CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-192

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: 9 January 2009

FROM: Donghao (Robert) Lu, Ph.D.
Division of Pre-Marketing Assessment - I
Office of New Drug Quality Assessment

TO: File NDA 22-192

SUBJECT: Amendments to Pending Application (Nov. 5 and Nov. 19, 2008)

RECOMMENDATION: The drug product Iloperidone immediate-release tablets, 1, 2, 4, 6, 8, 10, and 12 mg, is recommended as APPROVAL from a CMC perspective.

ACTION: These two CMC comments have been sent to the sponsor:

(1) The text "Protect from light and moisture" should be displayed on the draft bottle labels, carton labels, blister card labels and blister card carton labels.

(2) In the labeling text (package insert), the statement [redacted] ' should be changed to "Each round, uncoated tablet contains 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, or 12 mg of iloperidone".

b(4)

REVIEW NOTE:

Vanda submitted a Complete Response on November 5, 2008 to the Agency's action letter (July 25, 2008) and a request for reconsideration of proprietary name for iloperidone on November 19, 2008. For the original NDA 22-192, the drug product Iloperidone immediate-release tablets, 1, 2, 4, 6, 8, 10, and 12 mg, was recommended as APPROVAL from a CMC perspective. The amendments provided additional information on labeling, which has some modifications and is reviewed as shown below.

__4__ Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

__X__ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Donghao Lu
1/12/2009 03:27:42 PM
CHEMIST

Ramesh Sood
1/12/2009 03:39:44 PM
CHEMIST

Fanapta™
(iloperidone)
Tablets

NDA 22-192

Division Director Review
Chemistry, Manufacturing, and Controls

Applicant: Vanda Pharmaceuticals, Inc.
9605 Medical Center Drive, Suite 300
Rockville, MD 20850

Indication: Treatment of schizophrenia

Presentation: Immediate release, white, round, uncoated tablets are available in seven strengths (1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg) debossed with Vanda logo on one side and tablet strength on the other side.

Tablets of all strengths are packaged in 60 count, child-resistant, [redacted] bottles, wit[redacted], and in 2 count aluminum foil blisters on [redacted] for dose titration. Except for 1 mg and 2 mg strengths, tablets are provided in [redacted]. b(4)

EER Status: Acceptable 11-JAN-2008

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(a)
Methods Validation – Revalidation by Agency not requested.

Original Submission: 27-SEP-2007

Post-Approval Agreements: None

Drug Substance:

Iloperidone is a psychotropic agent belonging to the chemical class of piperidinylbenzisoxazole derivatives. The drug substance, iloperidone , is a small, synthetic, New Molecular Entity (NME) with an empirical formula of $C_{24}H_{27}N_2O_4F$ and a molecular weight of 426.5. Known chemically as 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3- yl)-1-piperidinyl]propoxy]-3-methoxyphenyl] ethanone, it forms white to off-white, crystals with a melting range of 120.0-125.0°C. Iloperidone is practically insoluble in water (0.012 mg/mL), sparingly soluble in basic aqueous solutions, slightly soluble in acidic aqueous solutions, and freely soluble in chloroform, ethanol,

methanol, and acetonitrile. The drug substance displays a [redacted] b(4)

The bulk drug substance is manufactured by [redacted] b(4)

[redacted] Comprehensive information for all the impurities at the starting material level, at the intermediate level and at the final [redacted] level was presented.

The structure of iloperidone was elucidated using several analytical and spectrophotometric techniques, including [redacted] b(4)

The proposed release specification for iloperidone includes [redacted] b(4)

The proposed regulatory methods are either [redacted] their intended purpose. The primary reference standard for drug substance, manufactured by [redacted] has been characterized by the proposed regulatory methods as well as additional methods. The impurity and degradation profiles have been investigated. Reference standards for known impurities and in-process intermediates have been synthesized and fully characterized.

The stability data for [redacted] commercial batches support a [redacted] retest period for the bulk drug substance stored inside [redacted] at controlled room temperature, 25°C /60%RH, [redacted] b(4)

Conclusion: Drug substance is acceptable.

Drug Product:

Fanapta (iloperidone) tablets are uncoated, immediate release tablets, available in seven strengths (1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg). Tablets for all strengths are white, round, flat, beveled-edge tablets with the tablet strength debossed on the one side and the Vanda company logo debossed on the other side. The tablet diameters are different for each strength, except for the 2 and 4 mg strengths which have the same diameter. Iloperidone tablets are packed in [redacted] b(4)

The drug product is manufactured beginning [redacted] Adequate information on the drug product manufacture has been provided. b(4)

The composition of the 1 mg strength, round tablet is iloperidone (1.00 mg), lactose monohydrate NF ([redacted]), microcrystalline cellulose NF [redacted] hypromellose USP [redacted] crospovidone NF ([redacted]), colloidal silicon dioxide NF [redacted] nagnesium stearate NF ([redacted]) to give a tablet weight of [redacted] and diameter of [redacted] Four [redacted] (1 mg; 2 mg; 4 or 8 mg; 6, 10, or 12 mg) use the same excipients to give tablets from 2 mg strength ([redacted] diameter) to 12 mg strength ([redacted] diameter). b(4)

The release specification for drug product includes: [redacted] b(4)

The stability data support expiration dating of 36 months for all strengths of drug product stored at controlled room temperature conditions [25° C (77° F); excursion permitted to 15-30° C (59-86° F)], and packaged in [redacted] bottles and in blister packages, protected from light and moisture. b(4)

Conclusion: Drug product is acceptable.

Additional Items:

- The applicant agreed to continue the primary stability studies on the [redacted] commercial scale lots of each strength to firmly establish the proposed shelf life.
- The sponsor agreed to placing at least [redacted] commercial production [redacted] the drug product, for each [redacted] in each package configuration, per year following the approved stability protocol. b(4)
- All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.
- The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug product.

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval,** pending agreement on product labeling.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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

/s/

Blair Fraser
6/24/2008 05:38:38 AM
CHEMIST

NDA 22-192

(Review #2)

Iloperidone Tablets
1, 2, 4, 6, 8, 10 and 12 mg

Vanda Pharmaceuticals Inc.

Division of Psychiatry Drug Products

Donghao (Robert) Lu, Ph.D.
Division I of Pre-Marketing Assessment
Office of New Drug Quality Assessment

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 3

The Executive Summary 7

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

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

II. Summary of Chemistry Assessments 7

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

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

C. Basis for Approvability or Not-Approval Recommendation 8

III. Administrative 9

A. Reviewer's Signature 9

B. Endorsement Block 9

C. CC Block 9

Chemistry Assessment 10

Review Of Additional CMC Information From Applicant 10-16

Chemistry Review Data Sheet

1. NDA 22-192
2. REVIEW NUMBER: 2
3. REVIEW DATE: 20 JUNE 2008
4. REVIEWER: Donghao (Robert) Lu, Ph.D.
5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE
NDA 22-192	27-SEPT-07
NDA 22-192 (Amendment 005, stability)	17-MAR-07
NDA 22-192 (Amendment 006, labeling)	18-APR-07
NDA 22-192 (Amendment 007, CMC response)	25-APR-07

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 22-192 (Amendment 009, CMC response)	16-MAY-08
NDA 22-192 (Amendment 010, CMC response)	13-JUNE-08
NDA 22-192 (Amendment 0011, CMC response)	18-JUNE-08

7. NAME & ADDRESS OF APPLICANT:

NAME:	Vanda Pharmaceuticals Inc.
ADDRESS:	9605 Medical Center Drive, Suite 300 Rockville, MD 20850
REPRESENTATIVE:	Paolo Baroldi, M.D., Ph.D., Chief Medical Officer
TELEPHONE:	240-599-4500

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	**DMETS did not approve the names**
NON-PROPRIETARY NAME (USAN)	**Iloperidone**
CODE NAME/NUMBER (ONDC ONLY)	**HP 873 (Hoechst-Roussel), P88 8736 (Hoechst-Roussel), ILO522 (Novartis) ILO522-NXA (Novartis), VYV-683 (Vanda),**
CHEMISTRY TYPE / SUBMISSION PRIORITY	**1S**

b(4)

9. LEGAL BASIS FOR SUBMISSION: 505(b)1

10. PHARMACOL. CATEGORY: Antagonist at selected dopaminergic, serotoninergic, and adrenergic receptors

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 1, 2, 4, 6, 8, 10 and 12 mg

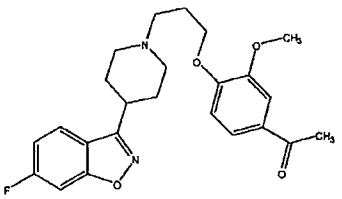
13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: _x_ R_x ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed
___x___Not a SPOTS product

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

Name (USAN, INN): Iloperidone
Name (CAS): 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone
Other Name: 1-[4-[3-[4-(6-fluorobenzo[d]isoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone
(CAS) Registry Num: 133454-47-4
Structural Formula:



Mol. Formula: $C_{24}H_{27}N_2O_4F$
Mol. Wt.: 426.5

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLET
				4	N/A	
				4	N/A	
				4	N/A	
				4	N/A	
				4	N/A	
				4	N/A	

b(4)

Note: DMFs of b(4)

– see CMC Review MaPP.

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A: There is enough data in the application, therefore the DMF did not need to be reviewed.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	11-JAN-08	Shawnte Adams
Methods Validation	No validation request	25-FEB-08	Donghao Lu, Ph.D.
ODS DMETS	Not acceptable	5-JUNE-08	Letter from T. Laughren
EA	Acceptable	11-FEB-08	Donghao Lu, Ph.D.
Micro Consultation	N/A		

APPEARS THIS WAY ON ORIGINAL

The Chemistry Review for NDA 22-192

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product Iloperidone immediate-release tablets, 1, 2, 4, 6, 8, 10, and 12 mg, is recommended as APPROVAL from a CMC perspective.

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

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substance is iloperidone. The chemical name is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone. It has a molecular formula of $C_{24}H_{27}N_2O_4F$ and its molecular weight is 426.5.

Data from the studies of elemental analysis, UV, IR, NMR and MS demonstrated that the structure was adequately defined. ——— appear adequate for the manufacturing of the iloperidone drug substance. b(4)

The impurities detected during the ——— development of the drug substance were evaluated. Analytical methods were developed for the control of the impurities listed in the submission. Comprehensive information for all the impurities at the starting material level, at the intermediate level and at the final ——— level were adequately presented. b(4)

Iloperidone was subjected to heat, heat and moisture, light, and chemical stresses. The drug substance was physically and chemically stable based on evaluation of the testing data. The drug substance has a retest period of ——— b(4)

2. Drug Product

The drug product is Iloperidone immediate-release tablets, 1, 2, 4, 6, 8, 10, and 12 mg. It is intended for oral administration.

The tablets contain 1, 2, 4, 6, 8, 10, and 12 mg iloperidone, respectively. All strengths are white, round, flat, beveled-edge tablets with the tablet strength debossed on the upper face (e.g., "8" for the 8 mg strength) and the Vanda (Vanda Pharmaceuticals Inc.) company logo debossed on the lower face. The tablet diameters are different for each strength except for the ——— g strengths. Iloperidone tablets are packed in ——— b(4)

placed inside dose titration/maintenance cards.

Inactive ingredients consist of lactose monohydrate, microcrystalline cellulose, hydroxypropyl methylcellulose, crospovidone, magnesium stearate, colloidal silicon dioxide. The manufacturing process for iloperidone tablets consists of ——— b(4)

It is noted that DMETS did not recommend the approval of Fiapta or Fanapta as the drug product name (per NDA Letter of June 5, 2008).

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

Iloperidone tablet drug products contain antagonist at selected dopaminergic, serotoninergic, and adrenergic receptors and are indicated for the treatment of schizophrenia.

The recommended target dosage of iloperidone tablets is 12 mg/day administered BID during the acute phase. The recommended titration schedule to target dose is 1, 2, 4, and 6 mg BID on days 1, 2, 3, and 4 respectively. After reaching the target 12 mg/day dose, titration to the maximum daily dose of 12 mg BID should occur over a 3-day period. During the maintenance phase, iloperidone can be administered at a target dose of ——— . Iloperidone can be administered without regard to meals. The products should be stored at controlled room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°- 86°F). The products should be protected from light and moisture. The products have an expiration period (shelf life) of 36 months. b(4)

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Vanda has submitted sufficient and appropriate information to support the approval of the drug product.

III. Administrative

A. Reviewer's Signature

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ramesh Sood, Ph.D.

C. CC Block

7 pages of CCI/TS (b4) was withheld after this page.

CMC_#2_7 pgs.pdf

__7__ Page(s) Withheld

__X__ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Donghao Lu
6/23/2008 10:38:15 AM
CHEMIST

Ramesh Sood
6/23/2008 10:49:06 AM
CHEMIST

NDA 22-192

FANAPTA (Iloperidone)
Tablets
1, 2, 4, 6, 8, 10 and 12 mg

Vanda Pharmaceuticals Inc.

Division of Psychiatry Drug Products

Donghao (Robert) Lu, Ph.D.
Division I of Pre-Marketing Assessment
Office of New Drug Quality Assessment

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 3

The Executive Summary 7

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

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

II. Summary of Chemistry Assessments 7

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

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

C. Basis for Approvability or Not-Approval Recommendation 8

III. Administrative 9

A. Reviewer's Signature 9

B. Endorsement Block 9

C. CC Block 9

Chemistry Assessment 10

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

S. DRUG SUBSTANCE 10

P. DRUG PRODUCT 48

A. APPENDICES 87

R. REGIONAL INFORMATION 87

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 90

A. Labeling & Package Insert 90

B. Environmental Assessment Or Claim Of Categorical Exclusion 94

III. Establishment Evaluation Report 94

IV. List Of Deficiencies And Responses 97

Chemistry Review Data Sheet

1. NDA 22-192
2. REVIEW NUMBER: 1
3. REVIEW DATE: 29 FEBRUARY 2008
4. REVIEWER: Donghao (Robert) Lu, Ph.D.
5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 22-192	**27-SEPT-07**
NDA 22-192 (Amendment 005, stability)	**17-MAR-07**
NDA 22-192 (Amendment 006, labeling)	**18-APR-07**
NDA 22-192 (Amendment 007, CMC response)	**25-APR-07**

7. NAME & ADDRESS OF APPLICANT:

NAME:	**Vanda Pharmaceuticals Inc.**
ADDRESS:	**9605 Medical Center Drive, Suite 300 Rockville, MD 20850**
REPRESENTATIVE:	**Paolo Baroldi, M.D., Ph.D., Chief Medical Officer**
TELEPHONE:	**240-599-4500**

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	**FANAPTA (Iloperidone)**
NON-PROPRIETARY NAME (USAN)	**Iloperidone**
CODE NAME/NUMBER (ONDC ONLY)	**HP 873 (Hoechst-Roussel), P88 8736 (Hoechst-Roussel), ILO522 (Novartis) ILO522-NXA (Novartis), VYV-683 (Vanda),** [redacted]
CHEMISTRY TYPE/SUBMISSION PRIORITY	**1S**

b(4)

9. LEGAL BASIS FOR SUBMISSION: 505(b)1

10. PHARMACOL. CATEGORY: Antagonist at selected dopaminergic, serotoninergic, and adrenergic receptors

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 1, 2, 4, 6, 8, 10 and 12 mg

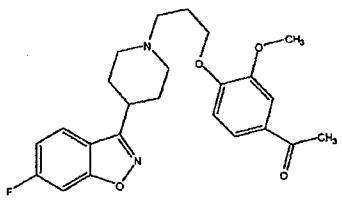
13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: _x_ R_x ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed
___x___Not a SPOTS product

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

Name (USAN, INN): Iloperidone
Name (CAS): 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone
Other Name: 1-[4-[3-[4-(6-fluorobenzo[d]isoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone
(CAS) Registry Num: 133454-47-4
Structural Formula:



Mol. Formula: $C_{24}H_{27}N_2O_4F$
Mol. Wt.: 426.5

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETE
				4	N/A	
				4	N/A	
				4	N/A	
				4	N/A	
				4	N/A	
				4	N/A	

b(4)

Note: DMFs

system is used for solid oral drug products – see CMC Review MaPP.

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A: There is enough data in the application, therefore the DMF did not need to be reviewed.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	11-JAN-08	Shawnte Adams
Methods Validation	No validation request	25-FEB-08	Donghao Lu, Ph.D.
ODS DMETS	Pending		
EA	Acceptable	11-FEB-08	Donghao Lu, Ph.D.
Micro Consultation	N/A		

APPEARS THIS WAY ON ORIGINAL

The Chemistry Review for NDA 22-192

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product FANAPTA (iloperidone) immediate-release tablets, 1, 2, 4, 6, 8, 10, and 12 mg, is recommended as APPROVAL from a CMC perspective, pending DMETS's recommendation.

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

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substance is iloperidone. The chemical name is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone. It has a molecular formula of $C_{24}H_{27}N_2O_4F$ and its molecular weight is 426.5.

Data from the studies of elemental analysis, UV, IR, NMR and MS demonstrated that the structure was adequately defined. The [redacted] appear adequate for the manufacturing of the iloperidone drug substance. b(4)

The impurities detected during the [redacted] and development of the drug substance were evaluated. Analytical methods were developed for the control of the impurities listed in the submission. Comprehensive information for all the impurities at the starting material level, at the intermediate level and at the final [redacted] level were adequately presented. b(4)

Iloperidone was subjected to heat, heat and moisture, light, and chemical stresses. The drug substance was physically and chemically stable based on evaluation of the testing data. The drug substance has a retest period of [redacted]

2. Drug Product

The drug product is Fanapta (iloperidone) immediate-release tablets, 1, 2, 4, 6, 8, 10, and 12 mg. It is intended for oral administration.

The tablets contain 1, 2, 4, 6, 8, 10, and 12 mg iloperidone, respectively. All strengths are white, round, flat, beveled-edge tablets with the tablet strength debossed on the upper face (e.g., "8" for the 8 mg strength) and the Vanda (Vanda Pharmaceuticals Inc.) company logo debossed on the lower face. The tablet diameters are different for each strength except for the [redacted] strengths. Iloperidone tablets are packed in [redacted] b(4)

placed inside dose titration/maintenance cards.

Inactive ingredients consist of lactose monohydrate, microcrystalline cellulose, hydroxypropyl methylcellulose, crospovidone, magnesium stearate, colloidal silicon dioxide. The manufacturing process for iloperidone tablets consists of [redacted] b(4)

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

Iloperidone tablet drug products contain antagonist at selected dopaminergic, serotoninergic, and adrenergic receptors and are indicated for the treatment of schizophrenia.

The recommended target dosage of iloperidone tablets is 12 mg/day administered BID during the acute phase. The recommended titration schedule to target dose is 1, 2, 4, and 6 mg BID on days 1, 2, 3, and 4 respectively. After reaching the target 12 mg/day dose, titration to the maximum daily dose of 12 mg BID should occur over a 3-day period. During the maintenance phase, iloperidone can be administered at a target dose of [redacted] Iloperidone can be administered without regard to meals. The products should be stored at controlled room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°- 86°F). The products should be protected from light and moisture. The products have an expiration period (shelf life) of 36 months. b(4)

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Vanda has submitted sufficient and appropriate information to support the approval of the drug product. There were several CMC concerns that were sent to the sponsor on April 2, 2008. Vanda has adequately addressed these CMC comments. Their responses and the CMC evaluations for these responses are described at the end of this document.

III. Administrative

A. Reviewer's Signature

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ramesh Sood, Ph.D.

C. CC Block

93 pages of CCI/TS (b4) was withheld after this page.

CMC_#1_93 pgs.pdf

93 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Donghao Lu
5/1/2008 11:46:02 AM
CHEMIST

Ramesh Sood
5/1/2008 04:42:41 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22192/000
Org Code : 130
Priority : 1

Sponsor: VANDA
9620 MEDICAL CENTER DR STE 201
ROCKVILLE, MD 20850

Stamp Date : 27-SEP-2007
PDUFA Date : 06-MAY-2009
Action Goal :
District Goal: 28-MAY-2008

Brand Name : ILOPERIDONE
Estab. Name:
Generic Name: ILOPERIDONE
Dosage Form: (TABLET)
Strength : 1,2,4,6,8,10, AND 12 MG

FDA Contacts:			
	K. KIEDROW	Project Manager	301-796-1924
	S. MCLAMORE	Review Chemist	301-796-1710
	T. OLIVER	Team Leader	301-796-1728

Overall Recommendation: ACCEPTABLE on 11-JAN-2008by S. FERGUSON(HFD-322) 301-796-3247

Establishment : CFN : _____ FEI : _____

b(4)

DMF No: AADA:

b(4)

Responsibilities:

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-OCT-07

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : FEI :

DMF No: AADA:

b(4)

Responsibilities:

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-NOV-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No:

AADA:

b(4)

Responsibilities:

APPEARS THIS WAY ON ORIGINAL

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-OCT-07

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : FEI :

DMF No: AADA: b(4)

Responsibilities:

Profile : CRU OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-NOV-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI : b(4)

DMF No: AADA:

Responsibilities: [redacted] b(4)

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-JAN-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted]

PATHEON INC. - BURLINGTON CENTURY OPERATIONS

977 CENTURY DRIVE

BURLINGTON, ONTARIO, CA

DMF No: AADA: b(4)

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-OCT-07

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : [redacted] FEI : [redacted]

PATHEON INC. - TORONTO REGION OPERATIONS b(4)

2100 SYNTEX COURT

MISSISSAUGA, ONTARIO, CA

DMF No:

AADA:

APPEARS THIS WAY ON ORIGINAL

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-NOV-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA: b(4)

Responsibilities:

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-JAN-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI : b(4)

b(4)

DMF No: AADA:

Responsibilities:

b(4)

Profile : OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-NOV-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA: b(4)

Responsibilities:

Profile : OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-OCT-07

Decision : ACCEPTABLE

Reason : BASED ON FILE REVIEW

APPEARS THIS WAY ON ORIGINAL