

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**200179Orig1s000**

**CHEMISTRY REVIEW(S)**

## **ADDENDUM TO CHEMISTRY REVIEW OF NDA 200179**

To: Addendum to CMC Review #2

Date: 16-Jun-2010

From: J. Salemme, Ph.D.  
CMC Reviewer

Through: Moo-Jhong Rhee, Ph.D.  
Branch Chief

Subject: Amendment dated 16-Jun-2010

The 16-Jun-2010 amendment provides revised labels as requested/suggested by the DMEPA reviewer. The revised carton labels are acceptable from a CMC perspective.

Therefore, the amendment of 16-Jun-2010 does not affect the previous "Approval" recommendation made in CMC Review #2, dated 4-Jun-2010.

### **Attachment: Revised Labels**

#### 2-count blister

**STAXYN™**  
(vardenafil hydrochloride)  
orally disintegrating tablet  
**10 mg** Manufactured by:  
Bayer HealthCare  
Pharmaceuticals Inc.

Batch:  
Expires:

Batch:  
Expires:

**STAXYN™**  
(vardenafil hydrochloride)  
orally disintegrating tablet  
**10 mg** Manufactured by:  
Bayer HealthCare  
Pharmaceuticals Inc.

Empty blister -  
does not contain tablet

Empty blister -  
does not contain tablet

#### 4-count blister card

Office of New Drug Quality Assessment  
Chemistry Review for Clinical Division, HFD-580

**STAXYN™**  
(vardenafil hydrochloride)  
orally disintegrating tablet  
**10 mg**  
Manufactured by:  
Bayer HealthCare  
Pharmaceuticals Inc.

Batch:  
Expires:

Batch:  
Expires:

**STAXYN™**  
(vardenafil hydrochloride)  
orally disintegrating tablet  
**10 mg**  
Manufactured by:  
Bayer HealthCare  
Pharmaceuticals Inc.

**STAXYN™**  
(vardenafil hydrochloride)  
orally disintegrating tablet  
**10 mg**  
Manufactured by:  
Bayer HealthCare  
Pharmaceuticals Inc.

Batch:  
Expires:

Batch:  
Expires:

**STAXYN™**  
(vardenafil hydrochloride)  
orally disintegrating tablet  
**10 mg**  
Manufactured by:  
Bayer HealthCare  
Pharmaceuticals Inc.

Carton:



Office of New Drug Quality Assessment  
Chemistry Review for Clinical Division, HFD-580



*Evaluation of Container/Carton: Acceptable.*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200179	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	WARDENAFIL HCL

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/s/

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JEAN SALEMME  
06/17/2010

MOO JHONG RHEE  
06/17/2010  
Chief, Branch IV

**NDA 200179**

**STAXYN**  
**(Vardenafil hydrochloride) orally disintegrating tablets**  
**10 mg**

**Bayer HealthCare Pharmaceuticals Inc.**

**J. Salemme, Ph.D.**

**Branch VI/Division of New Drug Quality Assessment II**  
**for**  
**Branch IV/Division of New Drug Quality Assessment II**  
**Office of New Drug Quality Assessment**

**Chemistry Review for**  
**Division of Reproductive and Urologic Products (HFD-580)**

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## CMC Review Data Sheet

1. **NDA** 200179
2. **REVIEW #:** 2
3. **REVIEW DATE:** 3-Jun-2010
4. **REVIEWER:** J. Salemme, Ph.D.
5. **PREVIOUS DOCUMENTS:**

<u>Submission Reviewed</u>	<u>Document Date</u>
Original	25-Aug-2009
Amendment	20-Oct-2009
Amendment	16-Nov-2009
Amendment	8-Dec-2009
Amendment	20-Apr-2010
Amendment	30-Apr-2010

6. **SUBMISSIONS REVIEWED:**

<u>Submission Reviewed</u>	<u>Document Date</u>
Amendment	2-Jun-2010

7. **NAME & ADDRESS OF APPLICANT:**

**Name:** Bayer HealthCare Pharmaceuticals Inc.  
**Address:** PO Box 1000, Montville, NJ 07045  
**Representative:** Alexandra Park, Deputy Director  
**Telephone:** (973) 487 2016

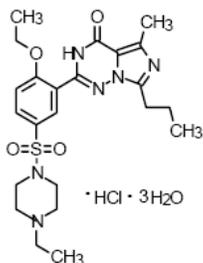
8. **DRUG PRODUCT NAME/CODE/TYPE:**

- a) **Proprietary Name:** STAXYN (proposed)
- b) **Non-Proprietary Name (USAN):** Vardenafil hydrochloride
- c) **Code Name/# (ONDQA only):** N/A
- d) **Chem. Type/Submission Priority (ONDQA only):**
  - **Chem. Type:** 3
  - **Submission Priority:** S

## CMC Review Data Sheet

9. **LEGAL BASIS FOR SUBMISSION:** FD&C Act 505(b)
10. **PHARMACOL. CATEGORY/INDICATION:** PDE-5 Inhibitor/ Treatment of Erectile Dysfunction
11. **DOSAGE FORM:** Tablet, orally disintegrating
12. **STRENGTH/POTENCY:** 10 mg
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:**



**Molecular formula:** C<sub>23</sub>H<sub>32</sub>N<sub>6</sub>O<sub>4</sub>S ••HCl ••3H<sub>2</sub>O

**Molecular weight:** 579.1

**Chemical name:** 2-[2-Ethoxy-5-(4-ethylpiperazine-1-sulfonyl)phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one, hydrochloride trihydrate

or

Piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl-, monohydrochloride

**VARDENAFIL HCl** CAS-224785-91-5 (as HCl salt); CAS-224785-90-4 (as free base)

CMC Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	3	Adequate	March 2009	Reviewed by Dr. W. Wilson

<sup>1</sup> 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")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore, the DMF was not reviewed)

**B. Other Document:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Right of Reference from Bayer HealthCare	21-400	All Drug Substance chemistry, manufacturing and controls information

## CMC Review Data Sheet

## 18. STATUS:

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
<b>Biometrics</b>	N/A		
<b>EES</b>	Acceptable.	May 2010	
<b>Pharm/Tox</b>	N/A		
<b>Biopharmaceutics (ONDQA)</b>	Disintegration test is acceptable.	23-Mar-2010	Dr. S. Suarez
<b>LNC</b>	N/A		
<b>Methods Validation</b>	N/A		
<b>DMETS</b>	N/A		
<b>EA</b>	Claim for Categorical Exclusion is granted.	February 2010	Dr. J. Salemme
<b>Microbiology</b>	N/A		

## Executive Summary Section

**The CMC Review for NDA 200179****The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

The previous Chemistry Review #1 noted two pending issues, labeling and cGMP compliance.

The Office of Compliance has now recommended the manufacturing sites for approval, and labeling and carton labels have been corrected.

Therefore, from a CMC perspective, this application is recommended for approval.

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

None

**II. Summary of CMC Assessments****A. Description of the Drug Product and Drug Substance**

Vardenafil hydrochloride orally disintegrating tablet (ODT) 10 mg is a white, round, (b) (4) tablet, 180 mg in weight and 9 mm in diameter, with no tablet markings. Each tablet contains 11.85 mg vardenafil hydrochloride (in trihydrate form) (b) (4) which corresponds to 10.0 mg vardenafil.

Vardenafil hydrochloride ODT 10 mg is manufactured, packaged and released by Bayer Schering Pharma AG, Leverkusen, Germany.

Vardenafil hydrochloride ODT contains (b) (4) drug substance, vardenafil hydrochloride trihydrate, peppermint flavor, and the following excipients: Pharmaburst B2, consisting of mannitol, sorbitol, crospovidone and silica; aspartame; and magnesium stearate. The tablet is formed by (b) (4)

Data provided in the submission for three validation, commercial scale batches support that the manufacturing process is validated.

The tablets are controlled by the following tests: description, identification, friability, disintegration, specified, unspecified and total degradation products, assay, uniformity of dose, and microbial purity.

## Executive Summary Section

Most of the methods for analysis of drug product are identical to methods approved for Levitra, NDA 21-400. An exception is the disintegration method, which is proposed in place of a dissolution method due to the rapid disintegration time of the tablet.

The tablets are packaged in a child-resistant, tear-apart, aluminum/aluminum blister, 4 blisters per blister card.

The drug substance, vardenafil hydrochloride, is a selective phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction. The drug substance is identical to the drug substance approved for Levitra (vardenafil hydrochloride), NDA 21-400. A Letter of Authorization from Bayer to access NDA 21-400 for chemistry, manufacturing and controls is provided in this submission.

Vardenafil hydrochloride is manufactured by Bayer Schering Pharma AG in Wuppertal, Germany, and (b) (4) at the Bayer Schering Pharma AG site in Leverkusen, Germany.

Vardenafil hydrochloride is controlled by the following tests: color, identity by HPLC, identity by IR, identity for chloride, particle size distribution, appearance of solution, sulfated ash, heavy metals, water content, residual solvents, impurities (specified, unspecified, and total), assay, and microbiological purity.

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

Vardenafil hydrochloride orally disintegrating tablet 10 mg is formulated to rapidly disintegrate in the mouth in (b) (4) seconds. This allows a convenient administration of the drug without water.

**C. Basis for Approvability or Not-Approval Recommendation**

The sponsor has provided sufficient information regarding raw material controls, manufacturing processes and process controls, and stability data that assure the quality of the drug product during the expiration dating period. Carton and container labeling are now acceptable. The Office of Compliance has recommended the manufacturing sites for approval.

Therefore, this application is recommended for approval from a chemistry, manufacturing and controls perspective.

## Executive Summary Section

**III. Administrative****A. Reviewer's Signature:**

(See appended electronic signature page.)

**B. Endorsement Block:**

(See appended electronic signature page.)

**C. CC Block:**

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200179	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	VARDENAFIL HCL

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/s/

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JEAN SALEMME  
06/03/2010

MOO JHONG RHEE  
06/04/2010  
Chief, Branch IV

**NDA 200179**

(b) (4)

**(Vardenafil hydrochloride) orally disintegrating tablets**

**Bayer HealthCare Pharmaceuticals Inc.**

**J. Salemme, Ph.D.**  
**Division of Post-Marketing Evaluation**  
**for**  
**Branch III/Division of Pre-Marketing Evaluation II**  
**Office of New Drug Quality Assessment**

**Chemistry Review for**  
**Division of Reproductive and Urologic Products (HFD-580)**

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## CMC Review Data Sheet

1. **NDA** 200179
2. **REVIEW #:** 1
3. **REVIEW DATE:** 9-April-2010
4. **REVIEWER:** J. Salemme, Ph.D.
5. **PREVIOUS DOCUMENTS:** N/A
6. **SUBMISSIONS REVIEWED:**

<u>Submission Reviewed</u>	<u>Document Date</u>
Original	25-Aug-2009
Amendment	20-Oct-2009
Amendment	16-Nov-2009
Amendment	8-Dec-2009
Amendment	20-Apr-2010
Amendment	30-Apr-2010

**7. NAME & ADDRESS OF APPLICANT:**

**Name:** Bayer HealthCare Pharmaceuticals Inc.  
**Address:** PO Box 1000, Montville, NJ 07045  
**Representative:** Alexandra Park, Deputy Director  
**Telephone:** (973) 487 2016

**8. DRUG PRODUCT NAME/CODE/TYPE:**

- a) **Proprietary Name:** PENDING [Vardenafil hydrochloride ODT]
- b) **Non-Proprietary Name (USAN):** Vardenafil hydrochloride [Vardenafil, vardenafil hydrochloride, and vardenafil dihydrochloride are adopted as USAN.]
- c) **Code Name/# (ONDQA only):** N/A
- d) **Chem. Type/Submission Priority (ONDQA only):**
  - **Chem. Type:** 3
  - **Submission Priority:** S

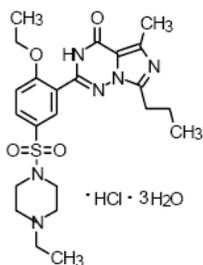
## CMC Review Data Sheet

- 9. LEGAL BASIS FOR SUBMISSION:** FD&C Act 505(b)
- 10. PHARMACOL. CATEGORY/INDICATION:** PDE-5 Inhibitor/ Treatment of Erectile Dysfunction
- 11. DOSAGE FORM:** Tablet, orally disintegrating
- 12. STRENGTH/POTENCY:** 10 mg
- 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:**



**Molecular formula:** C<sub>23</sub>H<sub>32</sub>N<sub>6</sub>O<sub>4</sub>S ••HCl ••3H<sub>2</sub>O

**Molecular weight:** 579.1

**Chemical name:** 2-[2-Ethoxy-5-(4-ethylpiperazine-1-sulfonyl)phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one, hydrochloride trihydrate

or

Piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl-, monohydrochloride

**VARDENAFIL HCl** CAS-224785-91-5 (as HCl salt); CAS-224785-90-4 (as free base)

CMC Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

<b>DMF #</b>	<b>TYPE</b>	<b>HOLDER</b>	<b>ITEM REFERENCED</b>	<b>CODE<sup>1</sup></b>	<b>STATUS<sup>2</sup></b>	<b>DATE REVIEW COMPLETED</b>	<b>COMMENTS</b>
(b) (4)	IV		(b) (4)	3	Adequate	March 2009	Reviewed by Dr. W. Wilson

<sup>1</sup> 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")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore, the DMF was not reviewed)

**B. Other Document:**

<b>DOCUMENT</b>	<b>APPLICATION NUMBER</b>	<b>DESCRIPTION</b>
Right of Reference from Bayer HealthCare	21-400	All Drug Substance chemistry, manufacturing and controls information

## CMC Review Data Sheet

## 18. STATUS:

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
<b>Biometrics</b>	N/A		
<b>EES</b>	PENDING		
<b>Pharm/Tox</b>	N/A		
<b>Biopharmaceutics (ONDQA)</b>	Disintegration test is acceptable.	23-Mar-2010	Dr. S. Suarez
<b>LNC</b>	N/A		
<b>Methods Validation</b>	N/A		
<b>DMETS</b>	N/A		
<b>EA</b>	Claim for Categorical Exclusion is granted.	February 2010	Dr. J. Salemme
<b>Microbiology</b>	N/A		

## Executive Summary Section

## The CMC Review for NDA 200179

**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

The information provided in this New Drug Application is sufficient to assure the identity, strength, purity and quality of the drug product.

Labeling issues have not yet been resolved, and no overall “Acceptable” recommendation from the Office of Compliance has been made as of the date of this review. Therefore, from a CMC perspective, this NDA is *not recommended* for approval until all pending issues are resolved.

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

None

**II. Summary of CMC Assessments****A. Description of the Drug Product and Drug Substance**

Vardenafil hydrochloride orally disintegrating tablet (ODT) 10 mg is a white, round, (b) (4) tablet, 180 mg in weight and 9 mm in diameter, with no tablet markings. Each tablet contains 11.85 mg vardenafil hydrochloride (in trihydrate form) (b) (4) which corresponds to 10.0 mg vardenafil.

Vardenafil hydrochloride ODT 10 mg is manufactured, packaged and released by Bayer Schering Pharma AG, Leverkusen, Germany.

Vardenafil hydrochloride ODT contains (b) (4) drug substance, vardenafil hydrochloride trihydrate, peppermint flavor, and the following excipients: Pharmaburst B2, consisting of mannitol, sorbitol, crospovidone and silica; aspartame; and magnesium stearate. The tablet is formed by (b) (4)

Data provided in the submission for three validation, commercial scale batches support that the manufacturing process is validated.

The tablets are controlled by the following tests: description, identification, friability, disintegration, specified, unspecified and total degradation products, assay, uniformity of dose, and microbial purity.

## Executive Summary Section

Most of the methods for analysis of drug product are identical to methods approved for Levitra, NDA 21-400. An exception is the disintegration method, which is proposed in place of a dissolution method due to the rapid disintegration time of the tablet.

The tablets are packaged in a child-resistant, tear-apart, aluminum/aluminum blister, 4 blisters per blister card.

The drug substance, vardenafil hydrochloride, is a selective phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction. The drug substance is identical to the drug substance approved for Levitra (vardenafil hydrochloride), NDA 21-400. A Letter of Authorization from Bayer to access NDA 21-400 for chemistry, manufacturing and controls is provided in this submission.

Vardenafil hydrochloride is manufactured by Bayer Schering Pharma AG in Wuppertal, Germany, and (b) (4) at the Bayer Schering Pharma AG site in Leverkusen, Germany.

Vardenafil hydrochloride is controlled by the following tests: color, identity by HPLC, identity by IR, identity for chloride, particle size distribution, appearance of solution, sulfated ash, heavy metals, water content, residual solvents, impurities (specified, unspecified, and total), assay, and microbiological purity.

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

Vardenafil hydrochloride orally disintegrating tablet 10 mg is formulated to rapidly disintegrate in the mouth in (b) (4) seconds. This allows a convenient administration of the drug without water.

**C. Basis for Approvability or Not-Approval Recommendation**

The sponsor has provided sufficient information regarding raw material controls, manufacturing processes and process controls, and stability data that assure the quality of the drug product during the expiration dating period.

Labeling issues have not yet been resolved, and no overall "Acceptable" recommendation from the Office of Compliance has been made as of the date of this review. Therefore, from a CMC perspective, this NDA is *not recommended* for approval until all pending issues are resolved.

## Executive Summary Section

**III. Administrative****A. Reviewer's Signature:**

(See appended electronic signature page.)

**B. Endorsement Block:**

(See appended electronic signature page.)

**C. CC Block:**

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200179	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	VARDENAFIL HCL

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/s/

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JEAN SALEMME  
05/10/2010

MOO JHONG RHEE  
05/11/2010  
Chief, Branch IV

Initial Quality Assessment  
Branch III  
Pre-Marketing Assessment Division II

**OND Division:** Division of Reproductive and Urologic Products  
**NDA:** 200-179  
**Applicant:** Bayer Healthcare Pharmaceuticals, Inc.  
**Stamp Date:** 26-Aug-2009  
**PDUFA Date:** 26-Jun-2010  
**Trademark:** (b) (4)  
**Established Name:** Vardenafil hydrochloride  
**Dosage Form:** Orally disintegrating tablets  
**Route of Administration:** Oral  
**Indication:** Erectile Dysfunction  
  
**PAL:** Donna F. Christner, Ph.D.

	YES	NO
<b>ONDQA Fileability:</b>	X	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	X	<input type="checkbox"/>

**Summary and Critical Issues:**

**A. Summary**

The drug product is an orodispersible white, round, biconvex, (b) (4) tablet containing 10 mg vardenafil hydrochloride (b) (4) for oral use. The tablet formulation is packaged in aluminum blister packages. The sponsor states that the orodispersible tablet has been developed for discreet intake without water and to improve convenience for patients with difficulties to swallow conventional tablets.

Drug substance information is cross-referenced to approved NDA 21-400.

**B. Critical issues for review**

*The sponsor has provided data in two different blisters, only one of which will be for the US market. The data for the non-US blister is more extensive than that for the US blister. It will require careful evaluation during the review cycle whether the US material will provide equivalent or better protection than the non-US material for full use of the primary stability data to support the requested expiration dating period.*

### C. Comments for 74-Day Letter

- *As per 21 CFR 206.10, a code imprint is required on solid oral dosage forms. The sponsor should add a code imprint to the dosage form or provide justification why an imprint is not provided.*
- *The proprietary and established names on all labels should be updated as follows to reflect the dosage form.*

***TRADENAME (vardenafil hydrochloride) orally disintegrating tablets***

- *As per 21 CFR 201.21(c), the following warning statement should be included on all package labeling. We note that it is included in the Physician Insert:*

***Phenylketonurics: Contains Phenylalanine (\_\_)mg per tablet***

- *Please provide a sample of the drug product or placebo packaged in the to-be-marketed packaging, including the { } secondary packaging.*
- *Provide updated stability data in the US container closure system by December 2009 for review.*

### D. Recommendation:

This NDA is fileable from a CMC perspective. There are five CMC comment for the 74-day letter. The ONDQA BioPharm group also has a comment to be conveyed in the 74-day letter concerning dissolution testing which is delineated in their consult memo. A single reviewer, Jean Salemme, Ph.D. has been assigned.

---

Donna F. Christner, Ph.D.

**NDA Number: 200-179**

**Applicant: Bayer Healthcare**

**Stamp Date: 26-Aug-2009**

**Drug Name:** (b) (4)

**NDA/BLA Type:3**

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		Categorical exclusion as per 21 CFR 25.31(b)
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		Cross-referenced to NDA 21-400
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	X		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	X		N/A

**IS THE CMC SECTION OF THE APPLICATION FILEABLE?** Yes

If the NDA/BLA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Donna F. Christner, Ph.D.

16-Oct-2009

Pharmaceutical Assessment Lead

Date

Moo-Jhong Rhee, Ph.D.

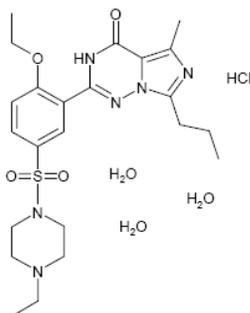
Branch Chief

Date



## DRUG SUBSTANCE

The drug substance is vardenafil HCl. The sponsor states that information on the drug substance is contained in Module 2.3.S. They have referenced to their approved NDA 21-400, LEVITRA (vardenafil HCl) tablets, for drug substance information.



Chemical name	2-[2-Ethoxy-5-(4-ethyl-piperazine-1-sulfonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one monohydrochloride trihydrate		
INN, USAN	Vardenafil (INN, USAN for the free base)		
CAS number	Vardenafil:	224785-90-4	
	Vardenafil monohydrochloride:	224785-91-5	
Internal codes	Vardenafil:	Bay 38-7268,	(b) (4)
	Vardenafil monohydrochloride:	Bay 38-9456,	

The following information is cross-referenced to NDA 21-400:

- Manufacture
- Characterization
- Analytical Methods and Validation
- Justification of Specification
- Reference Standards or Materials
- Container Closure System
- Stability

## MANUFACTURE

The sponsor states the following concerning the manufacture of the drug substance:

The drug substance vardenafil hydrochloride is manufactured at Bayer Schering Pharma AG, site Wuppertal, Germany, and is (b) (4) at Bayer Schering Pharma AG, site Leverkusen, Germany.

In response to a request by Catherine Tran-Zwanetz, ONDQA PM, the sponsor provided the following contact information for the manufacturer:

Bayer Schering Pharma AG  
Friedrich-Ebert Str 217-333  
42096 Wuppertal  
Germany

ERN 3003229486

Drug Substance – All Steps

Contact Name: Klaus-Helmut Mohrs  
Telephone Number +49 202 36 2307

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***Comment:*** EES was submitted on 06-OCT-2009 by Jeannie David, ONDQA PM.

#### SPECIFICATION

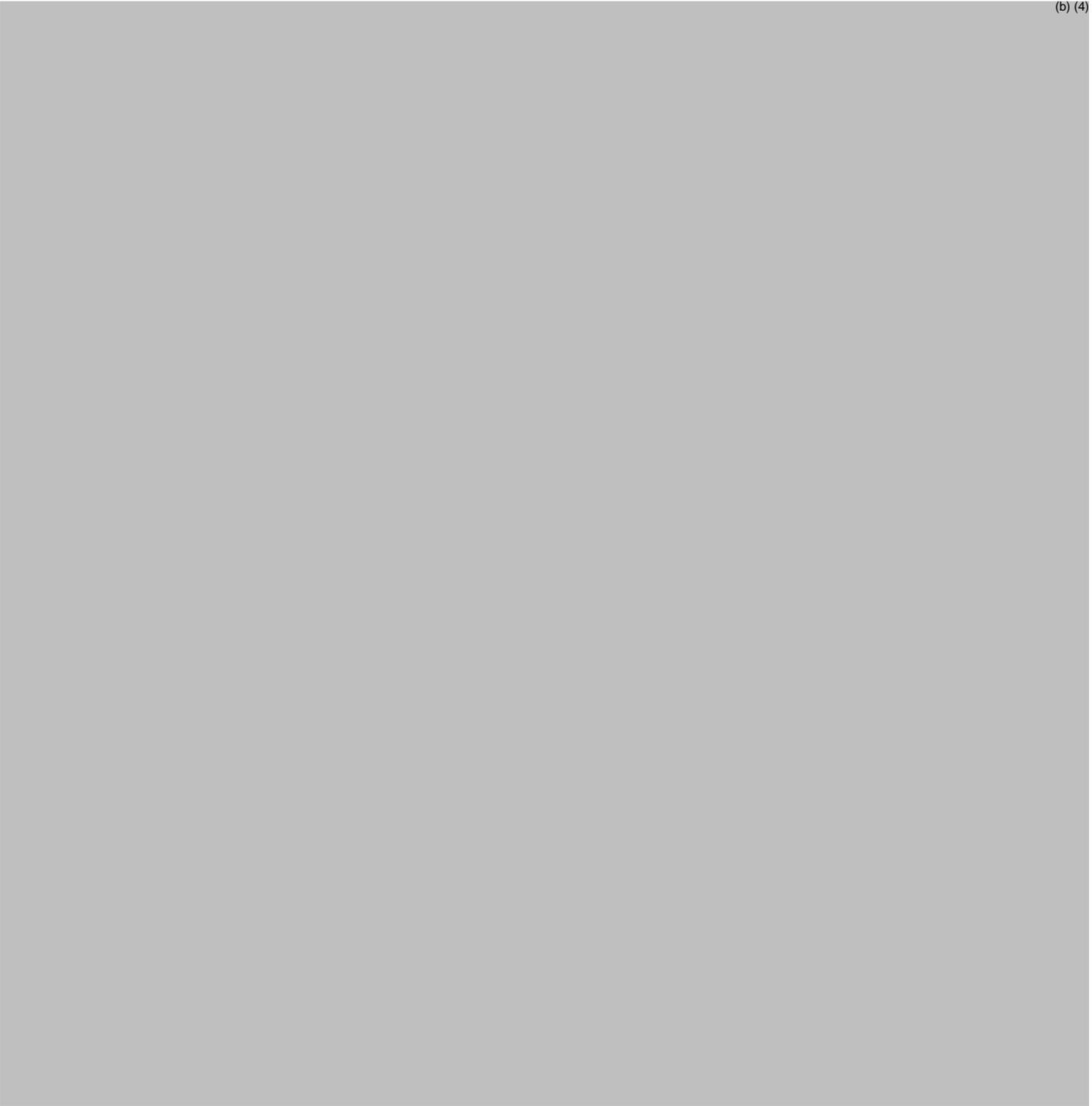
The quality of the drug substance is controlled by the following specification:

(b) (4)



The sponsor has provided the following batch results:

(b) (4)



***Comment:** Information is adequate to allow review.*

DRUG PRODUCT

The drug product is an orodispersible white, round, biconvex, (b) (4) tablet containing 10 mg vardenafil hydrochloride (b) (4) for oral use. The tablet formulation is packaged in aluminum blister packages. The sponsor states that the orodispersible tablet has been developed for discreet intake without water and to improve convenience for patients with difficulties to swallow conventional tablets.

The sponsor has provided the following information on the tablet composition:

**Table 1-1: Composition of Vardenafil hydrochloride orodispersible tablet 10 mg**

Composition	Reference to standard	Function	Amount [mg]		
<b>Drug substance</b>					
Vardenafil hydrochloride trihydrate micronized specification		drug substance	11.85 <sup>a</sup>		
<b>Excipients</b>					
Aspartame	Ph. Eur., NF specification <sup>b</sup>	(b) (4)	(b) (4)		
Flavor peppermint	Ph. Eur., NF, Ph. Jap. specification				
Magnesium stearate					
Pharmaburst B2 <sup>c</sup> consisting of:					
Crospovidone	Ph. Eur., NF				
Mannitol	Ph. Eur., USP				
Silica colloidal hydrated	Ph. Eur., NF				
Sorbitol	Ph. Eur., NF				
<b>Weight</b>				<b>180.00</b>	
(b) (4)					

b components of flavor peppermint are of Ph. Eur., FCC and BP quality  
c exact specification of the commercially available blend Pharmaburst<sup>TM</sup> B2 is stated in the composition of (b) (4)

All excipients are compendial with the exception of the peppermint flavor and the Pharmaburst B2. The components of the peppermint flavor are of Ph.Eur., FCC and BP quality. The components of the Pharmaburst B2 comply with the compendial standards, and full information is provided in the referenced DMF. Excipients are controlled by compendial methods. Additional controls are in place for the Pharmaburst B2 and peppermint flavor excipients.

The sponsor has provided a full Pharmaceutical Development section outlining the development of their dosage form.

**Comment:** Information is adequate to allow review.

The tablet contains aspartame. As per 21 CFR 201.21(c), the labeling should contain the statement: “Phenylketonurics: Contains Phenylalanine (\_\_\_) mg per tablet”. See the Labeling Section of this review.

MANUFACTURING

The sponsor has provided the following information on the manufacturing of the tablets:

Vardenafil hydrochloride orodispersible tablet 10 mg is manufactured, packaged, quality controlled and released by Bayer Schering Pharma AG, Leverkusen, Germany. Secondary packaging into the (b) (4)

In response to a request by Catherine Tran-Zwanetz, ONDQA PM, the sponsor provided the following contact information for the manufacturer:

Bayer Schering Pharma AG  
51368 Leverkusen  
Germany

ERN 3002806462

Drug Product- All steps

Contact Name: Matthias Herboth  
Telephone Number +49 214 30 57430



***Comment:*** EES was submitted on 06-OCT-2009 by Jeannie David, ONDQA PM.

The sponsor has provided the following flow chart for the manufacture of the tablets. A narrative is also provided.



The sponsor has provided the following process controls for the tablets.



***Comment:*** Information is adequate to allow review.

## SPECIFICATION

The sponsor has provided the following specification to control the quality of the drug product:

(b) (4)



The sponsor has provided analytical methods, validation and justification.

A consult was sent on 15-Sep-2009 to the ONDQA Biopharmaceutics team to evaluate if a test for Disintegration was adequate to assure that drug was released from the dosage form, or if Dissolution should also be added to the Specification. In a consult memo, Sandra Suarez-Sharp, the BioPharmaceutics reviewer, stated that Disintegration was not adequate for Quality Control and that a Dissolution test should be included. A comment will be included in the 74-day letter.

In discussion with Jean Salemmé, the primary CMC reviewer, it was noted that the dosage form does not contain a code imprint as required by 21 CFR 206.10. The following comment should be included in the 74-day letter.

***Comment:*** *As per 21 CFR 206.10, a code imprint is required on solid oral dosage forms. The sponsor should add a code imprint to the dosage form or provide justification why an imprint is not provided.*

## CONTAINER CLOSURE SYSTEM

For the US market, the sponsor plans to package the drug product in the following aluminum blisters:



*Comment: Information is adequate to allow review.*

## STABILITY

The sponsor has provided the following stability package in support of their requested expiration dating period.



**Comment:** The sponsor has provided data in two different blisters, only one of which will be for the US market. The data for the non-US blister is more extensive than that for the US blister. It will require careful evaluation during the review cycle whether the US material will provide equivalent or better protection than the non-US material for full use of the primary stability data to support the requested expiration dating period.

Since the stability study using the US container closure system was begun in December 2008, the sponsor should have additional stability data available. The sponsor should provide updated stability data by December 2009 for review.

## LABELING

Carton and container labels are provided in the original NDA submission. The SPL label is provided in Amendment 2 and contains the DLDE table which will require review. (b) (4)

The sponsor lists the proprietary and established names as : “ (b) (4) (vardenafil hydrochloride) for oral use”. This should be changed to read: “TRADENAME (vardenafil hydrochloride) orally disintegrating tablets”.

**Comment:** The proprietary and established names on all labels should be updated as follows to reflect the dosage form.

### **TRADENAME (vardenafil hydrochloride) orally disintegrating tablets**

The tablet contains aspartame. As per 21 CFR 201.21(c), the package labeling should contain the the statement: “Phenylketonurics: Contains Phenylalanine (b) (4) mg per tablet” . The warning is contained in the Physician’s Insert as required.

**Comment:** As per 21 CFR 201.21(c), the following warning statement should be included on all package labeling. We note that it is included in the Physician Insert:

### **Phenylketonurics: Contains Phenylalanine ( )mg per tablet**

**Comment:** Please provide a sample of the drug product or placebo packaged in the to-be-marketed packaging, including the secondary (b) (4)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DONNA F CHRISTNER  
10/16/2009

MOO JHONG RHEE  
10/19/2009  
Chief, Branch III