

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022567Orig1s000

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 22-567, VIIBRYD (vilazodone) 10 mg, 20 mg, and 40 mg Tablets
Date: 07-JAN-2011

Introduction

VIIBRYD (vilazodone) 10 mg, 20 mg, and 40 mg immediate release (IR) film coated (FC) tablets are indicated for the treatment of major depressive disorder. This product should be titrated with an initial dose of 10mg once daily for 7 days followed by 20mg once daily for an additional 7 days. This drug should be taken with food. **ONDQA recommends approval of this NDA.**

Administrative

The original submission of this 505(b)(1) NDA was received 22-MAR-2010 from PGx Health of New Haven, Connecticut. During the review cycle a CMC amendment dated 04-NOV-2010 was also reviewed.

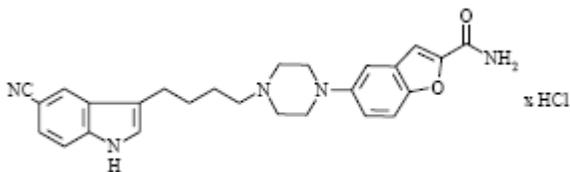
The NDA is supported by IND 54,613 and seven drug master files (DMF). Consults for EES (26-MAY-2010), PharmTox (16-NOV-2010), Biopharm (06-NOV-2010), and DMEPA (for Trade name, 03-NOV-2010) were all acceptable

This NDA is recommended for approval from a Chemistry, Manufacturing and Controls standpoint.

Drug Substance (vilazodone hydrochloride)

Chemical Name:

2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1*H*-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1)



Molecular Formula : C₂₆ H₂₇ N₅ O₂ x HCl

Molecular Weight : 477.99 (vilazodone HCl) and 441.2 (vilazodone)

The drug substance is a ^{(b) (4)} white to cream colored achiral solid manufactured via a ^{(b) (4)}. The drug substance is ^{(b) (4)}. The pKa is 7.1 and the aqueous solubility is 0.32 mg/mL. The assigned retest date for the drug substance is ^{(b) (4)}.

Drug Product VIIBRYD (vilazodone) 10 mg, 20 mg, and 40 mg Tablets

All three strengths are manufactured by [REDACTED] (b) (4)

Excipients used in the formulation are conventional and include lactose, microcrystalline cellulose, colloidal silicone dioxide, magnesium stearate and [REDACTED] (b) (4) film coating.

The [REDACTED] (b) (4) film coat varies according to strength: [REDACTED] (b) (4)

The HDPE bottles are sized to accommodate 30, 90, or 500 tablets/bottle. Each bottle also contains a 1 gm desiccant canister. The data support the proposed shelf life of 24 months when stored at room temperature.

Rik Lostritto, Director, ONDQA Division I, DPAMS

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

/s/

RICHARD T LOSTRITTO
01/07/2011

NDA 22-567

Vilazodone 10, 20, 40mg Tablets

PGxHealth, LLC

Pei-I Chu, Ph.D.

**Office of New Drug Quality Assessment DPA1
For Division of Psychiatry Drug Products**

Review of Chemistry, Manufacturing, and Controls

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Chemistry Review Data Sheet

1. NDA 22-567
2. REVIEW # 1:
3. REVIEW DATE: October 30, 2010
4. REVIEWER: Pei-I Chu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

22-March-2010

7. NAME & ADDRESS OF APPLICANT:

Name: PGx Health

Address: Five Science Park
New Haven, CT 06511

Representative: Kimberly Fabrizio

Telephone: 203-786-3502

8. DRUG PRODUCT NAME/CODE/TYPE: N/A

- a) Proprietary Name: TBD
- b) Non-Proprietary Name (USAN): Vilazodone Hydrochloride (vilazodone HCl)
- c) Code Name/# (ONDC only):N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION:

505(b)(1)

10. PHARMACOL. CATEGORY: Major Depressive Disorder

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10mg, 20mg, 40mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

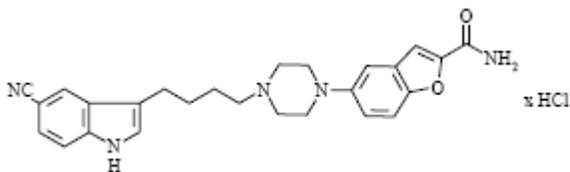
SPOTS product – Form Completed

 Not a SPOTS product

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

Chemical Name: 2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1*H*-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1)

5-{4-[4-(5-cyano-3-indolyl)-butyl]-1-piperazinyl}-benzofuran-2-carboxamide hydrochloride

Molecular Formula : C₂₆ H₂₇ N₅ O₂ x HCl

Molecular Weight : 477.99 (vilazodone HCl)

441.2 (vilazodone)

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	10/25/2010	
	III			4			Sufficient info provided
	III			1	Adequate	07/07/2010	
	III			4			Sufficient info provided
	III			4			Sufficient info provided
	III			4			Sufficient info provided
	III			4			Sufficient info provided

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)

Chemistry Review Data Sheet

I. B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	54613	Commercial IND

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	acceptable	5/26/2010	OC
Pharm/Tox	Pending (waiting for IR response)	10/16/2010	Violetta Klimek
Biopharm	Pending (waiting for IR response)	10/16/2010	Tien Min Chen
LNC	NA		
Methods Validation	NA		
OPDRA	NA		
DMEPA	NA		
EA	NA		
Microbiology	NA		

Chemistry Review Section

The Chemistry Review for NDA 22-567

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22567 is recommended approvable from the CMC standpoint. The approval is contingent upon satisfactory response from the applicant on the drug substance and drug product questions. A summary of CMC questions is listed at the end of this review. Office of compliance has determined that pre-approval inspections for the drug substance, drug product and packaging sites are not needed based on profile.

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

None as per this review.

II. Summary of Chemistry Assessments

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

Vilazodone HCl is a dual-acting and selective serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist. It is thought to optimize regulation of 5-HT circuitry at both pre- and postsynaptic sites to augment 5-HT neurotransmission, thereby producing an antidepressant effect. Its clinical indication is for the treatment of major depressive disorder. Vilazodone HCl is a new chemical entity belonging to the structural chemical group of the indolalkylamines. The full chemical designation is 2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1*H*-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1)

Vilazodone HCl drug substance is a white to cream-colored solid. It is achiral and slightly hygroscopic. Solid state form analysis demonstrates that it exists in multiple polymorphs (b) (4). (b) (4) form IV was chosen for development. The solubility in water is 0.32mg/mL. The partition coefficient between n-octanol and water is (b) (4). The pKa is 7.1. The melting point and decomposition starts at ~270°C.

Vilazodone HCl is manufactured, (b) (4) by:

ScinoPharm Taiwan, Ltd. (SPT) in Shan-Hua, Taiwan, R.O.C. The drug substance is manufactured in a (b) (4). A typical batch yield is from (b) (4). The resulting drug substance is (b) (4)

Seven batches of vilazodone HCl manufactured by ScinoPharm Taiwan, Ltd. (SPT) are being evaluated on stability. Three batches were manufactured using the intended commercial process. All batches were packaged in the container closure intended for commercial material. The initial submission included 9 months stability at 25°C/60%RH or for up to 6 months at 40°C/75%RH. 12 month stability data from the development batches has been provided at the mid cycle review period. No significant changes or trends have been observed. However, the firm has only provided two 6 month stability data under accelerated storage of 40°C/75% RH and 25°C/60%RH using the commercial manufacturing process. The assigned re-test date for the drug substance at this point is (b) (4). When additional stability data is provided, the re-test will be re-assessed.

Chemistry Review Section

Vilazodone HCl Tablets, 10 mg, 20 mg and 40 mg are immediate-release, oval, film-coated, tablets, manufactured from a (b) (4) with total tablet weights of 103 mg, 206 mg and 412 mg, respectively. The 10 mg tablets are pink; the 20 mg, orange; and the 40 mg, blue. The tablets are debossed with the strength on one side and plain on the other. The tablets are packaged in appropriately-sized, 30-count, 90-count and 500-count high-density polyethylene (HDPE) bottles, and in film/aluminum foil blisters.

The drug product will be manufactured by Patheon Puerto Rico, Inc. (Manati, Puerto Rico). Vilazodone HCl Tablets, 10 mg, 20 mg and 40 mg are manufactured from a (b) (4) process using standard techniques, equipment and controls. Manufacturing comprises of (b) (4)

Excipients used in the formulation include lactose, microcrystalline cellulose, colloidal silicone dioxide, magnesium stearate and (b) (4) film coating. (b) (4)

The batch formula for a commercial scale batch is (b) (4) for the 10mg, 20mg and 40mg tablets, which would results in (b) (4) 10mg tablets, (b) (4) 20mg tablets or (b) (4) 40mg tablets.

Vilazodone HCl tablets may be stored in bulk prior to packaging to accommodate for packaging schedule. The HDPE bottles are sized to accommodate 30, 90, or 500 tablets/bottle. Each bottle also contains a 1-g desiccant canister. The applicant has submitted 18 month stability data for 6 batches using drug substance manufactured by Merck (three each of 10mg and 40mg tablets) and 12 month stability data of drug product manufactured with API from Scino Pharm. Based on real time and accelerated stability data at the ICH conditions, the 10mg and 40mg tablets are considered stable under proposed storage container closure systems. Tablets manufactured with API from SPT have the same stability as those manufactured with API from Merck based on comparison of 12-month stability data for SPT-API tablets and Merck-API tablets. The data support the proposed shelf life of 24 months when stored at room temperature.

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

This product should be titrated with an initial dose of 10mg once daily for 7 days followed by 20mg once daily for an additional 7 days. Vilazodone HCl should be taken with food.

C. Basis for Approvability or Not-Approval Recommendation

The final approval of this NDA will be based on adequate responses to the Information Request sent to PGx Health Care on October 15, 2010.

III. Administrative

A. Reviewer's Signature

Endorsement Block

Chemist Name: Pei-I Chu, Ph.D./Date: Same date as draft review

Chemistry CMC Lead: Tom Oliver, Ph.D./Date

Chemistry Branch Chief Ramesh Sood, Ph.D.

Chemistry Project Manager Teshara Bouie/Date

Chemistry Review Section

C. CC Block
Orig. NDA-22-567

▼

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/s/

PEI-I CHU
11/03/2010

RAMESH K SOOD
11/03/2010

NDA 22-567

Vilazodone 10, 20, 40mg Tablets

PGxHealth, LLC

Pei-I Chu, Ph.D.

**Office of New Drug Quality Assessment DPA1
For Division of Psychiatry Drug Products**

Review of Chemistry, Manufacturing, and Controls

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A. Labeling & Package Insert	38
B. Environmental Assessment Or Claim Of Categorical Exclusion	38

Chemistry Review Data Sheet

1. NDA 22-567
2. REVIEW # 2:
3. REVIEW DATE: November 30, 2010
4. REVIEWER: Pei-I Chu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

22-March-2010

Amendment 17-Quality Response to IR

04-November-2010

7. NAME & ADDRESS OF APPLICANT:

Name: PGx Health

Address: Five Science Park
New Haven, CT 06511

Representative: Kimberly Fabrizio

Telephone: 203-786-3502

8. DRUG PRODUCT NAME/CODE/TYPE: N/A

- a) Proprietary Name: Viibryd
- b) Non-Proprietary Name (USAN): Vilazodone Hydrochloride (vilazodone HCl)
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S

Chemistry Review Data Sheet

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

10. PHARMACOL. CATEGORY: Major Depressive Disorder

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10mg, 20mg, 40mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

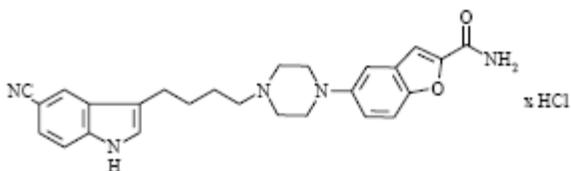
SPOTS product – Form Completed

Not a SPOTS product

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

Chemical Name: 2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1*H*-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1)

5-{4-[4-(5-cyano-3-indolyl)-butyl]-1-piperazinyl}-benzofuran-2-carboxamide hydrochloride



Molecular Formula : C₂₆ H₂₇ N₅ O₂ x HCl

Molecular Weight : 477.99 (vilazodone HCl)

441.2 (vilazodone)

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	10/25/2010	
	III			4			Sufficient info provided
	III			1	Adequate	07/07/2010	
	III			4			Sufficient info provided
	III			4			Sufficient info provided
	III			4			Sufficient info provided
	III			4			Sufficient info provided
	III			4			Sufficient info provided

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Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

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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)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	54613	Commercial IND

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	---	---
EES	acceptable	5/26/2010	Office of compliance
Pharm/Tox	acceptable	11/16/2010	Violetta Klimek
Biopharm	acceptable	11/06/2010	Tien Min Chen
LNC	NA	---	---
Methods Validation	NA	---	---
OPDRA	NA	---	---
DMEPA	Viibryd	11/03/2010	Loretta Holmes
EA	NA	---	---
Microbiology	NA	---	---

The Chemistry Review for NDA 22-567

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22567 is recommended **approval** from the perspective of chemistry, manufacturing, and controls. . An information request letter was sent to the applicant on October 15, 2010. An amendment dated November 04, 2010 included adequate quality responses to the CMC issues. The response to the genotoxic impurities is found adequate by the Pharmatox reviewer. The biopharm reviewer has also determined that the response to the question on dissolution method and dissolution data is adequate. All CMC issues have now been adequately resolved.

Office of compliance has determined the drug substance, drug product and packaging facilities are adequate. Pre-approval inspections for the drug substance, drug product and packaging sites are not needed based on profile.

The sponsor has committed to the following actions in the first NDA annual report:

- Provide a revised (b) (4) validation report to demonstrate the limit of quantitation for Form IV (b) (4)
- Include an updated dissolution method validation report using a stability indicating analytical method.

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

None as per this review.

II. Summary of Chemistry Assessments

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

Vilazodone HCl is a dual-acting and selective serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist. It is thought to optimize regulation of 5-HT circuitry at both pre- and postsynaptic sites to augment 5-HT neurotransmission, thereby producing an antidepressant effect. Its clinical indication is for the treatment of major depressive disorder. Vilazodone HCl is a new chemical entity belonging to the structural chemical group of the indolalkylamines. The full chemical designation is 2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1*H*-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1)

Chemistry Review Section

Vilazodone HCl drug substance is a white to cream-colored solid. It is achiral and slightly hygroscopic. Solid state form analysis demonstrates that it exists in multiple polymorphs (b) (4) (b) (4) form IV was chosen for development. The solubility in water is 0.32mg/mL. The partition coefficient between n-octanol and water is (b) (4). The pKa is 7.1. The melting point and decomposition starts at ~270°C.

Vilazodone HCl is manufactured, (b) (4) by

ScinoPharm Taiwan, Ltd. (SPT) in Shan-Hua, Taiwan, R.O.C. The drug substance is manufactured in a (b) (4) A typical batch yield is from (b) (4). The resulting drug substance is (b) (4). The drug substance is (b) (4).

Seven batches of vilazodone HCl manufactured by ScinoPharm Taiwan, Ltd. (SPT) are being evaluated on stability. Three batches were manufactured using the intended commercial process. All batches were packaged in the container closure intended for commercial material. In the IR response dated November 4, 2010, the applicant has committed to provide a revised validation report to include (b) (4) data in the first NDA annual report.

The initial submission included 9 months drug substance stability data at 25°C/60%RH or for up to 6 months at 40°C/75%RH. 12 month stability data from the development batches has been provided at the mid cycle review period. No significant changes or trends have been observed. However, the firm has only provided two 6 month stability data under accelerated storage of 40°C/75% RH and 25°C/60%RH using the commercial manufacturing process. The assigned re-test date for the drug substance at this point is (b) (4). When additional stability data is provided, the re-test will be re-assessed.

Vilazodone HCl Tablets, 10 mg, 20 mg and 40 mg are immediate-release, oval, film-coated, tablets, manufactured from a (b) (4) with total tablet weights of 103 mg, 206 mg and 412 mg, respectively. The 10 mg tablets are pink; the 20 mg, orange; and the 40 mg, blue. The tablets are debossed with the strength on one side and plain on the other. The tablets are packaged in appropriately-sized, 30-count, 90-count and 500-count high-density polyethylene (HDPE) bottles, and in film/aluminum foil blisters.

The drug product will be manufactured by Patheon Puerto Rico, Inc. (Manati, Puerto Rico). Vilazodone HCl Tablets, 10 mg, 20 mg and 40 mg are manufactured from a (b) (4) (b) (4) process using standard techniques, equipment and controls.

Manufacturing comprises of (b) (4) Excipients used in the formulation include lactose, microcrystalline cellulose, colloidal silicone dioxide, magnesium stearate and (b) (4) film coating. The film coat is comprised of: (b) (4)

The batch formula for a commercial scale batch is (b) (4) for the

Chemistry Review Section

10mg, 20mg and 40mg tablets, which would results in (b) (4) 10mg tablets, (b) (4) 20mg tablets or (b) (4) 40mg tablets. Vilazodone HCl tablets may be stored in bulk prior to packaging to accommodate for packaging schedule. The HDPE bottles are sized to accommodate 30, 90, or 500 tablets/bottle. Each bottle also contains a 1-g desiccant canister. The applicant has submitted 18 month stability data for 6 batches using drug substance manufactured by Merck (three each of 10mg and 40mg tablets) and 12 month stability data of drug product manufactured with API from Scino Pharm. Based on real time and accelerated stability data at the ICH conditions, the 10mg and 40mg tablets are considered stable under proposed storage container closure systems. Tablets manufactured with API from SPT have the same stability as those manufactured with API from Merck based on comparison of 12-month stability data for SPT-API tablets and Merck-API tablets. The data support the proposed shelf life of 24 months when stored at room temperature.

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

This product should be titrated with an initial dose of 10mg once daily for 7 days followed by 20mg once daily for an additional 7 days. Vilazodone HCl should be taken with food.

C. Basis for Approvability or Not-Approval Recommendation

This NDA (22-567) is recommended for **APPROVAL** from the perspective of chemistry, manufacturing, and controls. All deficiencies have been adequately resolved.

II. Administrative**A. Reviewer's Signature**

Pei-I Chu, Ph.D.

Endorsement Block

Chemist Name:	Pei-I Chu, Ph.D.
Chemistry CMC Lead:	Tom Oliver, Ph.D.
Chemistry Branch Chief :	Ramesh Sood, Ph.D.
Chemistry Project Manager :	Teshara Bouie

C. CC Block

Orig. NDA-22-567

29 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PEI-I CHU
12/06/2010

RAMESH K SOOD
12/06/2010

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number: 22567

**Supplement Number and Type:
Original**

**Established/Proper Name:
Vilazodone HCl tablets**

Applicant: (b) (4)

Letter Date: 22-March-2010

Stamp Date: 22-March-2010

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for (b) (4) API.			Not Applicable

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Answers to Questions 12-18 are based on information contained within DMF
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

APPEARS THIS WAY ON ORIGINAL.

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not Applicable
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?			Not Applicable

{See appended electronic signature page}

Name of
Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Name of
Branch Chief
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22567	ORIG-1	PGXHEALTH LLC	VILAZODONE HCL

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/s/

PEI-I CHU
05/05/2010

RAMESH K SOOD
05/05/2010

Initial Quality Assessment Branch I

OND Division: Division of Psychiatry Products
NDA: 22-567
Applicant: PGxHealth, LLC
Letter Date: 22-MAR-10
Stamp Date: 22-MAR-10
PDUFA Date: 22-JAN-11
Trademark: Tradename has not been proposed
Established Name: vilazodone hydrochloride
Dosage Form: 10, 20, and 40 mg Tablets
Route of Administration: Oral
Indication: Major Depressive Disorder
Assessed by: Thomas F. Oliver, Ph.D.

Summary

Vilazodone, a dual-acting potent and selective serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist, is indicated for the treatment of major depressive disorder. It was developed under IND 54,613. The applicant had an EOP2 meeting (December 20, 2005) but there were no specific CMC questions. The applicant had a CMC pre-NDA meeting (September 29, 2009) where the following CMC issues were discussed: starting material designation, residual solvent testing (b) (4), drug substance stability data, drug substance overage in DP, dissolution specification, and drug product stability data. Minutes for both meetings can be found in DARTS and should be read by the reviewer.

Drug Substance

Vilazodone HCl is achiral and appears as a white to cream-colored solid. Vilazodone HCl is slightly hygroscopic and can exist in multiple polymorphs (b) (4). (b) (4) Form IV has been chosen for commercial development. Solubility in water is 0.32 mg/mL (20°C). The drug substance will be manufactured by ScinoPharm Taiwan, Ltd. (Shan-Hua, Taiwan). Vilazodone HCl is manufactured in a (b) (4). Vilazodone HCl is (b) (4). The applicant has assigned a (b) (4) retest date. Seven batches of vilazodone HCl manufactured by ScinoPharm Taiwan, Ltd. (SPT), the intended supplier of commercial material are being evaluated on stability. Three batches were manufactured using the intended commercial process. Four batches were manufactured using a modified commercial process, which differs from the commercial process only (b) (4). All batches were packaged in the container closure intended for commercial drug substance.

Drug Product

Vilazodone HCl tablets will be available in 10, 20, and 40 mg strengths. The recommended dose for Vilazodone HCl is 40 mg once daily. Vilazodone HCl should be titrated, starting with an initial dose of 10 mg once daily for 7 days followed by 20 mg once daily for an additional 7 days. Vilazodone HCl should be taken with food.

Vilazodone HCl Tablets are immediate-release, oval, film-coated, tablets, manufactured from a (b) (4). The 10 mg tablets are pink; the 20 mg, orange; and the 40 mg, blue. The tablets are debossed with the strength on one side and plain on the other. The tablet cores are comprised of: vilazodone HCl, microcrystalline cellulose, lactose monohydrate, magnesium stearate, and colloidal silicon dioxide. The film coat is comprised of: (b) (4)

The drug product will be manufactured by Patheon Puerto Rico, Inc. (Manati, Puerto Rico). Vilazodone HCl Tablets, 10 mg, 20 mg and 40 mg are manufactured from a (b) (4)

The batch formula for the commercial scale batches is (b) (4) for the 10mg, 20 mg and 40 mg tablets, which would result in (b) (4) (10 mg), (b) (4) (20 mg) and (b) (4) (40 mg) tablets. Vilazodone HCl tablets may be stored in bulk prior to packaging to accommodate manufacturing schedules. For this interim storage, bulk Vilazodone HCl Tablets are (b) (4)

Two container closure systems (bottles and blisters) will be used for packaging of commercial vilazodone HCl Tablets. The bottles are high density polyethylene (HDPE), sealed with (b) (4) closures with inner seals. The bottles are sized to accommodate 30, 90, or 500 tablets/bottle. Each bottle also contains a 1-g desiccant canister. The blisters are formed using (b) (4) blister film and aluminum foil blister lidding. The tablets are also supplied in a Patient Starter Kit (blister card containing seven 10 mg tablets, seven 20 mg tablets, and sixteen 40 mg tablets). The sponsor submitted 12-month data for six batches (three each of 10 mg and 40 mg tablets) of primary stability data. The applicant has requested a 24 month expiry for vilazodone HCl tablets.

Critical Issues for Review

- The applicant states that the drug substance can exist in multiple polymorphic forms (b) (4) (b) (4) have been observed). (b) (4) Form IV has been chosen for commercial development. It will need to be determined whether the applicant has adequately characterized the various polymorphs and determined the different properties (e.g., solubility, stability) of each form [refer to ICH Q6a]. The applicant tests for the correct solid state form as part of the release and stability testing. It will need to be determined whether the control for (b) (4) Form IV is acceptable (e.g., can small amounts of the other potential polymorphic forms be detected by the analytical solid state method).

- Characterization data will need to be evaluated to determine if the data are consistent with the proposed structure of vilazodone HCl.

- Six impurities with genotoxic structure alerts are controlled at the (b) (4) (b) (4) for improved analytical method sensitivity. These are: (b) (4)

(b) (4) It will need to be determined the adequacy of this specification limits and the acceptability of the test method.

(b) (4)

- The applicant lists the impurity (b) (4) as a potential genotoxic impurity, which could be formed from (b) (4). An acceptance specification limit was set at (b) (4) as part of the drug substance specification. It will need to be determined the adequacy of this specification limit and the acceptability of the GC test method.
- The applicant has proposed a residual solvent limit for (b) (4) (Option 2) as part of the drug substance release testing. It will need to be determined the adequacy of the specification limit and method for controlling (b) (4).
- Vilazodone HCl is (b) (4). The applicant has proposed a particle size distribution specification (b) (4). Graphical depiction of the particle size distribution should be provided. It should be noted there currently isn't a (b) (4) control. It will need to be determined whether particle size used in the clinical batches supports the proposed commercial specification and whether a (b) (4) control is needed. It will also need to be determined whether (b) (4). The amount of (b) (4) material will need to be determined and the reviewer will need to ensure it is properly controlled.
- The applicant has proposed that if vilazodone HCl does not meet the drug substance specification, (b) (4). The reviewer will need to evaluate the (b) (4) procedure outlined by the applicant and determine the acceptability (b) (4).
- The (b) (4) is used in Step 1 in the (b) (4). It is used as a (b) (4). It will need to be determined whether the applicant has adequate controls for residual levels of (b) (4).
- The compatibility of the drug product excipients will need to be evaluated.
- The applicant states that the physicochemical properties of the excipients can influence the manufacturability and performance of the drug product. (b) (4). It will need to be determined whether the applicant has adequate controls for each of the excipients.
- The applicant has developed a number of drug product formulations [(b) (4)

(b) (4) throughout development. The commercial formulation is PG-10/PG-20/PG-40. The adequacy of this formulation will need to be determined in terms of clinical performance, manufacturability, and stability.

• Laboratory-scale experiments led to the conclusion that the best results are obtained by making (b) (4)

• The applicant states that the drug substance can exist in multiple polymorphic forms (b) (4). (b) (4) Form IV has been chosen for commercial development. It will need to be evaluated whether the drug product manufacturing process converts Form IV to one of the other forms. The sponsor does not monitor for the correct polymorphic form as part of the current drug product release or stability testing. It will need to be determined whether this approach is acceptable (refer to ICH Q6a).

• The applicant states that the batch formulas for commercial Vilazodone HCl Tablets, 10 mg, 20 mg and 40 mg include a (b) (4) overage of vilazodone HCl API to compensate for loss during tablet manufacture. It will need to be determined whether there is adequate justification for this overage.

• Four processes were evaluated (Process I, II, III, and IV). It will need to be determined whether the various modifications have corrected the associated problems. The performance of the commercial product will need to be linked to the performance of the clinically studied product (e.g., formulation, manufacturing process, packaging, stability).

• Vilazodone HCl Tablets, 10 mg, 20 mg and 40 mg are manufactured by a (b) (4)

• Vilazodone HCl tablets (film-coated) are differentiated by color, size, and debossing [with strength debossed on one side and plain on the other]. Samples will need to be requested and the acceptability of the appearance specification will need to be evaluated.

• The applicant has proposed a drug product (b) (4) specification limit of (b) (4). It will need to be determined how that upper limit has been justified (i.e., stability data demonstrating product with (b) (4) is chemically and physically stable and delivers active as outlined in labeling).

• The applicant states that vilazodone HCl tablets may be stored in bulk. For this interim storage, bulk Vilazodone HCl Tablets are (b) (4)

(b) (4) It will need to be determined how long tablets will be stored in bulk packaging before being packaged into the commercial presentations and whether there is adequate data to support this hold (refer to ICH Q7).

• Vilazodone HCl Tablets are packaged in (b) (4) of high density polyethylene (HDPE) bottles sealed with either (b) (4). All closures have tamper-evident, inner seals. All bottles are packed with 1-g desiccant canisters. It will need to be determined how the sponsor calculated the adequate amount of desiccant to be used. Stability data (long term, accelerated, stress) will need to be evaluated to determine the container-closure offers adequate protection.

• The applicant performed photostability testing of the tablets. The reviewer will need to determine whether all types of packaging (b) (4) bottles, blisters) offer adequate protection. In particular, the effect of light on the fading of the tablet color [10 mg/pink; 20 mg/orange; 40 mg/blue] will need to be evaluated. It will need to be determined whether any statement is needed in labeling about the effects of light on the tablets.

• The applicant has proposed an expiry of 24 months. The primary drug product stability batches were manufactured using drug substance from Merck KGaA, Darmstadt, Germany. The supplier for commercial drug substance is ScinoPharm Taiwan, Ltd. (SPT). The applicant has compared drug substance manufactured by SCT and Merck and drug product using the respective sourced drug substance. It will need to be determined whether there are any differences in drug product sourced with the different drug substance suppliers.

• It appears the dose strengths (10, 20, and 40 mg vilazodone HCl) are correctly labeled as 10, 20, and 40 mg in the (b) (4) HCl label. Reviewer will need to confirm.

Comments and Recommendation:

The NDA appears to be fileable from a CMC perspective. My recommendation would be for a single reviewer to be assigned to the NDA. As Dr. Thomas Wong was involved in the previous CMC meeting, he would be a prudent choice for reviewer. The applicant claims a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR § 25.31(b) as the expected introduction concentration (EIC) of (b) (4) in the aquatic environment is below 1 parts per billion and states that to the applicant's knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment. The manufacturing, testing, and packaging sites will need to be submitted into EES (by the ONDQA PM), however, the reviewer will need to confirm that these sites are correct and that there are no additional sites that need to be entered.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22567	ORIG-1	PGX HEALTH LLC	VILAZODONE HCL

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/s/

THOMAS F OLIVER
04/14/2010

RAMESH K SOOD
04/23/2010