the amount of space on the PDP and the size of the large graphic on the PDP.

2. The statement of strength below the established name lacks prominence which may contribute to wrong strength selection errors.

3. The "Rx only" statement and net quantity statement are too prominent.

4. The location of the lot number and expiration date is not shown on the container labels.

5. As presented, the proposed formatting of the expiration date on the professional sample carton labeling and blister pack labeling is confusing.

6. The professional sample packaging contains 7 tablets/capsules but the statement of strength is not expressed in terms of milligrams per single unit (i.e., XX mg per tablet or XX mg per capsule). Thus, we are concerned with risk of wrong dose medication error.

7. The presentation of the product identifying information (i.e., the proprietary and established names and the statement of strength) is not consistently presented on the professional sample blister pack labeling and carton labeling.

5 CONCLUSION & RECOMMENDATIONS

We identified areas of needed improvement in the positioning, prominence, and presentation of certain statements on the commercial container labels and professional sample blister packs and carton labeling. Additionally, there is certain information that needs to be added or deleted. We provide recommendations in Section 5.1, below.

5.1 RECOMMENDATIONS FOR ACADIA PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of NDA 210793 and NDA 207318/S-003:

A. General Comments (Commercial Container Labels and Professional Sample Blister Pack and Carton Labeling)

   1. The proprietary name and established name lack sufficient prominence which may pose risk of wrong drug medication error. To improve visibility, increase the relative size of the proprietary and established names.

   2. The statement of strength located below the established name lacks prominence. We recommend you increase the size of the statement of strength that is located below the established name to decrease risk of wrong strength selection error.

3. The “Rx only” statement and net quantity statement are too prominent due to their bold font type. Their prominence distracts from important product identifying information such as the proprietary name, established name and strength. For the “Rx only” and net quantity statements, we recommend use a font that is not bold.

B. Commercial Container Labels

1. The proposed location of the lot number and expiration date is not indicated on the container labels. Identify the intended location of the lot number and expiration date. Additionally, indicate the expiration date formatting that you intend to use. To minimize confusion and reduce the risk of use of expired drug product, we recommend using one of the following (or similar) formats:

DDMMMYYYY (e.g., 31JAN2013)
MMMYYYY (e.g., JAN2013)
YYYY-MMM-DD (e.g., 2013-JAN-31)
YYYY-MM-DD (e.g., 2013-01-31)

C. Professional Sample Blister Packs and Carton Labeling

1. As presented, the proposed formatting of the expiration date is confusing (i.e., MMYYY). To minimize confusion and reduce the risk of use of expired drug product, we recommend using one of the following (or similar) formats:

DDMMMYYYY (e.g., 31JAN2013)
MMMYYYY (e.g., JAN2013)
YYYY-MMM-DD (e.g., 2013-JAN-31)
YYYY-MM-DD (e.g., 2013-01-31)

2. The statement of strength on the professional sample carton labeling and blister pack labeling does not indicate the milligram strength per unit. This may contribute to wrong dose medication error. To minimize this potential risk, add the statement “per capsule” or “per tablet” to the statement of strength (e.g., 10 mg per tablet or 34 mg per capsule, as appropriate).

D. Professional Blister Packs

The left outside panel which contains the tablets or capsules, does not have a statement of strength. Add the statement of strength to the left outside panel.

E. Professional Sample Blister Pack (10 mg strength)

The right inside panel which contains the tablets has the statement of strength but does not state the proprietary and established names. Move the proprietary and established names from the center inside panel to the right inside panel so that all of the product identifying information is on the right inside panel.

F. Professional Sample Blister Pack (34 mg strength)

The right inside panel which contains the capsules has the proprietary and established names but not the statement of strength. Add the statement of strength to the right inside panel. If additional space is needed, consider moving the "Not Child Resistant" statement to another panel.

G. Professional Sample Carton Labeling

The top panel does not include the statement of strength which may contribute to wrong strength medication error. Include all of the product identifying information (i.e., proprietary name, established name, and strength) on the top panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nuplazid received on August 31, 2017 (NDA 210793) and October 27, 2017 (NDA 207318/S-003) from ACADIA Pharmaceuticals, Inc.

Table 2. Relevant Product Information for Nuplazid	
Initial Approval Date	NDA 207318 (approved on 04/29/2016)
Active Ingredient	pimavanserin
Indication	Treatment of hallucinations and delusions associated with Parkinson's disease psychosis
Route of Administration	Oral
Dosage Form	Tablets (NDA 207318/S-003); Capsules (NDA 210793)
Strengths	10 mg tablets and 34 mg capsules
Dose and Frequency	The recommended dose is 34 mg once daily. Coadministration with Strong CYP3A4 Inhibitors The recommended dose when coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole) is 10 mg, taken orally as one tablet once daily Coadministration with Strong CYP3A4 Inducers Monitor patients for reduced efficacy if Nuplazid is used concomitantly with strong CYP3A4 inducers; an increase in Nuplazid dosage may be needed
How Supplied	30-count bottles
Storage	**34 mg Capsule:** Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]. To prevent potential capsule color fading, protect from light. **10 mg Tablet:** Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 16, 2018, we searched DMEPA's previous reviews using the terms, Nuplazid and pimavanserin. Our search did not retrieve any reviews that inform this current review.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On April 16, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care
Search Strategy and Terms	Match Exact Word or Phrase: Nuplazid

D.2 Results[a]

We retrieved one article. However, the article described adverse drug events that did not inform this labels and labeling review.

[a] Institute for Safe Medication Practices. QuarterWatch: Safety signals for two novel drugs, Nuplazid and Entresto. ISMP Med Saf Alert Acute Care. 2017;22(22):1-3.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Nuplazid labels and labeling submitted by ACADIA Pharmaceuticals, Inc.

- Commercial container label received on August 31, 2017 (NDA 210793) and October 27, 2017 (NDA 207318/S-003)
- Professional sample carton labeling received on August 31, 2017 (NDA 210793) and October 27, 2017 (NDA 207318/S-003)
- Professional sample blister pack labeling received on August 31, 2017 (NDA 210793) and October 27, 2017 (NDA 207318/S-003)
- Physical samples of the professional sample blister packs and carton labeling provided by ACADIA Pharmaceuticals, Inc.
- Prescribing Information (Image not shown) received on August 31, 2017 (NDA 210793) and October 27, 2017 (NDA 207318/S-003)

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[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LORETTA HOLMES
04/30/2018

LOLITA G WHITE
04/30/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 12/1/2017

TO: Division of Psychiatry Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 210793

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below and the outcome of the inspections was classified as No Action Indicated (NAI). OSIS is notifying the review division that a dosing error was observed at Vince and Associates under the previously inspected BLA 761039. The clinical investigator (Dr. Martin Kankam, M.D., Ph.D.) who conducted the clinical portion of the study under BLA 761039 is the same investigator conducting the clinical portion of the current study.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Vince & Associates Clinical Research	10103 Metcalf Avenue, Overland Park, KS.
Analytical		(b) (4)

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/s/

SHILA S NKAH
12/01/2017