

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200179Orig1s000

OTHER REVIEW(S)

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information	
NDA # 200179	
Proprietary Name: (b) (4) Established/Proper Name: vardenafil hydrochloride Dosage Form: tablet Strengths: 10mg	
Applicant: Bayer Healthcare Pharmaceuticals Agent for Applicant (if applicable):	
Date of Application: August 26, 2009 Date of Receipt: August 26, 2009 Date clock started after UN: N/A	
PDUFA Goal Date: June 26, 2010 (Saturday)	Action Goal Date (if different): June 25, 2010 (Friday)
Filing Date: October 25, 2009	Date of Filing Meeting: October 14, 2009
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3	
Proposed indication: treatment of male erectile dysfunction	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 57,703				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>			X	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes , explain in comment column.				
If affected by AIP , has OC/DMPQ been notified of the submission? If yes , date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
 <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?																				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).																				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>																				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:																				
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>		X																		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: 3 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X																			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA</i> s only)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i> s/ <i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i> s/ <i>BLA</i> efficacy supplements) including: <input checked="" type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.				
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #				

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			<p>New Dose Form (oral disintegrating table)</p> <p>George Greeley of PeRC will be contacted.</p>
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>				
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>				

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			Will be submitted separately to DMEPA.
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			PPI Only
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): April 14, 2008 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA meeting communication Date: October 8, 2008 <i>If yes, distribute minutes before filing meeting</i>	X			Bayer cancelled meeting but responses were conveyed.
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 14, 2009

NDA/Supp #: 200179

PROPRIETARY NAME: [REDACTED] (b) (4)

ESTABLISHED/PROPER NAME: vardenafil hydrochloride

DOSAGE FORM/STRENGTH: 10 mg

APPLICANT: Bayer Healthcare

INDICATION: treatment of erectile dysfunction

BACKGROUND: Levitra (vardeafil hydrochloride) was approved in August 2003 for the treatment of male erectile dysfunction. This new NDA 200179 submitted on August 26, 2009 is a new dose form, orally disintegrating tablet.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	DeGuia	Y
	CPMS/TL:	Mercier	N
Cross-Discipline Team Leader (CDTL)	Kaul		Y
Clinical	Reviewer:	McNellis	Y
	TL:	Kaul	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Apparaju	Y
	TL:	Kim	Y
Biostatistics	Reviewer:	Fang	Y
	TL:	Sobhan	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Shin	Y
	TL:	Reid	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Salemme	Y
	TL:	Christner	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Abdus-Samad	Y
	TL:	Bridges	N
OSE/DRISK (REMS)	Reviewer:	Wasilik	Y
	TL:	Willy	N
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: See statistician filing memo for requests</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>Comments:</p> <ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: Clinical team determined DSI audit is not needed.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

--	--

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Benson	
21st Century Review Milestone:	
Comments: Review timeline was distributed to all the review teams at the Filing Meeting.	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. See 74-day letter in DARRTS. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

EUFRECINA P DEGUIA
10/23/2009

JENNIFER L MERCIER
10/26/2009

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: May 21, 2010

To: Freshnie DeGuia – Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (DRUP)

From: Emily Baker – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Through: Mathilda Fienkeng – Regulatory Reviewer Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 200179 (b) (4) **(vardenafil hydrochloride) orally disintegrating tablets**

DDMAC has reviewed the proposed product labeling (PI) for (b) (4) (vardenafil hydrochloride) orally disintegrating tablets (b) (4) submitted for consult on October 23, 2009.

The following comments are provided using the updated proposed PI sent via email on May 20, 2010 by Nenita Crisostomo. If you have any questions about DDMAC's comments, please do not hesitate to contact me.

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

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

/s/

EMILY K BAKER
05/21/2010

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: May 24, 2010

To: Eufrecina DeGuia – Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (DRUP)

From: Carrie Newcomer, PharmD
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 200179 (b) (4) (vardenafil hydrochloride) orally
disintegrating tablets

DDMAC has reviewed the proposed patient labeling (PPI) for (b) (4) (vardenafil hydrochloride) orally disintegrating tablets (b) (4) submitted for consult on October 23, 2009.

The following comments are provided using the updated proposed PI and PPI sent via email on May 21, 2010, by Nenita Crisostomo. If you have any questions about DDMAC's comments, please do not hesitate to contact me.

21 Page(s) of Draft Labeling have 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

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

/s/

CARRIE A NEWCOMER
05/24/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: May 28, 2010

To: Scott Monroe, M.D., Division Director
Division of Reproductive and Urologic Products (DRUP)

Through: Mary Willy, PhD, Deputy Director
Division of Risk Management (DRISK)
LaShawn Griffiths, MSHS-PH, BSN, RN
Patient Product Information Reviewer, Acting Team Leader
Division of Risk Management

From: Melissa Hulett, MSBA, BSN, RN
Patient Product Information Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Product Information)

Drug Name(s): (b) (4) (vardenafil hydrochloride) orally disintegrating tablet

Application Type/Number: NDA 200179

Applicant/sponsor: Bayer Healthcare Pharmaceuticals Inc

OSE RCM #: 2010-1144

1 INTRODUCTION

Bayer Healthcare Pharmaceuticals Inc submitted an original 505 (b) (1) New Drug application, NDA #200179, (b) (4) (vardenafil hydrochloride) orally disintegrating tablet, on August 26, 2009. Levitra (vardenafil hydrochloride), is the Reference Listed Drug.

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Product Information (PPI) for (b) (4) (vardenafil hydrochloride) orally disintegrating tablet. Please let us know if DRUP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft (b) (4) (vardenafil hydrochloride) orally disintegrating tablet Prescribing Information (PI) submitted August 26, 2009, revised by the Review Division throughout the current review cycle, and received by DRISK on May 24, 2010.
- Draft (b) (4) (vardenafil hydrochloride) orally disintegrating tablet Patient Product Information (PPI) submitted on August 26, 2009, revised by the review division throughout the review cycle, and received by DRISK on May 24, 2010.

3 RESULTS OF REVIEW

Based on a request from DRUP, this review focuses on two lines of revised language in the PPI. DRISK recommends a complete review of this PPI as well the PPI of the Reference Listed Drug in the future to update the PPIs to current Patient Labeling standards.

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

21 Page(s) of Draft Labeling have 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	WARDENAFIL HCL

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

/s/

MELISSA I HULETT
05/28/2010

MARY E WILLY
05/30/2010
I concur



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: June 9, 2010

To: Scott Monroe, MD, Director
Division of Reproductive and Urologic Products (DRUP)

Through: Todd Bridges, RPh, Team Leader
Kellie Taylor, PharmD, MPH, Associate Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Jibril Abdus-Samad, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Staxyn (Vardenafil Hydrochloride) Orally Disintegrating Tablets,
10 mg

Application Type/Number: NDA# 200179

Applicant: Bayer HealthCare Pharmaceuticals, Inc.

OSE RCM #: 2009-1971

1 INTRODUCTION

This review responds to a request from the Division of Reproductive and Urologic Products (DRUP) for DMEPA's assessment of labels and labeling for Staxyn (Vardenafil Hydrochloride) Orally Disintegrating Tablets for their vulnerability to medication errors.

2 REGULATORY HISTORY

DMEPA participated in the labeling meeting with DRUP's review team on May, 5 2010. During the meeting, DMEPA discussed the potential for healthcare providers and patients to inappropriately interchange Staxyn and Levitra. DMEPA communicated to the review Division that we recommend the Applicant educate healthcare providers and patients that Staxyn and Levitra are not interchangeable through their marketing campaign at product launch. Furthermore, we e-mailed our additional recommendations for the insert labeling to DRUP on May 21, 2010. DRUP and the Office of New Drug Quality Assessment concurred with our recommendations (see Appendix A). Lastly, DRUP incorporated our recommendations into the insert labeling prior to sending it to the Applicant on May 21, 2010.

For this product, the Applicant initially proposed the proprietary name, (b) (4). However, the name was found unacceptable for promotional concerns. These promotional concerns and additional safety concerns were discussed during a teleconference held on December 14, 2009, and communicated to the Applicant in a letter dated January 28, 2010. Subsequently, in a letter dated February 15, 2010, the Applicant requested review of the proposed proprietary names, (b) (4) and (b) (4). A teleconference was held on April 13, 2010, to discuss safety issues with the proposed proprietary names (b) (4) and (b) (4). These concerns were also communicated to the Applicant in a letter dated May 19, 2010. The Applicant subsequently proposed a new proprietary name, (b) (4) in a letter dated April 20, 2010. In a teleconference held May 27, 2010, DMEPA communicated that the proposed name (b) (4) was unacceptable. Subsequently, the Applicant submitted the proposed proprietary name, Staxyn, for review on June 2, 2010. This proposed proprietary name is currently under review in OSE Review 2010-1246, and there has not been a decision made regarding the acceptability of this proprietary name.

3 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis¹ (FMEA), DMEPA evaluates container labels, carton labeling, and insert labeling. This review summarizes our evaluation of the labels and labeling submitted by the Applicant on April 20, 2010 and the updated container labels and carton labeling submitted by the Applicant on June 2, 2010 (see Appendix B through H; no image of insert labeling).

4 RECOMMENDATIONS

The proposed proprietary name, Staxyn, is currently under review by DMEPA. The container labels and carton labeling bear this proposed proprietary name, therefore the labels and labeling for this product are not acceptable for marketing bearing this proposed proprietary name. Our evaluation noted areas where information on the label and labeling can be clarified and improved upon to minimize the potential for medication errors. Section 4.1 (*Comments to the Applicant*) contains our recommendations for the container labels and carton labeling. We request these recommendations be communicated to the Applicant prior to approval.

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Karen Townsend, OSE Regulatory Project manager, at 301-796-5413.

4.1 COMMENTS TO THE APPLICANT

A. General Comment

1. The proposed proprietary name, Staxyn, is currently under review by DMEPA. The container labels and carton labeling bear this proposed proprietary name, therefore the labels and labeling for this product are not acceptable for marketing bearing this proposed proprietary name.
2. Clarify which manufacturer, distributor or marketing entity patients and healthcare providers must contact for inquiries or to report adverse events for your product. There are multiple companies present on the carton labeling without clear indication of who receives correspondence for your product.

B. All Blister Container Labels

Revise the dosage form statement from ‘orally disintegrating tablets’ to read ‘orally disintegrating tablet’ since there is only one tablet contained in each unit dose blister.

C. Sample Blister Container Labels

1. Relocate the strength to appear after the dosage form. As currently presented, the strength is located between the established name and dosage form. Thus, the statement should read as follows:

Staxyn
(vardenafil hydrochloride)
orally disintegrating tablet 10 mg

2. Delete the graphic of what appears as a crossed out tablet. It is unclear what this graphic represents and may lead to confusion. Consider substituting the graphic with a statement to convey your intended message.

D. All Carton Labeling

1. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. Decrease the prominence of the quantity of tablets and increase the prominence of the strength. As currently presented, the quantity of tablets has more prominence than the product strength. The product strength is more important than the quantity in regards to identifying the correct drug product and thus must be more prominent.
3. Revise the statement ‘DOSAGE: Take one tablet as needed’ to read ‘USUAL DOSAGE: Take on tablet as needed.’

E. Sample Carton Labeling (2 tablets) and Carton Labeling (4 tablet tablets)

1. Revise the strength statement to read 10 mg per tablet since this product will be a unit dose blister pack. As currently presented, patients may potentially conclude all the tablets in the package are needed to achieve the 10 mg dose.
2. Include the product strength on the side panel attached to the principal display panel.

3. Relocate the two schematics and associated text that instruct patients to place Staxyn on the tongue and take Staxyn without liquid from its current location to directly below the strength. This improves readability of the labeling and decreases crowding of information.

F. Sample Carton Labeling

Decrease the prominence of the statement ‘Professional sample. Not for sale’ and relocate it to another space on the principle display panel to make room for the two schematics and associated text that instruct patients to place Staxyn on the tongue and take Staxyn without liquid.

G. Carton Labeling (4 tablets)

Delete the statement *Staxyn Pack*. *Staxyn Pack* appears to be a proprietary name of a pack configuration; however, *Staxyn* was submitted for review as a proprietary name for this product.

H. Carton Labeling (40 tablets)

Include the product strength on the rear panel after the dosage form statement.

APPENDICES

Appendix A: DMEPA Insert Labeling recommendations forwarded to DRUP on May 21, 2010

1. Highlights of Prescribing Information

The statement reads:

STAXYN (vardenafil hydrochloride) orally disintegrating tablets
for oral use.

We are unsure if the statement 'for oral use' belongs in this location.

2. Highlights of Prescribing Information – WARNINGS AND PRECAUTIONS

Revise the abbreviation 'NAION' to read 'non-arteritic anterior ischemic optic neuropathy (NAION)'. The abbreviation should be defined prior its use throughout the insert labeling.

3. Patient Information

Revise the following sentence to include Levitra:

'STAXYN is not interchangeable with vardenafil film-coated tablets'.

Patients may understand the name *Levitra* more so than *vardenafil film-coated tablets*. This is the presentation used in the Dosage and Administration section. Thus, the sentence should read:

STAXYN is not interchangeable with vardenafil film-coated tablets (Levitra).

7 Page(s) of Draft Labeling have 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

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

/s/

JIBRIL ABDUS-SAMAD
06/09/2010

TODD D BRIDGES
06/09/2010

KELLIE A TAYLOR
06/09/2010

CAROL A HOLQUIST
06/10/2010

NDA 200-179

Vardenafil HCL orodispersible tablet (b) (4)

Medical Officer's Filing Review Memorandum

Application Letter Date: August 26, 2009
45-Day Filing Review Date: October 10, 2009
PDUFA Goal Date: June 26, 2010
Product and Dose: Vardenafil HCL orodispersible tablet 10 mg
Indication: Erectile Dysfunction

1. Executive Summary Objective: This review is conducted to fulfill a regulatory requirement of reviewing **NDA 200-179** (vardenafil HCl orodispersible tablet) to determine its suitability for filing under 21 CFR 314.50. This document will also serve as the basis for communicating to the sponsor the review issues identified during the initial filing period.

Recommendation: Following a preliminary review of results from the two pivotal studies, as well as the safety data, it is the impression of the clinical reviewer that the application is sufficiently complete to permit a substantive clinical review and should be filed.

2. NDA Filing Review

Drug Product: Vardenafil HCl (Levitra®) is a phosphodiesterase type 5 (PDE5) inhibitor and was approved by the Agency in 2003 under NDA 21-400 for treatment of erectile dysfunction.

The recommended vardenafil oral starting dose for the treatment of erectile dysfunction is 10 mg, once daily as needed. A starting dose of 5 mg should be considered in patients ≥65 years of age. The dose may be titrated upward to 20 mg, or downward to 5 mg, depending on response to the starting dose. A 2.5 mg dose is available for patients receiving concomitant CYP3A4 inhibitors.

Penile erection is a hemodynamic process initiated by the relaxation of smooth muscle in the corpus cavernosum and its associated arterioles. During sexual stimulation, nitric oxide is released from nerve endings and endothelial cells in the corpus cavernosum. Nitric oxide activates the enzyme guanylate cyclase resulting in increased synthesis of cyclic guanosine monophosphate (cGMP) in the smooth muscle cells of the corpus cavernosum. The cGMP in turn triggers smooth muscle relaxation, allowing increased blood flow into the penis, resulting in erection. The tissue concentration of cGMP is

regulated by both the rates of synthesis and degradation via phosphodiesterases (PDEs). The most abundant PDE in the human corpus cavernosum is the cGMP-specific phosphodiesterase type 5 (PDE5); therefore, the inhibition of PDE5 enhances erectile function by increasing the amount of cGMP.

Vardenafil is rapidly absorbed after oral administration. Maximum observed plasma concentrations after a single 20 mg dose in healthy volunteers are usually reached between 30 minutes and 2 hours after oral dosing in the fasted state. In a healthy volunteer study of elderly males (≥ 65 years) and younger males (18–45 years), mean C_{max} and AUC were 34% and 52% higher, respectively, in the elderly males. Consequently, the current labeling indicates that a lower starting dose of LEVITRA (5 mg) should be considered in patients ≥ 65 years of age.

Vardenafil is metabolized predominantly by the hepatic enzyme CYP3A4, with contribution from the CYP3A5 and CYP2C isoforms. The major circulating metabolite, M1, results from desethylation at the piperazine moiety of vardenafil. The plasma concentration of M1 is approximately 26% that of the parent compound. This metabolite shows a phosphodiesterase selectivity profile similar to that of vardenafil and an *in vitro* inhibitory potency for PDE5 28% of that of vardenafil. Therefore, M1 accounts for approximately 7% of total pharmacologic activity.

After oral administration, vardenafil is excreted as metabolites predominantly in the feces (approximately 91-95% of administered oral dose) and to a lesser extent in the urine (approximately 2-6% of administered oral dose).

In this application, the Sponsor is requesting approval of a new formulation of vardenafil, an orodispersible tablet. This tablet dissolves in the patients mouth, and is not taken with water. The Sponsor has developed the tablet in only one strength, 10 mg. Because of the single 10 mg formulation, (b) (4)

Criteria for Filing: This review is based on the three criteria proposed in the FDA Guidance “New Drug Evaluation Guidance Document: Refusal to File” (July 12, 1993), which represents FDA’s interpretation of 21 CFR 314.50. These criteria are:

- Omission of a section of the NDA required under 21 CFR 314.50, or presentation of a section in an incomplete manner
- Failure to include evidence of effectiveness compatible with the statute and regulations
- Omission of critical data, information or analyses needed to evaluate effectiveness and safety or failure to provide adequate directions for use.

Question 1: Does this NDA omit a section required under CFR 314.50 or was a particular section presented in such a manner to render it incomplete for clinical review?

Answer: No

This NDA contains the critical sections in sufficient detail to permit a substantive Clinical review. The Sponsor has submitted study reports for two Phase 3 Efficacy studies, safety data that is consistent with ICH requirements, labeling, and Safety/Efficacy summaries.

Question 2: Does the NDA clearly fail to include evidence of effectiveness compatible with the statute and regulations, for example:

- **Lack of any adequate and well-controlled studies, including use of obviously inappropriate or clinically irrelevant study endpoints**
- **Presentation or what appears to be only a single adequate and well-controlled trial without adequate explanation**
- **Use of study design clearly inappropriate**

Answer: No

As per the requirement of the Agency, the sponsor submitted data from two adequate and well-controlled Phase 3 trials (Trials 12093 and 12094). The trial design and endpoints of each were appropriate and consistent with those of the Phase 3 trials used for the initial approval of Levitra. Both were randomized, multi-center, double-blinded, placebo-controlled, parallel-group trials to determine the efficacy and safety of the 10 mg orodispersible formulation of vardenafil, taken as needed, in the treatment of erectile dysfunction. The design of the two trials was identical.

Trial Design

These trials compared the efficacy and safety of vardenafil orodispersible tablet (ODT) to that of placebo in the treatment of erectile dysfunction. Trial 12093 was carried out at 40 centers in Belgium, France, Germany, Spain, South Africa, and The Netherlands. A total of 362 patients were randomized into trial 12093 and received at least one dose of study treatment. Trial 12094 was carried out at 35 centers in the US, Canada, Mexico, and Australia. A total of 339 patients were randomized into trial 12094 and received at least one dose of trial treatment.

In each trial patients received either a 10 mg vardenafil ODT or a matching placebo. The trial medication was taken as needed, but not more than once in 24 hours. The treatment period was 12 weeks.

Diagnosis and main criteria for inclusion: Men, 18 years-of-age or older with erectile dysfunction (defined according to the NIH Consensus Development Panel on Impotence) for more than 6 months. Approximately 50% of the patients on treatment should be 65

years-of-age or older. Subjects must be in a stable, heterosexual relationship for at least 6 months and they should be highly motivated to obtain treatment for ED.

Primary Endpoint

Three primary efficacy variables were evaluated:

- International Index of Erectile Function, Erectile Function Domain, (IIEF-EF) score at Visit 4 (Week 12) or LOCF
- Sexual Encounter Profile (SEP) Question 2 (success rates of penetration) at Visit 4 (Week 12) overall
- Sexual Encounter Profile (SEP) Question 3 (maintenance of erection) at Visit 4 (Week 12) overall

The primary measures of efficacy were the changes in the SEP 2 and SEP 3 success rates reported over the entire treatment course (cumulated attempts from baseline to Week 12) and the IIEF-EF at the last available observation (LOCF) compared to baseline. These variables were tested simultaneously and the difference between treatment and placebo cohorts for all three variables was required to be significant at the 5% level ($p < 0.05$). The primary analyses were based on the ITT population.

Secondary Endpoints

- Percentage of subjects achieving “back to normal” erectile function (IIEF-EF \geq 26) at Visit 4 (Week 12) or LOCF
- All diary questions other than SEP 2 and 3 that concerned erectile function that were assessed over the entire treatment period
- Number of sexual attempts under medication till first successful attempt (SEP 3)
- The Treatment Satisfaction Scale (TSS); baseline versus endpoint
- A Global Assessment Question (GAQ) to be administered at the final visit only (or at Premature Discontinuation)

Efficacy

In Study 12093 172 patients were randomized to placebo and 183 randomized to vardenafil ODT.

The efficacy result based on IIEF-EF is shown in **Table 1. Study 12093 - EF Domain Scores of IIEF**, based on the SEP 2 response rate in **Table 2. Study 12093 - Success Rates for penetration (SEP 2)**, and based on the SEP 3 response rate in **Table 3. Study 12093 - Success rates for maintenance (SEP 3)** Each of these endpoints indicates significant efficacy with $p < 0.0001$.

Table 1. Study 12093 - EF Domain Scores of IIEF

ITT population		Placebo	(b) (4) (b) (4) 10 mg
Summary statistics			
< 65 years		n = 80	n = 85
(arithmetic mean ± SD)	Baseline	13.4 ± 4.74	13.4 ± 4.78
	Week 12 (LOCF)	15.4 ± 7.64	23.0 ± 6.95
	Change from Baseline	2.1 ± 7.33	9.6 ± 6.28
≥ 65 years		n = 92	n = 96
(arithmetic mean ± SD)	Baseline	12.3 ± 5.44	12.2 ± 4.87
	Week 12 (LOCF)	13.2 ± 7.42	19.9 ± 8.81
	Change from Baseline	0.9 ± 6.42	7.7 ± 8.19
Total		n = 172	n = 181
(arithmetic mean ± SD)	Baseline	12.8 ± 5.14	12.8 ± 4.85
	Week 12 (LOCF)	14.2 ± 7.59	21.4 ± 8.12
	Change from Baseline	1.4 ± 6.86	8.6 ± 7.40
(LS-mean)	Baseline	12.85	12.86
	Week 12 (LOCF)	14.38	21.48
Comparison (LS-mean difference [95% CI]; p-values [ANCOVA])			
	Treatment: Placebo – Active	-7.11 [-8.56 to -5.66]	
	Age group: < 65 years – ≥ 65 years	2.00 [0.54 to 3.47]	
	Treatment	p < 0.0001	
	Age group	p = 0.0076	

CI: confidence interval; IIEF: International Index of Erectile Function; LS: least squares; SD: standard deviation

Table 2. Study 12093 - Success Rates for penetration (SEP 2)

ITT population		Placebo	(b) (4) (b) (4) 10 mg
Summary statistics			
< 65 years		n = 79	n = 85
(arithmetic mean ± SD)	Baseline	43.1% ± 36.86%	44.7% ± 36.68%
	Overall	48.6% ± 39.55%	80.5% ± 26.84%
	Change from Baseline	5.5% ± 42.82%	35.8% ± 33.63%
≥ 65 years		n = 90	n = 94
(arithmetic mean ± SD)	Baseline	32.5% ± 34.77%	34.6% ± 33.85%
	Overall	41.2% ± 37.22%	69.8% ± 35.87%
	Change from Baseline	8.7% ± 28.41%	35.2% ± 38.06%
Total		n = 169	n = 179
(arithmetic mean ± SD)	Baseline	37.5% ± 36.04%	39.4% ± 35.48%
	Overall	44.7% ± 38.38%	74.9% ± 32.26%
	Change from Baseline	7.2% ± 35.79%	35.5% ± 35.93%
(LS-mean)	Baseline	38.76	40.38
	Overall	46.68	73.73
Comparison (LS-mean difference [95% CI]; p-values [ANCOVA])			
	Treatment: Placebo – Active	-27.04% [-33.66% to -20.43%]	
	Age group: < 65 years – ≥ 65 years	3.78% [-2.79% to 10.35%]	
	Treatment	p < 0.0001	
	Age group	p = 0.2591	

CI: confidence interval; IIEF: International Index of Erectile Function; LS: least squares; SD: standard deviation

Table 3. Study 12093 - Success rates for maintenance (SEP 3)

ITT population		Placebo	(b) (4) 10 mg
Summary statistics			
< 65 years		n = 78	n = 85
(arithmetic mean ± SD)	Baseline	14.5% ± 21.63%	16.3% ± 21.95%
	Overall	29.7% ± 35.05%	70.8% ± 33.33%
	Change from Baseline	15.2% ± 31.30%	54.5% ± 32.72%
≥ 65 years		n = 86	n = 93
(arithmetic mean ± SD)	Baseline	14.5% ± 20.27%	10.4% ± 18.89%
	Overall	22.3% ± 28.94%	59.6% ± 38.71%
	Change from Baseline	7.7% ± 25.72%	49.2% ± 37.28%
Total		n = 164	n = 178
(arithmetic mean ± SD)	Baseline	14.5% ± 20.86%	13.2% ± 20.56%
	Overall	25.8% ± 32.11%	65.0% ± 36.57%
	Change from Baseline	11.3% ± 28.67%	51.7% ± 35.18%
(LS-mean)	Baseline	15.16	13.60
	Overall	26.70	64.89
Comparison (LS-mean difference [95% CI]; p-values [ANCOVA])			
	Treatment: Placebo – Active	-38.19% [-45.02% to -31.37%]	
	Age group: < 65 years – ≥ 65 years	7.10% [0.37% to 13.83%]	
	Treatment	p < 0.0001	
	Age group	p = 0.0386	

CI: confidence interval; IIEF: International Index of Erectile Function; LS: least squares; SD: standard deviation

In Study 12094 162 patients were randomized to placebo and 169 randomized to vardenafil ODT.

The efficacy result based on IIEF-EF is shown in **Table 4**, based on the SEP 2 response rate in **Table 5**, and based on the SEP 3 response rate in Table 3. Study 12093 - Success rates for **maintenance (SEP 3)** Again, each of these endpoints indicates significant efficacy with $p < 0.0001$.

Table 4. Study 12094 - EF Domain Scores of IIEF

ITT population		Placebo	(b) (4) (b) (4) 10 mg
Summary statistics			
< 65 years		n = 80	n = 83
(arithmetic mean ± SD)	Baseline	13.3 ± 5.08	12.6 ± 5.57
	Week 12 (LOCF)	15.0 ± 7.58	22.9 ± 8.43
	Change from Baseline	1.7 ± 6.28	10.3 ± 7.78
≥ 65 years		n = 80	n = 84
(arithmetic mean ± SD)	Baseline	12.5 ± 6.35	11.1 ± 5.79
	Week 12 (LOCF)	13.6 ± 7.82	17.8 ± 9.08
	Change from Baseline	1.1 ± 6.01	6.7 ± 8.06
Total		n = 160	n = 167
(arithmetic mean ± SD)	Baseline	12.9 ± 5.75	11.8 ± 5.72
	Week 12 (LOCF)	14.3 ± 7.71	20.4 ± 9.11
	Change from Baseline	1.4 ± 6.14	8.5 ± 8.11
(LS-mean)	Baseline	12.76	11.70
	Week 12 (LOCF)	13.88	20.80
Comparison (LS-mean difference [95% CI]; p-values [ANCOVA])			
	Treatment: Placebo – Active	-6.92 [-8.46 to -5.38]	
	Age group: < 65 years – ≥ 65 years	2.35 [0.81 to 3.89]	
	Treatment	p < 0.0001	
	Age group	p = 0.0029	

CI: confidence interval; IIEF: International Index of Erectile Function; LS: least squares; SD: standard deviation

Table 5. Study 12094 - Success Rates for penetration (SEP 2)

ITT population		Placebo	(b) (4) (b) (4) 10 mg
Summary statistics			
< 65 years		n = 81	n = 84
(arithmetic mean ± SD)	Baseline	44.2% ± 33.53%	42.9% ± 35.61%
	Overall	48.8% ± 38.83%	76.1% ± 33.85%
	Change from Baseline	4.6% ± 34.12%	33.2% ± 33.27%
≥ 65 years		n = 80	n = 84
(arithmetic mean ± SD)	Baseline	34.1% ± 36.11%	31.6% ± 36.11%
	Overall	37.1% ± 37.18%	58.9% ± 39.33%
	Change from Baseline	3.0% ± 33.33%	27.3% ± 37.39%
Total		n = 161	n = 168
(arithmetic mean ± SD)	Baseline	39.2% ± 35.10%	37.2% ± 36.20%
	Overall	43.0% ± 38.35%	67.5% ± 37.59%
	Change from Baseline	3.8% ± 33.63%	30.2% ± 35.40%
(LS-mean)	Baseline	38.33	36.37
	Overall	43.02	68.99
Comparison (LS-mean difference [95% CI]; p-values [ANCOVA])			
	Treatment: Placebo – Active	-25.97% [-32.69% to -19.26%]	
	Age group: < 65 years – ≥ 65 years	7.68% [0.88% to 14.48%]	
	Treatment	p < 0.0001	
	Age group	p = 0.0270	

CI: confidence interval; IIEF: International Index of Erectile Function; LS: least squares; SD: standard deviation

Table 6. Study 12094 - Success rates for maintenance (SEP 3)

ITT population		Placebo	(b) (4) 10 mg
Summary statistics			
< 65 years		n = 81	n = 84
(arithmetic mean ± SD)	Baseline	15.5% ± 19.68%	16.4% ± 18.71%
	Overall	30.7% ± 33.33%	69.6% ± 35.27%
	Change from Baseline	15.2% ± 29.55%	53.2% ± 33.22%
≥ 65 years		n = 79	n = 84
(arithmetic mean ± SD)	Baseline	15.5% ± 22.29%	9.3% ± 18.50%
	Overall	24.3% ± 31.47%	48.1% ± 39.81%
	Change from Baseline	8.7% ± 29.15%	38.8% ± 38.32%
Total		n = 160	n = 168
(arithmetic mean ± SD)	Baseline	15.5% ± 20.94%	12.9% ± 18.89%
	Overall	27.5% ± 32.48%	58.8% ± 39.01%
	Change from Baseline	12.0% ± 29.44%	46.0% ± 36.47%
(LS-mean)	Baseline	15.18	12.52
	Overall	26.59	60.02
Comparison (LS-mean difference [95% CI]; p-values [ANCOVA])			
	Treatment: Placebo – Active	-33.43%	[-40.44% to -26.43%]
	Age group: < 65 years – ≥ 65 years	10.87%	[3.83% to 17.90%]
	Treatment		p < 0.0001
	Age group		p = 0.0026

CI: confidence interval; IIEF: International Index of Erectile Function; LS: least squares; SD: standard deviation

Question 3: Does the NDA omit critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use, for example:

- **Total patient exposure at relevant doses that is clearly inadequate to evaluate safety**
- **Clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age and racial subsets**
- **Absence of comprehensive analysis of safety data**
- **Absence of an analysis of data supporting the proposed dose and dose interval**

Answer: No

In the phase 3 studies, 701 patients were randomized to either placebo or vardenafil ODT. Six subjects (3 in the placebo group and 3 in the vardenafil ODT group) were excluded from the safety population because of failure to take any study medication. Therefore, 695 subjects made up the safety population. The safety population included all randomized subjects who had taken the study medication and had post baseline safety assessments. Of the 701 randomized subjects, 343 were randomized to the placebo group and 358 to the vardenafil ODT group. A total of 357 of the 695 subjects in the safety

population were ≥ 65 years of age (175 subjects in the placebo group and 182 subjects in the vardenafil ODT group).

Table 7 shows the subject's duration of exposure to the study medication.

Table 7. Treatment duration by stratum for the 2 phase 3 vardenafil ODT studies

Duration of interval	Placebo	(b) (4)	10 mg	Total
	n (%)		n (%)	n (%)
Summary statistics (N)	333		348	681
Mean (Days)	71.7		75.7	73.7
Standard deviation (Days)	20.0		19.2	19.7
Minimum (Days)	1.0		1.0	1.0
Median (Days)	78.0		81.0	80.0
Maximum (Days)	111.0		117.0	117.0
Missing	7 (2.1)		7 (2.0)	14 (2.0)
>0 to 7 Days	5 (1.5)		6 (1.7)	11 (1.6)
>7 to 14 Days	2 (0.6)		3 (0.8)	5 (0.7)
>14 to 21 Days	7 (2.1)		4 (1.1)	11 (1.6)
>21 to 28 Days	6 (1.8)		5 (1.4)	11 (1.6)
>28 to 35 Days	7 (2.1)		4 (1.1)	11 (1.6)
>35 to 42 Days	6 (1.8)		5 (1.4)	11 (1.6)
>42 to 49 Days	11 (3.2)		3 (0.8)	14 (2.0)
>49 to 56 Days	17 (5.0)		8 (2.3)	25 (3.6)
>56 to 63 Days	12 (3.5)		14 (3.9)	26 (3.7)
>63 to 70 Days	18 (5.3)		16 (4.5)	34 (4.9)
>70 to 77 Days	62 (18.2)		51 (14.4)	113 (16.3)
>77 to 84 Days (Week 12)	121 (35.6)		151 (42.5)	272 (39.1)
>84 to 91 Days	46 (13.5)		55 (15.5)	101 (14.5)
>91 to 98 Days	5 (1.5)		8 (2.3)	13 (1.9)
>98 Days	8 (2.4)		15 (4.2)	23 (3.3)

In addition, 52 males were exposed to single doses of vardenafil ODT during the course of two phase 1 studies.

The Sponsor has also provided an analysis of 16 additional placebo-controlled studies, involving 4294 subjects, in which the subjects were exposed to LEVITRA film-coated tablets. They have also provided a supportive analysis of 42 additional, non-placebo-controlled, studies in which 12,611 subjects were exposed to LEVITRA film-coated tablets. These analyses were provided in order to assist in evaluating a safe starting dose of vardenafil in elderly subjects.

Overall, the NDA contains safety information for 348 patients with erectile dysfunction, who have been exposed to vardenafil ODT, and 16,905 subjects who have been exposed to vardenafil film-coated tablets during controlled trials.

The patient population studied is adequate.

Altogether 70 subjects prematurely discontinued the phase 3 studies, 42 (12%) in the placebo group and 34 (9%) in the vardenafil ODT group. The most common reasons for premature termination were withdrawal of consent (3% each in the placebo and the vardenafil ODT group) and insufficient therapeutic effect (6% in the placebo group and 1% in the vardenafil ODT group). Table 8 shows the primary reasons for premature discontinuation.

Table 8. Primary Reasons for premature termination of study treatment

	Placebo n (%)	(b) (4)	Total
		n (%)	
Randomized	343	358	701
Premature termination	42 (12%)	34 (9%)	76 (11%)
Adverse events	2 (<1%)	7 (2%)	9 (1%)
Consent withdrawn	11 (3%)	11 (3%)	22 (3%)
Insufficient therapeutic effect	20 (6%)	4 (1%)	24 (3%)
Lost to follow-up	4 (1%)	6 (2%)	10 (1%)
Non-compliant with study medication	1 (<1%)	0 (0%)	1 (<1%)
Protocol violation	4 (1%)	6 (2%)	10 (1%)

Source: [Integrated Analysis of Safety PH-35849 in Module 5.3.5.3.1, Table 14.1/2](#)

Note: All subjects who terminated the study before “End of study” were considered to have the study prematurely terminated.

There were no deaths in the phase 3 studies. Table 9 shows the treatment emergent adverse events, by treatment, in the phase 3 vardenafil ODT studies.

Table 9. Incidence of treatment emergent adverse events > 1% by treatment Vardenafil ODT phase 3 studies

System Organ Class / Preferred Term	Placebo	(b) (4)
	(N = 340)	(b) (4) 10 mg (N = 355)
Any event, n (%)	25 (7.4)	86 (24.2)
Cardiac disorders	4 (1.2)	3 (0.8)
Eye Disorders	1(0.3)	7 (2.0)
Gastrointestinal disorders	3 (0.9)	12 (3.4)
Dyspepsia	0 (0.0)	8 (2.3)
General disorders and administration site conditions	2 (0.6)	7 (2.0)
Musculoskeletal and connective tissue disorders	1 (0.3)	7 (2.0)
Back pain	0 (0.0)	4 (1.1)
Nervous system disorders	10 (2.9)	61 (17.2)
Dizziness	0 (0.0)	8 (2.3)
Dysgeusia	4 (1.2)	4 (1.1)
Headache	5 (1.5)	49 (13.8)
Respiratory, thoracic and mediastinal disorders	4 (1.2)	13 (3.7)
Nasal congestion	0 (0.0)	11 (3.1)
Social circumstances	4 (1.2)	0 (0.0)
Pharm. product complaint	4 (1.2)	0 (0.0)
Vascular disorders	2 (0.6)	27 (7.6)
Flushing	2 (0.6)	27 (7.6)

Table 10 shows the treatment emergent adverse events in the 59 studies of Levitra film-coated tablets.

Table 10. Incidence of treatment emergent adverse events ≥1% in 59 studies of Levitra film-coated tablets

Medical entity – MedDRA terms of primary path	Vardenafil (N = 17748)
Number of subjects with any adverse event, n (%)	7443 (41.9)
Headache	2015 (11.4)
Vasodilatation	1619 (9.1)
Nasal congestion	797 (4.5)
Dyspepsia	485 (2.7)
Pain	458 (2.6)
Hypertension	275 (1.5)
Dizziness	269 (1.5)
Increase in cpk (creatine phosphokinase)	240 (1.4)
Gastrointestinal and abdominal pains	227 (1.3)
Nausea	209 (1.2)
Diarrhea	201 (1.1)
Sinus congestion	191 (1.1)
Other events	3274 (18.4)

In order to provide a more direct comparison of the adverse events associated with vardenafil ODT and those that have been seen with Levitra film-coated tablets, the Sponsor has analyzed 8 placebo-controlled, fixed dose studies with the film-coated

tablets and provided a comparison to the ODT phase 3 studies. These results are shown in Table 11.

Table 11. Incidence of TEAEs by Medical Entity in ≥ 1 % in any vardenafil group

Medical Entity	Placebo		Placebo ^{(b) (4)} tablet		^{(b) (4)} tablet		Levitra film-coated tablet			
					10 mg		10 mg		20 mg	
	(N = 1102)		(N = 340)		(N = 355)		(N = 1353)		(N = 1346)	
	n	%	n	%	n	%	n	%	n	%
ANY EVENT	326	29.6	74	21.8	135	38.0	648	47.9	706	52.5
Arrhythmias	0	0.0	3	0.9	4	1.1	1	<0.1	1	<0.1
Diarrhea	8	0.7	3	0.9	6	1.7	16	1.2	21	1.6
Dizziness	11	1.0	0	0.0	8	2.3	24	1.8	29	2.2
Dyspepsia	3	0.3	0	0.0	10	2.8	29	2.1	50	3.7
Feeling unwell	5	0.5	1	0.3	4	1.1	18	1.3	13	1.0
Gastrointestinal and Abdominal pains	5	0.5	1	0.3	1	0.3	28	2.1	22	1.6
Headache	45	4.1	6	1.8	52	14.6	142	10.5	191	14.2
Hyperlipidemia	3	0.3	1	0.3	2	0.6	12	0.9	13	1.0
Hypertension	10	0.9	3	0.9	4	1.1	16	1.2	9	0.7
Increase in CPK	13	1.2	n.r.	n.r.	n.r.	n.r.	24	1.8	16	1.2
Increase in Transaminases	5	0.5	0	0.0	1	0.3	13	1.0	5	0.4
Increased muscle tone and cramping	4	0.4	2	0.6	4	1.1	7	0.5	8	0.6
Nasal congestion	13	1.2	2	0.6	14	3.9	63	4.7	80	5.9
Nausea	7	0.6	0	0.0	1	0.3	18	1.3	25	1.9
Pain	25	2.3	3	0.9	10	2.8	36	2.7	31	2.3
Palpitations	7	0.6	1	0.3	1	0.3	25	1.8	17	1.3
Sinus congestion	4	0.4	2	0.6	1	0.3	15	1.1	21	1.6
Sleep disorders	4	0.4	n.r.	n.r.	n.r.	n.r.	13	1.0	12	0.9
Taste disorders	0	0.0	4	1.2	4	1.1	0	0.0	1	<0.1
Vasodilatation	16	1.5	2	0.6	29	8.2	168	12.4	199	14.8
Visual disturbances	2	0.2	2	0.6	2	0.6	8	0.6	20	1.5
Other events	160	14.5	38	11.2	40	11.3	271	20.0	265	19.7

In addition, the Sponsor has provided an analysis of adverse events in the first four weeks of treatment, stratified by age. They have provided this analysis to support their request to have the recommended starting dose for patients >65 years of age raised from 5mg to 10 mg. This would remove any age-related restriction on recommended starting dose.

3. Reviewer's Conclusions

A preliminary review of the Sponsor's submission indicates that they have submitted adequate evidence of efficacy. This is provided by two studies, involving 701 subjects, that appear to be well-designed with respect to inclusion criteria, exclusion criteria, treatment, endpoints and analysis.

The Sponsor has submitted sufficient data to allow a substantive review of the safety of vardenafil ODT to be conducted. A preliminary review indicates that the safety profile of vardenafil ODT appears to be similar to that of Levitra film-coated tablets.

The Sponsor has also submitted sufficient data to allow a review of the safety profile, in patients ≥ 65 years of age, associated with a 10 mg starting dose of Levitra film-coated tablets or vardenafil ODT.

4. Recommended Regulatory Action

The Sponsor should be notified, in the 74-day letter, that the application may be filed. In that letter they should be asked to provide the following additional information:

- (b) (6) at site (b) (6) has disclosable financial information. Please submit that information.
- There was no Financial Disclosure Form collected for investigator (b) (6) at site (b) (6). Please explain.
- With respect to your Integrated Summary of Safety of 59 Phase 2, 3, and 4 studies involving 17,748 subjects, please provide “extent of exposure” information for the subjects.
- Please provide a dataset with the following information for each phase 3 subject:
 - Study Number
 - Patient Number
 - Country
 - Trial Unit
 - Subject Age
 - Baseline IIEF-EF Total
 - Visit 3 IIEF-EF Total
 - Visit 4 IIEF-EF Total
 - Baseline SEP2 %
 - Visit 4 SEP2 %
 - Baseline SEP3 %
 - Visit 4 SEP3 %
 - Treatment Group
 - Analysis Population

Donald McNellis
Medical Officer
Division of Reproductive and Urological Products

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 12093 Indication: Erectile Dysfunction Pivotal Study #2 12094 Indication: Erectile Dysfunction				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			A Thorough QT study was done for Levitra and presented to AC
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			Adequate numbers are exposed using the data from prior Levitra film-coated tablet trials
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			MEDRA 11.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Safety Analysis by age group
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?				NA
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?				NA
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				NA
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical 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.

Donald McNellis	October 10, 2009
Reviewing Medical Officer	Date

Clinical Team Leader	Date
----------------------	------

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

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

/s/

DONALD R MCNELLIS
06/11/2010

SURESH KAUL
06/11/2010

PMR/PMC Development Template – PMR #1

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: An in vivo drug-drug interaction study of vardenafil hydrochloride orally disintegrating tablets (ODT) in elderly men (over 65 years of age) with erectile dysfunction and hypertension on a stable dose of a vasodilator

PMR/PMC Schedule Milestones: Final protocol Submission Date: December 2010
Study/Clinical trial Completion Date: February 2012
Final Report Submission Date: August 2012
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Vardenafil ODT was shown to have a higher C_{max} and AUC following administration of a 10 mg ODT dose when compared to the approved 10 mg vardenafil product by 15% and 44%, respectively.

For the vardenafil 10 mg ODT formulation, the C_{max} and AUC values in the elderly (≥65 years) were higher by 21% and 38%, respectively, compared to the young patients (18-45 years).

Previous safety data with the approved vardenafil product has shown that some patients experience orthostatic hypotension when vardenafil is used concomitantly with vasodilators. Based on the available clinical safety data for vardenafil ODT, it is not possible to conclude that the altered pharmacokinetic parameters of vardenafil ODT, when used in elderly patients, would not have an effect on blood pressure when concomitant vasodilators are used.

Therefore, the sponsor is required to conduct an *in vivo* drug-drug interaction study with in elderly men using vardenafil ODT and a concomitant vasodilator as a PMR.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this study is to address the issue of the potential risk of a drug-drug interaction (orthostatic hypotension) with concomitant use of vardenafil ODT and vasodilators in an elderly population (over 65 years) with erectile dysfunction (ED).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMR is a clinical drug interaction study in elderly men (over 65 years of age) with erectile dysfunction (ED) who are using vardenafil ODT and a stable dose of a vasodilator.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200179	PMR/PMC-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	VARDENAFIL HCL
NDA-200179	ORIG-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	VARDENAFIL HCL

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

/s/

AUDREY L GASSMAN
06/14/2010
Revised PMR Template with Timeline