

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207318Orig1s000

CHEMISTRY REVIEW(S)



MEMORANDUM

Date: April 14, 2016
From: David Claffey, Ph.D., CMC Lead, OPQ/ONDP and ATL for NDA 207318
To: NDA 207318
Subject: OPQ Approval Recommendation for NDA 207318, NUPLAZID (pimavanserin) tablets

This memorandum is an addendum to the Office of Pharmaceutical Quality (OPQ) 19 FEB 2016 review for NDA 207318 where an approval recommendation was made on receipt of an acceptable recommendation from the OPF facilities reviewer. On 12 APR 2016 OPF facilities made an overall acceptable recommendation (Attached).

Therefore this application is recommended for approval from an OPQ perspective.

David J.
Claffey -S

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ou=HHS, ou=FDA, ou=People,
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Amendment to NDA 207318 Review #1

April 12, 2016

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

S.2.1 Manufacturer(s)

1. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

TABLE 1: DS Manufacturing and Testing Sites

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
(b) (4)				NME	Acceptable based on file review.
				NME	Acceptable based on file review.

Reviewer's Assessment:								
Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
(b) (4)								



2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

P.3.1 Manufacturer(s)

2. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

TABLE 2: DP Manufacturing and Testing Sites

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
(b) (4)				NME	Acceptable based on pre-approval inspection.

Reviewer's Assessment:								
Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
(b) (4)								



OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

The overall manufacturing inspection recommendation is acceptable.

**Steven Hertz
Consumer Safety Officer
OPF Division of Inspectional Assessment, Branch 1
4/12/16**

Secondary Review Comments and Concurrence:

I concur with the facility reviewer's recommendation.

Zhihao Peter Qiu, Ph.D., OPF/DIA, 4/12/2016

Recommendation: Pending

NDA 207318

Review #1

19 FEB 2016

Drug Name/Dosage Form	Nuplazid (Pimavanserin) Tablets
Strength	17 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Acadia Pharmaceuticals
Indication	Psychosis associated with Parkinson's Disease

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Initial N-000	1 SEP 2015	All
N-0013	14 DEC 2015	Drug substance, Drug product, Facilities, Biopharm
N-0017	21 JAN 2016	Drug substance, facilities
N-0018	18 FEB 2016	Drug product

Quality Review Team

DISCIPLINE	REVIEWER (primary/secondary)
Drug Substance	Gaetan Ladouceur/Kasturi Srinivasachar
Drug Product	Rao Kambhampati/Wendy Wilson-Lee
Process and Microbiology	Xuhong Li/ Akm Khairuzzaman
Facility	Steven Hertz/ Peter Qiu
Biopharmaceutics	Jing Li/ Okpo Eradiri
Regulatory Business Process Manager	Dahlia Woody & Grafton Adams
Application Technical Lead	David Claffey

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: Only container closure DMFs reference, refer to P.7.

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	Adequate		
	Type III		Adequate			
	Type III		Adequate			
	Type III		Adequate			
	Type III					
	Type III		Adequate			
	Type III		Adequate			
	Type III		Adequate			
	Type II		Adequate			
	Type III		Adequate			
	Type III		Adequate			
	Type III		Adequate			
	Type III		Adequate			
	Type III		Adequate			
	Type IV	Adequate				

			(b) (4)			

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68384	Supporting IND

2. CONSULTS: None

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommended for Approval on receipt of an acceptable recommendation from the facilities reviewer.

Recommend that the following be added to the action letter - A drug product expiration dating period of 24 months is granted when stored at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

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

N/A

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

The drug substance is pimavanserin tartrate, a new molecular entity. It contains two pimvanserin molecules per one tartrate. Molecular weight of the entire salt is 1005.20 and the base is 427.55. It is a white powder. It is a highly water soluble in (b) (4) pHs. (b) (4)

(b) (4)

(b) (4) The drug substance review team found these controls acceptable. The drug substance specification is typical. It includes an identification test (b) (4)

(b) (4) (b) (4) e distribution control was put in place at Agency request (b) (4)

The primary stability data support the proposed retest period of (b) (4) months at room temperature as no degradation trends were observed in the long term stability studies (25°/75% RH) or the accelerated condition (40°/60% RH).

A retest period of (b) (4) months at room temperature storage was found acceptable.

B. Drug Product [Established Name] Quality Summary

This application proposes the marketing of pimvanserin as immediate release tablets in one strength – 17 mg. Each tablet contains 20 mg of pimavanserin tartrate. The labeled strength is expressed in terms of pimavanserin free-base equivalents. The tablets are round, white to off-white, contain a (b) (4) film coat and are debossed with “P” on one side and “17” on the other. They are packaged (60-count commercial) in a 40 cc white round HDPE bottle (b) (4)

The drug product composition is relatively simple containing (b) (4)% active, (b) (4)% MCC as (b) (4)% pregelatinized starch (b) (4) and (b) (4)% Mg Stearate (b) (4)

The commercial product will contain (b) (4)% film coat, whereas the clinical and registration batches contained (b) (4)% film-coat. (b) (4)

The drug product specification is typical of an immediate release tablet (b) (4). This limit was found acceptable by pharm/tox. Dissolution has a $Q = \frac{w}{(b) (4)}\%$ at 15 minutes. (b) (4)

Three registration drug product batches were manufactured and were packaged into both 60- and 14- count HDPE bottles. Data up to 18 months were provided to support the proposed (b) (4) month expiry period, however a 24 month expiry period was found to be more appropriate. (b) (4)

The drug product manufacturing process is relatively straightforward (b) (4)

The proposed in vitro dissolution test (USP 1, 0.1 N HCl, 100 rpm, 900 ml, 37°C) and the acceptance criterion ($Q = \frac{w}{(b) (4)}\%$ in 15 minutes) were found adequate. A BCS Class (b) (4) claim was made but, this was not evaluated.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Nuplazid™
Non Proprietary Name of the Drug Product	Pimavanserin tablets
Non Proprietary Name of the Drug Substance	Pimavanserin tartrate
Proposed Indication(s) including Intended Patient Population	Psychosis associated with Parkinson’s Disease
Duration of Treatment	Chronic
Maximum Daily Dose	34 mg (two 17 mg tablets)
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification:

- Drug Substance: The Applicant noted that the drug substance is highly soluble and highly permeable, and provided a BCS classification report. The Applicant was advised to submit under their IND an official BCS designation request with the complete supporting data.
- Drug Product: Not established.

2. Biowaivers/Biostudies

- Biowaiver Requests: Not applicable.
- PK studies: The PK studies will be reviewed by the Office of Clinical Pharmacology.
- IVIVC: Not Applicable.

E. Novel Approaches N/A

F. Any Special Product Quality Labeling Recommendations None

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature: Recommend approval from an OPQ perspective pending an acceptable recommendation from facilities.

David J.
Claffey -S



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ou=FDA, ou=People,
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cn=David J. Claffey -S
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Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE

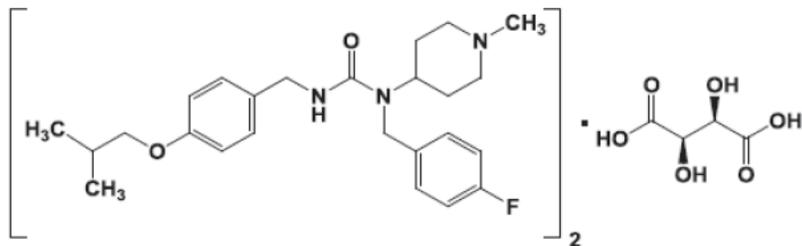
2.3.S.1 General Information

Applicant's Response:

- U.S. Adopted Name (USAN): Pimavanserin tartrate
- CAS Registry number: 706782-28-7 (free base: 706779-91-1)
- Chemical name (IUPAC): Urea, N-[(4-fluorophenyl) methyl]-N-(1-methyl-4-piperidinyl)-N'-[[4-(2-methylpropoxy)phenyl]methyl]-, (2R,3R)-2,3-dihydroxybutanedioate (2:1)
- Company or Laboratory Codes: ACP-103;



- Molecular formula: $(C_{25}H_{34}FN_3O_2)_2 \cdot C_4H_6O_6$, or free base = $C_{25}H_{34}FN_3O_2$
- Molecular weight: 1005.20 (free base = 427.55)
- Molecular Structure:



- Appearance: White to off-white powder
- Melting Point: Melts with decomposition in the range of 167 - 177°C
- pKa: 8.6

- Partition: Log P: 4.67 (calculated)

- BCS classification: Class [redacted] (b) (4)

- Polymorphic form: [redacted] (b) (4)

- Solubility:

Solvent	Pimavanserin tartrate solubility ^a
Water	Freely soluble
[redacted]	

(b) (4)

Reviewer's Assessment:

Adequate information on the main physicochemical properties of the drug substance has been provided.

2.3.S.2 Manufacture

S.2.2 Description of the Manufacturing Process and Controls

1. Is the commercial manufacturing process adequately described and controlled to ensure consistent manufacturing of acceptable drug substance batches?

2. Is there any proposal for online/at line/in line monitoring technologies for routine commercial production that allows for real-time process monitoring and control? If so, is it acceptable?

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2.3.S.6 Container Closure System

13. Is the proposed container closure system(s) for commercial packaging of the drug substance adequate to protect the drug substance from the environment (oxygen, moisture, microorganism, etc.) during the storage?

Applicant's Response:

Pimavanserin tartrate is packaged (b) (4)

The container closure system's suitability and compatibility with the drug substance have been demonstrated by the stability tests.

Packaging Components	Drug Substance Package	Stability Sample Package
(b) (4)		

Reviewer's Assessment:
 The proposed container closure system is adequate for the intended use.

2.3.S.7 Stability

14. What is the proposed retest period for the drug substance? Do the drug substance stability data support the proposed retest period and storage conditions in the commercial container closure system? How does statistical evaluation of the stability data, if any and any observed trends support your proposed retest period?

15. Are the post-approval stability protocols and other stability commitments for the drug substance satisfactory?

Applicant's Response:

Pimavanserin tartrate registration stability batches were manufactured according to the intended commercial manufacturing process at the intended commercial manufacturing site. The summary of the pimavanserin tartrate registration is provided in the table below.

The registration batches were packaged (b) (4) in (b) (4) container closure system proposed for commercial bulk drug substance. The registration stability protocol required testing batches stored at long-term (25°C/60% RH) and accelerated (40°C/75% RH) conditions for appearance, identification, morphology, assay, impurities, (b) (4) microbial limits, and specified microorganisms. The stability data from the three registration batches show that the drug substance is stable for (b) (4) months in the commercial packaging configuration when stored (b) (4)

Based on the stability data from the three registration batches, a retest period of (b) (4) months is proposed for pimavanserin tartrate in the commercial packaging configuration and stored (b) (4). No special precautions for light protection of the drug substance are required.

Table 2.3.S.7-1 Pimavanserin Tartrate Registration Stability Batches

Batch Number	Date of Manufacture	Site of Manufacture	Batch Size	Storage Conditions	Time Point
1157439	Aug 2008	(b) (4)	(b) (4)	25°C/60%RH	60 months
				40°C/75%RH	6 months
1158304	Aug 2008			25°C/60%RH	60 months
				40°C/75%RH	6 months
1158306	Aug 2008			25°C/60%RH	60 months
				40°C/75%RH	6 months

- Post-approval Stability Commitment:

The applicant committed (b) (4) (shown below).

Table 2.3.S.7-2 Post-Approval Stability Protocol

(b) (4)

Reviewer’s Assessment:

The primary stability data support the proposed retest period of (b) (4) months at room temperature as no degradation trends were observed in the long term stability studies (25°/75% RH) or the accelerated condition (40°/60% RH). A retest period of (b) (4) months has been granted at the recommended storage conditions, “room temperature”.

OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

Reviewer’s Assessment and Signature:

From a drug substance perspective, NDA 207318 is recommended for APPROVAL.

Gaetan Ladouceur, DS Reviewer
 New Drug API Division, ONDP
 February 1, 2016

Secondary Review Comments and Concurrence: I concur.

Kasturi Srinivasachar, Ph.D.
 Acting Branch Chief, Division of New Drug API, ONDP
 February 1, 2016

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

2.3.P.1 Description and Composition of the Drug Product

Parameters*	Reference Product	Product under Review
Type	Not applicable	Tablet
Description	Not applicable	Immediate release, white to off-white, round tablet, debossed on one side with “P” and “17” on the other side.
Target Weight	Not applicable	(b) (4)
Dimensions/Size	Not applicable	
Container/Closure Design	Not applicable	40-cc, white round HDPE bottle (b) (4)
Excipients (not in RLD) which require label warning		Not applicable

16. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

Yes, in the following components and composition table, the applicant proposed (b) (4) mg of film-coat (b) (4) per tablet, however, in the initial NDA no data were provided for the batches manufactured using the proposed film-coat (b) (4). All the data that were provided in the NDA for registration/stability batches contained (b) (4) % film-coat.

Components and Composition Proposed for Commercial Drug Product Tablets:

Component	Function	Quality Standard	Quantity Per Tablet	
			mg/Tablet	% w/w (Coated Tablets)
Pimavanserin tartrate	Active ingredient	In-house	20.0 ^a	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
microcrystalline cellulose				
Pregelatinized starch				
Magnesium stearate				
(b) (4)				
Film Coated Tablet				
(b) (4)				
Total for Coated Tablet				(b) (4)

NF = National Formulary; USP = United States Pharmacopoeia; NA = Not applicable

a 20 mg of pimavanserin tartrate salt is equivalent to 17 mg of pimavanserin free base.

Reviewer's Assessment: Acceptable. All the proposed components are commonly used in the tablet dosage formulations. All the components used are of compendial grade (b) (4). However, it should be noted that the film coat is made of (b) (4) excipients (b) (4). It should be noted that the film-coat of the proposed commercial tablet formulation is (b) (4).

(b) (4)

(b) (4) Weight and percentage of each component in the (b) (4) coated tablet were provided. The amounts and percentages of the excipients present in each tablet are (b) (4)

(b) (4) Each tablet contains 20 mg of pimavanserin tartrate salt, which is equivalent to 17 mg of pimavanserin free base.

2.3.P.2 Pharmaceutical Development

17. Does the information described in the pharmaceutical development section support the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product?

No, the proposed product design, dosage form, compatibility, specification, and overall control strategy of the drug product support the drug product tablets containing (b) (4)% film-coating, however, the applicant proposed tablets with (b) (4)% film-coating, therefore, the applicant needs to provide relevant data that support the proposed commercial formulation.

During development, the applicant studied the following:

(b) (4)

21. Is the proposed control strategy for the drug product manufactured at commercial stage acceptable? Is there any residual risk upon implementation of the control strategy at the commercial scale (refer to question #33 of the process section)?

Reviewer's Assessment: Answer to this question is referred to the Process section of the review. From drug product reviewer stand point, the proposed revised control strategy is acceptable.

2.3.P.6 Reference Standards or Materials

22. Are the proposed drug product reference standards acceptable?

The applicant stated that the primary reference standards, including the impurity standards, used in the analysis of pimavanserin tablets are the same as those used for testing pimavanserin tartrate drug substance. Information regarding the reference standards was provided in Section 3.2.S.5 of the NDA.

Reviewer's Assessment: Acceptable but refer to the drug substance section of this review for details.

2.3.P.7 Container Closure System

23. Is the proposed container closure system (describe it briefly with diagrams, if available) adequate to protect the product from the environment (oxygen, moisture) to ensure the strength, purity (extractables/leachables), and performance of the drug product through the proposed expiration dating period?

Yes. The applicant stated that the proposed container closure system complies with USP <661> and USP <671> requirements. LOAs were provided for all appropriate DMFs, which are currently adequate. The applicant also stated that

all of the container closure components used for the primary packaging of drug product (bottle, cap, (b) (4)) are certified to comply with the current federal regulations for contact with food products.

Bottle Configurations

- 1) Trade Product: 60-count in 40 cc, white round high-density polyethylene (HDPE) bottles (b) (4)
- 2) Physician Sample: 14-count in 40 cc, white round HDPE bottles (b) (4)

The applicant provided the following table containing a summary of the description of the packaging components used for the trade product and physician’s sample packaging configurations:

Table 3.2.P.7-1 Description of Packaging Components

Component Description	Manufacturer	Materials of Construction
40 cc, round, wide mouth, white, HDPE bottle	(b) (4)	(b) (4)

HDPE = high-density polyethylene

In the NDA, (b) (4) specifications (b) (4) were provided.

Bottle Diagram:

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Reviewer's Assessment: Acceptable. The applicant proposed commonly used container closure system for the packaging of tablets. HDPE bottles and (b) (4) closures are commonly used for packaging of the tablets of this type. (b) (4)

(b) (4) The stability studies support storage of the tablets in the proposed container and closure system through the proposed expiration dating period.

2.3.P.8 Stability

24. What is the proposed shelf-life for the drug product? Do the product stability studies and data support the proposed shelf life and storage conditions in the commercial container/closure system? Does the statistical evaluation of the stability data and observed trends support the proposed shelf-life?

The proposed shelf-life is (b) (4) months but the applicant provided in the initial submission 18 months of long-term data and later updated with 24 months of long-term data for three NDA registration stability batches. These batches were not exactly same as the proposed commercial tablets (b) (4). These batches were stored in the proposed commercial container closure system. In addition, 36 months of long-term stability data were provided for the supportive batches (not debossed). However, 24 months of expiration dating period (shelf-life) is more appropriate for this drug product (b) (4).

In the NDA, the following table containing the stability batches' information was provided:

Table 3.2.P.8.1-1 Pimavanserin 17 mg Tablets NDA Registration and Primary Stability Batches

Packaged Batch No.	Bulk Batch No.	Drug Substance Batch No.	Batch Size(kg)/ No. of Tablets	Mfg. Site	Package Configuration	Storage Condition	Time Point		
Registration Stability Batches									
3115192	3115360R.	1157439	(b) (4)		60-count bottle	25°C/60% RH	18 months		
3115195					14-count bottle	40°C/75% RH	6 months		
3115193	3115361R.	1158306			60-count bottle	25°C/60% RH	18 months		
3115196					14-count bottle	40°C/75% RH	6 months		
3115194	3115362R.	1158304			60-count bottle	25°C/60% RH	18 months		
3115197					14-count bottle	40°C/75% RH	6 months		
Clinical (Supportive) Stability Batches									
3056538	3055442R.	1046433			(b) (4)		20-count bottle	25°C/60% RH	36 months
3060314	3059846R.	1046433					20-count bottle	40°C/75% RH	6 months
3061783	3061264R.	1046433					20-count bottle	25°C/60% RH	36 months
3065722	3064663R.	1046433					20-count bottle	40°C/75% RH	6 months
3073659	3073650R.	1046433					20-count bottle	25°C/60% RH	36 months
3075678	3075677R.	1046433	20-count bottle	40°C/75% RH			6 months		
3079488	3079486R.	1046433	20-count bottle	25°C/60% RH			36 months		
3085109	3085089R.	1046433	20-count bottle	40°C/75% RH			6 months		
3087969	3080698R.	1046433	20-count bottle	25°C/60% RH			36 months		
3087970	3081256R.	1046433	20-count bottle	25°C/60% RH			36 months		
3102264	3102263R.	1158306	20-count bottle	25°C/60% RH			24 months		
3105692	3105691R.	1158306	20-count bottle	25°C/60% RH			18 months		
3111274	3110903R.	1158306	20-count bottle	25°C/60% RH			12 months		

Are the post-approval stability protocols and other stability commitments for the drug product adequate?

The revised protocol is acceptable. (b) (4)

(b) (4)

Reviewer’s Assessment: Acceptable.

No specific trends were noticed in the stability data provided for the NDA registration batches (b) (4)

(b) (4) Based on the 24 months of long-term data and 6 months of accelerated stability data for the three NDA registration batches (b) (4) and 36 months of long-term data for the supportive batches (b) (4) a 24 months of expiration dating period should be granted for the commercial drug product tablets. The supportive drug product

tablets are not same as the commercial tablets because they were not debossed on either side of the tablet. Photostability study was conducted as according to the ICH conditions on one batch, which showed no significant difference from the control samples, therefore, no special precautions for light protection are necessary. The proposed storage condition of Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59 °F and 86°F) [See USP Controlled Room Temperature] is acceptable. The revised stability commitment [REDACTED] (b) (4) [REDACTED] is [REDACTED] is acceptable.

R.2 Comparability Protocols

25. Is a Comparability Protocol included in the application for post approval changes that might affect drug product quality including sterility assurance? If so, what post-approval changes are anticipated? How will the changes be reported and how will the validation studies be designed to support these changes?

Not applicable.

Reviewer's Assessment: No comparability protocols were provided in the initial NDA submission.

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:

The applicant proposed an immediate release, film-coated tablet containing commonly used excipients. (b) (4)

The proposed drug product specification is expected to assure the identity, assay, quality, and purity of the tablets. (b) (4)

The proposed dissolution method's acceptance criteria are acceptable to the ONDP Biopharm reviewer. The proposed analytical methods and their validation reports are acceptable. The tablets are packaged in commonly used HDPE bottles (b) (4)

Stability data did not indicate any unusual trends. The applicant committed to conduct the (b) (4) stability study (b) (4)

From the drug product review stand point, the NDA is recommended for approval.

Rao V. Kambhampati, Ph.D.
Senior Chemist, OPQ/ONDP/DNDP I/NDPB I

Secondary Review Comments and Concurrence: I concur with Dr. Kambhampati's assessment.

Wendy I. Wilson-Lee, Ph.D.
Branch Chief (Acting), ONDP/DNDP 1/Branch 1
02/19/2016

ASSESSMENT OF THE PROCESS

2.3.P DRUG PRODUCT

2.3.P.2.3 Manufacturing Process Development

26. Does the information described in the pharmaceutical development section support the proposed drug product manufacturing process?

Applicant's Response:

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ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

S.2.1 Manufacturer(s)

35. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

TABLE 1: DS Manufacturing and Testing Sites

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
(b) (4)				NME	Acceptable based on file review.
				NME	Acceptable based on file review.

Reviewer's Assessment:								
Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
(b) (4)								



(b) (4)

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

P.3.1 Manufacturer(s)

36. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

TABLE 2: DP Manufacturing and Testing Sites

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
(b) (4)				NME	Due to additional cGMP flags, PAI request sent to domestic district office. Final recommendation pending outcome of PAI.

Reviewer's Assessment:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
(b) (4)								

(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES**Reviewer's Assessment and Signature:**

The overall manufacturing inspection recommendation is pending the results of the upcoming pre-approval inspection (b) (4)

Steven Hertz
Consumer Safety Officer
OPF Division of Inspectional Assessment, Branch 1
1/27/16

Secondary Review Comments and Concurrence:

I concur with the facility reviewer's recommendation.

Zhihao Peter Qiu, Ph.D., OPF/DIA, 1/27/2016

APPEARS THIS WAY ON
ORIGINAL

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

37. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Yes. The proposed in vitro dissolution test is adequate for quality control. The selection of the dissolution conditions (e.g., apparatus, medium, rotation speed) was adequately justified. The method was validated. The proposed acceptance criterion is supported by the dissolution data for the phase 3 clinical batches and the registration stability batches.

The review is focused on the following aspects pertaining to in vitro dissolution test:

- Solubility of the drug substance, pimavanserin tartrate
- Drug product formulation
- Dissolution method and method development
- Proposed dissolution acceptance criteria

➤ Solubility of Pimavanserin Tartrate:

The drug substance, Pimavanserin Tartrate, has a pKa of 8.6±0.1. Pimavanserin is freely soluble (b) (4) as summarized in Table 37-1.

Table 37-1. Solubility of Pimavanserin Tartrate

	Solvent	Pimavanserin tartrate solubility ^a
Solubility	Water	Freely soluble (b) (4)
	(b) (4)	

The Applicant further investigated the solubility of pimavanserin at pH (b) (4)

(b) (4)

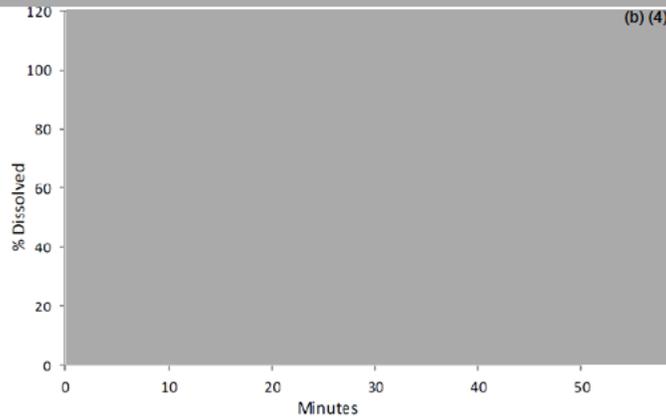


Figure 37-1. Effect of pH (b) (4) on the dissolution profiles

➤ **Drug Product Formulation:**

Pimavanserin 17 mg tablets are formulated as immediate release tablets intended for oral administration. Table 37-2 lists the components of the pimavanserin tablet, their functions, quality standards and quantities per tablet.

Table 37-2. Composition of Pimavanserin Tablets, 17 mg

Component	Function	Quality Standard	Quantity Per Tablet	
			mg/Tablet	% w/w (Coated Tablets)
Pimavanserin tartrate	Active ingredient	In-house	20.0 ^a	(b) (4)
(b) (4)				(b) (4)
microcrystalline cellulose				(b) (4)
Pregelatinized starch				(b) (4)
Magnesium stearate				(b) (4)
(b) (4)				(b) (4)
Film Coated Tablet				(b) (4)
(b) (4)				(b) (4)
Total for Coated Tablet				(b) (4)

NF = National Formulary; USP = United States Pharmacopoeia; NA = Not applicable

a 20 mg of pimavanserin tartrate salt is equivalent to 17 mg of pimavanserin free base.

(b) (4)

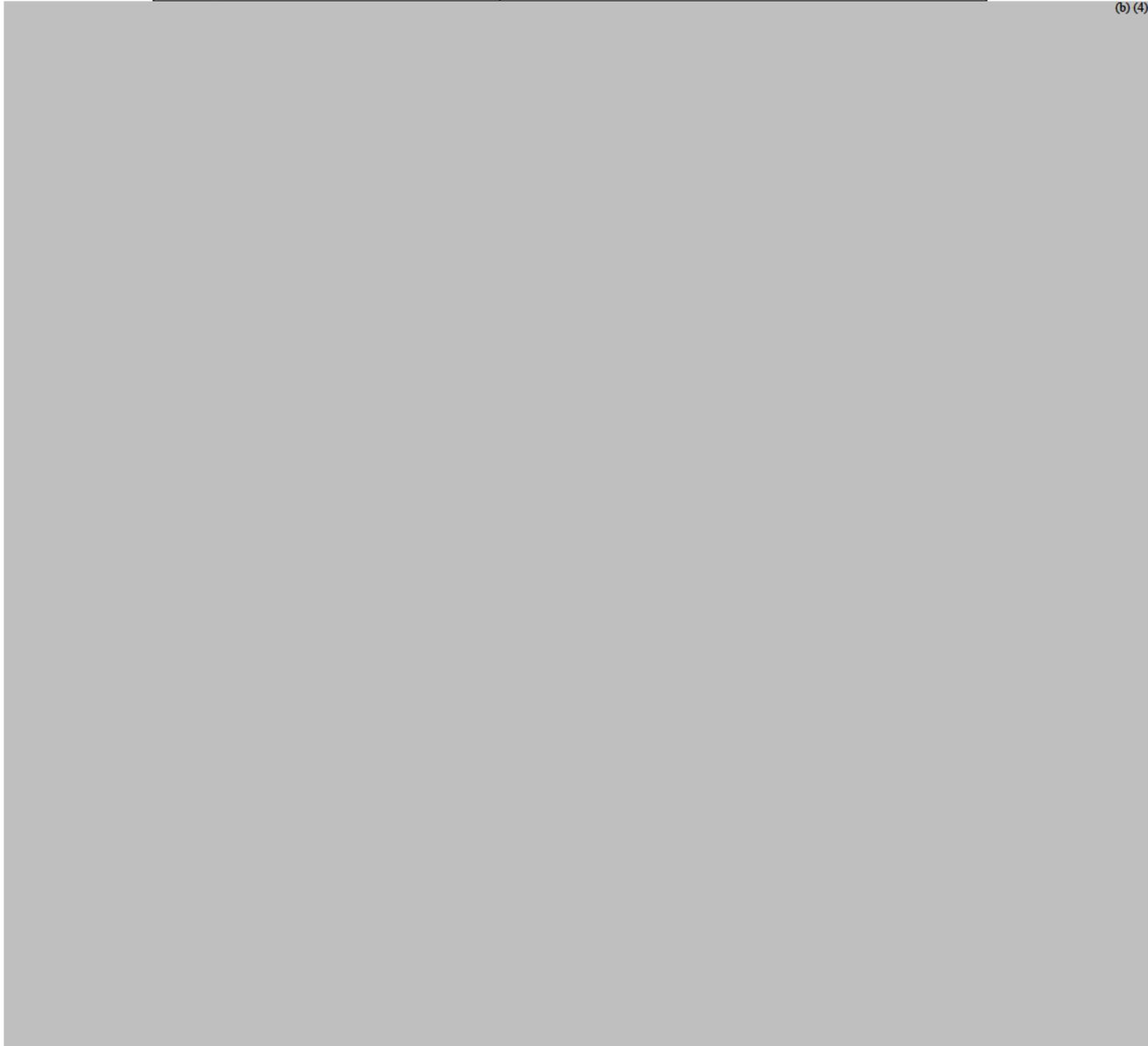
➤ **Dissolution Method and Method Development:**

The proposed dissolution method is summarized in Table 37-3:

Table 37-3. Proposed Dissolution Method for Pimavanserin Tablets, 17 mg

Apparatus	USP Apparatus 1 (basket)
Rotation Speed	100 rpm
Dissolution Medium	0.1 N HCl
Media volume	900 mL
Test Temperature	37.0±0.5 °C
Analytcs	HPLC

(b) (4)



➤ **Dissolution Acceptance Criterion**

Based on the dissolution profiles observed and considering that pimavanserin 17 mg tablets are an immediate release dosage form of a highly soluble drug substance, a single-point dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in 15 minutes using USP <711> Apparatus 1 (baskets) at 100 RPM in 0.1 N HCl is proposed for commercial batches. The dissolution data of the phase 3 clinical and registration stability batches are summarized in the tables below. All batches tested met the proposed acceptance criterion at S1, which supports the acceptance criterion of “ $Q = \frac{(b)}{(4)}\%$ in 15 min”.

Table 37-4 Dissolution results for phase 3 clinical stability batches

Packaged Batch No.	Storage Condition	Packaging Configuration	Sample Pull	Mean (%)	Min (%)	Max (%)
3087969	39-month 25°C/60% R/H					
3087970	39-month 25°C/60% R/H					
3102264	23-month 25°C/60% R/H					
3105692	19-month 25°C/60% R/H					
3111274	14-month 25°C/60% R/H					

Mean = Average $\frac{(b)}{(4)}$ tablets; Min = Minimum; Max = Maximum

Table 37-5 Dissolution results for registration stability batches stored at 25 °C/60% RH

Packaged Batch No.	(b) (4)	Bottle Count	Date of Manufacture	Test Interval (Months)					
				T=0	3	6	9	12	18
3115192			Sep-2013						
3115195			Sep-2013						
3115193			Sep-2013						
3115196			Sep-2013						
3115194			Sep-2013						
3115197			Sep-2013						

Table 37-6 Dissolution results for registration stability batches stored at 40 °C/75% RH

Packaged Batch No.	(b) (4)	Bottle Count	Date of Manufacture	Test Interval (Months)			
				T=0	1	3	6
3115192			Sep-2013				
3115195			Sep-2013				
3115193			Sep-2013				
3115196			Sep-2013				
3115194			Sep-2013				
3115197			Sep-2013				

Reviewer's Assessment:

- The drug product, pimavanserin tablets 17 mg, is an immediate release product. The drug product is indicated for the treatment of Parkinson's disease psychosis (PDP). The recommended dosing regimen is to take two 17 mg tablets once daily.
- The drug substance is highly soluble and the Applicant claims that this drug can be classified as BCS-Class (b) (4) drug and a BCS classification report was included in section 3.2.P.2. However, an official request for BCS assignment was not included in the NDA and therefore this information was not reviewed under the NDA. The following comment was sent to the Applicant in the 74-day letter on Nov 13, 2015:

We acknowledge the receipt of the BCS classification report for pimavanserin tartrate contained in section 3.2.P.2. However, we note that the BCS classification is unlikely to hold up the evaluation of your Application as there is no BCS-based biowaiver request in the NDA. Therefore, we recommend that you submit an official request for BCS classification separately to the supporting IND Application.

It is noted that the BCS report has to be evaluated by the Biopharmaceutics Reviewer, as well as by the FDA's BCS committee. The review will be conducted when the BCS-Class (b) (4) designation request is received under the IND application.

- The proposed in vitro dissolution test is adequate for quality control. The selection of the dissolution conditions (e.g., apparatus, medium, rotation speed) were adequately justified. The method was adequately validated.
- The dissolution profiles provided for the phase 3 clinical batch and the registration stability batch appear to suggest that the phase 3 clinical batch (b) (4)

Nevertheless this difference is not significant from the clinical/quality perspective and both batches met the criterion of "Q=(b) (4)% in 15 minutes".

- The discriminating ability of the dissolution method could not be demonstrated, (b) (4) This is acceptable, considering the product is for immediate release (b) (4)
- The proposed acceptance criterion is supported by the dissolution data for the phase 3 clinical batches and the registration stability batches.
- The dissolution method and acceptance criterion are summarized below:

Apparatus	USP Apparatus 1 (basket)
Rotation Speed	100 rpm
Dissolution Medium	0.1 N HCl
Media volume	900 mL
Test Temperature	37.0±0.5 °C
Analytcs	HPLC
Acceptance criterion	Q= ^{(b) (4)} % in 15 min

38. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

No formulation bridging is needed. (b) (4)

Table 38-1. Composition of phase 3 clinical and intended commercial formulations of pimavanserin 17mg tablets

Component	Quantity	
	Phase 3 Formulation	Intended Commercial Formulation
	mg/Tablet	mg/Tablet
Pimavanserin tartrate	20.0 ^a	20.0 ^a
^{(b) (4)} microcrystalline cellulose, NF	(b) (4)	
Pregelatinized starch, NF		
Magnesium stearate, ^{(b) (4)} NF		
Total		
Film Coat		
(b) (4)		

NA = Not applicable.

a 20 mg of pimavanserin tartrate salt is equivalent to 17 mg of pimavanserin free base.

(b) (4)

Reviewer's Assessment:

- (b) (4)

(b) (4)

Both the phase 3 clinical batches and the registration stability batches met the proposed dissolution acceptance criterion ($Q = \frac{(b)}{(4)}\%$ in 15 minutes) at S1. The data support the similarity between these two formulations.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

From a Biopharmaceutics perspective, NDA 207318 for Pimavanserin Tartrate tablet (17 mg) is recommended for **APPROVAL**.

Jing Li, Ph.D., 1/15/2016

Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Review Comments and Concurrence:

I concur with Dr. Jing Li's evaluation and approval recommendation for NDA 207318 for Pimavanserin Tartrate tablet (17 mg).

Angelica Dorantes, Ph.D., 1/26/2016

Acting Biopharmaceutics Branch Chief
Division of Biopharmaceutics-Branch 1
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

39. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant’s Response:

Microbiology testing is proposed as part of the drug product release specification:

Microbiology	Total aerobic microbial count	NMT (b) (4) cfu/g	USP <61> and <62>
	Total yeasts and molds count	NMT cfu/g	
	<i>Escherichia coli</i>	Absent	

Reviewer’s Assessment: Acceptable.

The drug product is an immediate release tablet for oral administration. The applicant demonstrated that the drug product (b) (4) is considered highly unlikely to support microbial growth. The proposed acceptance criteria comply with USP <1111>.

2.3.P.7 Container/Closure System

40. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant’s Response:

The primary package components are:

- Trade Product: 60-count in 40 cc, white round high-density polyethylene (HDPE) bottles (b) (4)
- Physician Sample: 14-count in 40 cc, white round HDPE bottles (b) (4)

The proposed container closure system complies with USP <661> and USP <671> requirements.

Reviewer's Assessment: Acceptable.

The applicant proposed commonly used container closure system for the packaging of tablets. HDPE bottles and (b) (4) closures are commonly used for packaging of the tablets of this type. The applicant demonstrated that the primary package combination can be considered as tight containers through USP <671> moisture vapor transmission tests.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

41. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk (b) (4) contamination (b) (4)?

Applicant's Response:

No excipient from human or animal origin is used in the manufacture of the drug product.

Reviewer's Assessment: Acceptable.

There is no excipient from human or animal origin used in the drug product manufacturing. It is unlikely that the starting materials or solvents used in the drug substance manufacturing are from human or animal sources. (b) (4)

42. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: NA

Reviewer's Assessment: Acceptable.

See assessment for item 41.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Acceptable

Primary Reviewer:

Xuhong Li
Branch I/Division I,
Office of Process & Facility (OPF)

Secondary Review Comments and Concurrence:

I concur.

Akm Khairuzzaman, Ph.D.
Acting Branch Chief,
Branch I/Division I,
Office of Process & Facility (OPF)

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

43. Is the applicant's claim for categorical exclusion acceptable?
Yes. The applicant stated that pursuant to 21 CFR 25.15(d) and 21 CFR 25.31(b), the company affirms that to the best of their knowledge, no extraordinary circumstances exist (as defined by 21 CFR 25.21) that indicate approval of this application may significantly affect the quality of the human environment.
44. Is the applicant's Environmental Assessment adequate for approval of the application?
Yes. The calculated EIC information is summarized in the following table:

Table 1.12.14-1 Calculation of Expected Introduction Concentration (EIC)

EIC – Aquatic (ppb) = A × B × C × D				
where	A = kg/year produced for direct use (as active moiety)			
	B = 1/liters per day entering Publicly Owned Treatment Works (POTWs)			
	C = year/365 days			
	D = 10 ⁹ µg/kg (conversion factor)			
(b) (4)	millions of gallons per day (mgd) entering POTWs =		(b) (4) liters per day ^a	
EIC	=	(b) (4)		
	=	(u) (4) ppb		
Drug Product	# of tablets/year^b	API (mg/tablet)^c	API (kg/year)	EIC (ppb)
Pimavanserin Tablets, 17 mg	(b) (4)	17 mg		(b) (4)

- a Source: EPA Clean Watersheds Needs Survey 2008 Report to Congress (EPA-832-R-10-002)
- b Based on the highest forecasted one year volume over the next five years
- c Calculated as pimavanserin free base (active moiety)

Reviewer’s Assessment: Acceptable. The calculated maximum EIC is (b) (4) ppb, (b) (4). The calculation was conducted as according to the FDA Guidance (1998).

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer’s Assessment and Signature: Categorical exclusion from the requirement to prepare an EA for the drug product in this NDA is granted on the basis of the data submitted in the NDA.

Rao V. Kambhampati, Ph.D.
Senior Chemist, ONDP/DNDP I/NDPB I

Secondary Review Comments and Concurrence: : I concur with Dr. Kambhampati’s assessment.

Wendy I. Wilson-Lee, Ph.D.
Branch Chief (Acting), ONDP/DNDP 1/Branch 1
02/19/2016

**I. Review of Common Technical Document-Quality (Ctd-Q) Module 1
Labeling & Package Insert**

1. Package Insert

(a) “Highlights” Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Nuplazid TM (pimavanserin)	Acceptable
Dosage form, route of administration	Tablets, Oral	Acceptable
Controlled drug substance symbol (if applicable)	Not applicable	Not applicable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Round, white to off-white, immediate-release, film-coated tablet debossed with “P” one side and “17” on the other side. Each tablet contains 20 mg of pimavanserin tartrate, which is equivalent to 17 mg of pimavanserin free base.	Acceptable

Conclusion: Acceptable. The above described information will be reflected in the final package insert.

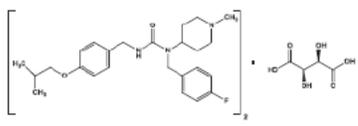
(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

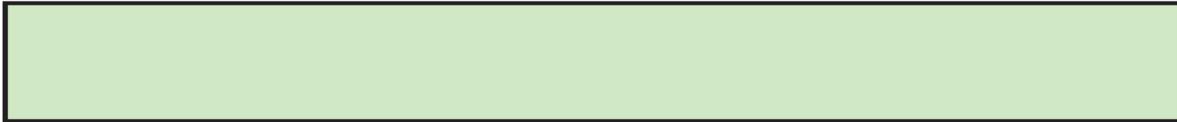
Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	Oral tablet	Acceptable
Strengths: in metric system	17 mg (present as tartrate salt 20 mg)	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Round, white to off-white, immediate-release, film-coated tablet debossed with “P” on one side and “17” on the other side. ^(b) ₍₄₎	Acceptable.

Conclusion: Acceptable. The above described information will be reflected in the final package insert.

#11: Description (21CFR 201.57(c)(12))

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Nuplazid™ (pimavanserin)	Acceptable
Dosage form and route of administration	Tablet, Oral	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	17 mg of pimavanserin free base per tablet, which is present in the form of its tartrate salt, 20 mg.	Acceptable.
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Pregelatinized starch, magnesium stearate, microcrystalline cellulose, and white film-coat, which is made of hypromellose, talc, titanium dioxide, polyethylene glycol, and saccharin sodium.	Acceptable
Statement of being sterile (if applicable)	Not applicable	Acceptable
Pharmacological/ therapeutic class	Serotonin inverse agonist	Acceptable
Chemical name, structural formula, molecular weight	<p>Urea, <i>N</i>-[(4-fluorophenyl)methyl]-<i>N</i>-(1-methyl-4-piperidinyl)-<i>N'</i>-[[[4-(2-methylpropoxy)phenyl]methyl]-<i>(2R,3R)</i>-2,3-dihydroxybutanedioate (2:1)</p>  <p>(C₂₅H₃₄FN₃O₂)₂·C₄H₆O₆ (pimavanserin tartrate salt); M.W. = 1005.20; C₂₅H₃₄FN₃O₂ (pimavanserin free base), M.W. = 427.55</p>	Acceptable
If radioactive, statement of important nuclear characteristics.	Not applicable	
Other important chemical or physical properties (such as pKa, solubility, or pH)	<p>Pimavanserin tartrate is freely soluble in water (b) (4)</p> <p>It has a pKa of 8.6 and pH of 5 to 6 (b) (4)</p>	Acceptable.

Conclusion: Acceptable. The above described information will be reflected in the final package insert.



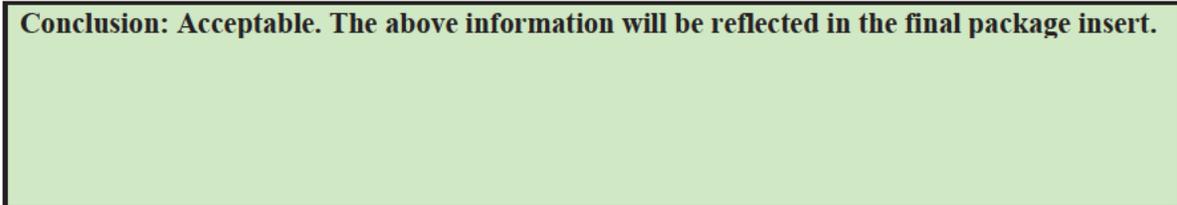
#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	17 mg Tablet	Acceptable
Available units (e.g., bottles of 100 tablets)	Bottles of 60 tablets	Acceptable.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	White to off-white, round tablet debossed with "P" on one side and "17" on the reverse side.	Acceptable.
Special handling (e.g., protect from light, do not freeze)	Not applicable	
Storage conditions	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]	Acceptable.

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributed by: ACADIA Pharmaceuticals Inc. San Diego, CA 92130 USA	Acceptable.

Conclusion: Acceptable. The above information will be reflected in the final package insert.



2. Container and Carton Labeling

1) Immediate Container Label

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Nuplazid™ (pimavanserin)	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	17 mg	Acceptable
Route of administration 21.CFR 201.100(b)(3))	Oral	Acceptable
Net contents* (21 CFR 201.51(a))	60 Tablets (commercial) and 14 Tablets (physician sample)	Acceptable
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not included because dosage form is an oral tablet	Acceptable
Lot number per 21 CFR 201.18	Proposed for commercial product	Acceptable
Expiration date per 21 CFR 201.17	Proposed for commercial product	Acceptable
“Rx only” statement per 21 CFR 201.100(b)(1)	Rx Only	Acceptable
Storage (not required)	Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature}	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 63090-170-60	Acceptable
Bar Code per 21 CFR 201.25(c)(2)***	Proposed for commercial product	Acceptable.
Name of manufacturer/distributor (21 CFR 201.1)	Distributed by: Acadia Pharmaceuticals Inc., San Diego, CA 92130-3331	Acceptable.
Others	Equivalency Statement: Each tablet contains 17 mg pimavanserin (as pimavanserin tartrate salt 20 mg).	Acceptable.

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s

sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

**Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Acceptable. The above information will be reflected in the final container labels.

2) Carton Labeling

Not applicable

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))		
Net contents (21 CFR 201.51(a))		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]		
Sterility Information (if applicable)		
“Rx only” statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		
Storage Conditions		
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		
Bar Code per 21 CFR 201.25(c)(2)**		
Name of manufacturer/distributor		
“See package insert for dosage information” (21 CFR 201.55)		
“Keep out of reach of children” (optional for Rx, required for OTC)		
Route of Administration (not		

required for oral, 21 CFR 201.100(d)(1) and (d)(2))		
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Conclusion: Not applicable. Applicant did not propose to package the drug product bottles in cartons, therefore, no carton labels were provided.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer’s Assessment and Signature: The final revised package insert and bottle labels will reflect all the above described information, which is acceptable.

Rao V. Kambhampati, Ph.D.
Senior Chemist, OPQ/ONDP/DNDP I/NDPB I

Secondary Review Comments and Concurrence: : I concur with Dr. Kambhampati’s assessment.

Wendy I. Wilson-Lee, Ph.D.
Branch Chief (Acting), ONDP/DNDP 1/Branch 1
02/19/2016

II. List of Deficiencies To Be Communicated

None

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments

		H, M, or L	N	Acceptable or Not Acceptable	
Assay/stability	Drug substance appears relatively stable.	(b) (4)	Release and stability tests	Acceptable	
Physical stability of Tablet Hardness, Friability	Typical IR tablet		In-process, release and stability test	Acceptable	
Content Uniformity	Tested at release. (b) (4) % (b) (4)		Process development studies, in-process controls on drug substance (b) (4)	Acceptable	(b) (4)
Physical stability (solid state)			Drug substance and drug product release testing, including polymorph test.	Acceptable	
Microbial Limits			Release test. (b) (4)	Acceptable	
Dissolution			Dissolution test found adequate	Acceptable	

David J.
Claffey -S

Digitally signed by David J. Claffey -S
 DN: c=US, o=U.S. Government,
 ou=HHS, ou=FDA, ou=People,
 0.9.2342.19200300.100.1.1=1300225
 565, cn=David J. Claffey -S
 Date: 2016.02.20 19:58:59 -05'00'