CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-400

Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-400

INFORMATION REQUEST LETTER

Bayer Corporation
Attention: Mary Taylor, M.P.H.
Vice President, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear Ms. Taylor:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levitra® (vardenafil hydrochloride).

We also refer to your February 17, 2003 Complete Response to our July 23, 2002 approvable letter.

In accordance with 21 CFR 314.50 (d)(vi)(b), we request that you submit to this NDA the following safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in draft labeling for Levitra® (vardenafil hydrochloride):

> Report on Study 100535 (An Interaction Study to Evaluate Changes in Blood Pressure and Pulse Rate Following Vardenafil Compared to Placebo Treatment on the Background of the Alpha Blockers, Tamsulosin and Terazosin in Separate Cohorts of Patients with Benign Prostatic Hypertrophy), including SAS transport files containing the electronic datasets for this study.

We request a prompt written response by August 18, 2003 in order to continue our evaluation of your NDA.

If you have any questions, please call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel

8/13/03 06:18:30 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-400

Bayer Pharmaceuticals Corporation
Attention: Mary E. Taylor, M.P.H.
Vice President, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Ms.Taylor:

We acknowledge receipt on February 19, 2003 of your February 17, 2003 resubmission to your new drug application for Levitra™ (vardenafil hydrochloride).

We consider this a complete, class 2 response to our July 23, 2002 action letter. Therefore, the user fee goal date is August 18, 2003.

If you have any question, please call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

/S/

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Division of Reproductive and
Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
3/18/03 11:32:18 AM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-400

DISCIPLINE REVIEW LETTER

Bayer Corporation
Attention: Gautam Shah, Ph.D.
Director Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Dr. Shah:

Please refer to your September 24, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nuviva (vardenafil hydrochloride).

We also refer to your submissions dated September 28, and December 7, 2001 and April 23, 2002.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

Regarding Drug Substance:

1. Please specify the duration of exposure to ——— that you have indicated in your stress stability studies for the ——— starting material.

2. Please clarify whether the drug substance production scale is ———

3. Please provide the specifications (tests and acceptance criteria) for the drug substance reference standard.

4. Please clarify the following discrepancy in the drug substance release acceptance criteria for any unspecified organic impurities. In document T.03.46-03, page 8 it is max. — while in document T.03.45-01, page 3, it is max. —

5. The organic impurities limits in the drug substance specifications at release and stability should be set according to the data presented to the NDA. Therefore it is recommended that the limit for ——— and for ——— be revised to max. — and max. — respectively.

6. Based on the data from the drug substance batches provided to the NDA the limit for residual ——— should be revised to max. ——and max. —, respectively.

7. Please submit the SOP and the method validation data for the drug substance particle size distribution test. Validation criteria should include specificity, and intermediate precision for the laser diffraction method used in determination of particle size distribution.

8. Please provide information on the composition of the primary and secondary container closure system for the drug substance.

9. Please provide a copy of the bulk drug substance label.

10. The data presented to the NDA demonstrates that drug substance particle size is a critical parameter to the bioavailability of the drug product tablet. Therefore, it is recommended that drug substance particle size distribution be tested in the stability program.

11. There are two sets of acceptance criteria listed in the drug substance stability tables on pages 4-15 of document T.05.02-02. Although the values do not differ much from each other please clarify the difference between the two sets.

Regarding Drug Product:

1. Please provide the certificate of analyses for the excipient, [redacted]

2. Please provide information concerning any reprocessing of the drug product during the manufacturing operation.

3. Please provide information concerning the holding time (length, storage conditions, etc) of the bulk tablets after manufacturing in Germany and before it is packaged in bottles and blisters for marketing.

4. The reported level of the organic impurities in the pilot scale batches at release are all either [redacted], below [redacted] or not detected. However, in order to set more objective acceptance criteria for the level of specified organic impurities the exact value for that impurity should be reported rather than reported as [redacted] In the absence of such values the following revised limits are recommended:

Revised Acceptance Criteria for the Drug Product Organic Impurities at Release:

Degradation products	**Proposed Limits**	**Revised Limits**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Any unspec. deg. Product	[redacted]	[redacted]
Total degradation products	[redacted]	[redacted]

5. The reported level of the organic impurities in the pilot scale batches at stability are all either [redacted] below [redacted] or not detected. However, in order to set more objective acceptance criteria for the level of specified organic impurities the exact value for that impurity should

be reported rather than reported as ——. In the absence of such values the following revised limits are recommended:

Revised Acceptance Criteria for the Drug Product Organic Impurities During Stability:

Degradation products	**Proposed Limits**	**Revised Limits**
Any unspec. deg. Product		
Total degradation products		

6. Please include the following statement in your stability commitment section: The first 3 commercial batches will be put on stability in their to be marketed packaging configuration and will be tested according to the Stability Protocol including the hardness and color testing.

7. The proposed expiration dating period of —— is not acceptable. Based on the available data an expiry of —— can be granted.

8. Please correct the word embossed "BAYER" to debossed "BAYER" in the How Supplied Section of the package insert.

9. Please confirm that there is no secondary packaging component for the bottles.

10. Please include the storage statement and expiration date on the blister and tri-fold immediate packaging label.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

David Lin
Chemistry Team Leader, DNDC II for the
Division of Reproductive and Urologic Drug
Products, HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

David T. Lin
5/15/02 03:40:28 PM
I concur.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-400

Bayer Corporation
Attention: Gautam Shah, Ph.D.
Director Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Dr. Shah:

Please refer to your new drug application (NDA) for vardenafil hydrochloride.

We also refer to your submission dated February 5, 2002 containing your rebuttal and request to reconsider your tradename proposal.

We also refer to the teleconference held on April 3, 2002 between you and the Division wherein the tradename issue was discussed.

We have completed the review of your correspondence, and in consultation with the Division of Medication Errors and Technical Support (DMETS), have the following comments and recommendations:

DMETS does not recommend the use of the name "Nuviva." DMETS believes the products having the greatest potential for confusion with Nuviva are Norvasc and Navane. DMETS agreed with the [redacted] conclusion that, although Sustiva and Nuviva are similar, the clinical context of use, differences in patient population, and daily dosage decreases the potential for confusion. Therefore, DMETS did not address comments pertaining to Sustiva. The following are selected comments from DMETS in response to your February 5, 2002 submission:

A. Interpretation of Prescription Analysis and Differentiation

1. Nuviva has an entirely different dosing regimen compared to the other three products.

   A product's dosage interval is only one factor which can influence the probability of an error and lead to the administration of the wrong drug product. Post-marketing experience has demonstrated that medication errors occur between products that sound-alike or look-alike despite having different dosage intervals. For example, Norvasc is given once daily and Navane may be given up to three to four times a day. Medication errors between these two products, however, are well documented.

   Nuviva may not always be prescribed on a prn basis, but could also be prescribed daily as well. This once daily dosing regimen overlaps with the dosing regimens of Norvasc and Navane. This overlap increases the likelihood of confusion between these products.

2. The number of tablets filled in a typical Nuviva prescription would be much smaller compared to Norvasc, Navane, and Sustiva.

   The sponsor states that Nuviva prescriptions will be written for smaller quantities (e.g., 6 units) and Norvasc and Navane prescriptions will be written for much larger quantities (e.g., >30 units). Thus, the prescription quantity size will serve as an indicator of the drug. Prescriptions, however, may be prescribed for any quantity. For example, if therapy is initiated with Norvasc or Navane, the prescriptions may be written for a one to two week supply corresponding to a dispensed amount of 7 to 14 units.

3. There are significant differences in the physical appearance between Nuviva and products of concern.

   Differences in physical appearance do not always eliminate the risk of error. Post-marketing experience has demonstrated that errors occur between sound-alike/look-alike names despite the differences in physical characteristics (e.g., different color, shapes, tablet formulation versus injectable, etc.).

4. All four products are for different indications.

   Generally, indications of use do not appear on a prescription. Not all pharmacies provide information concerning a product's intended use. Even in pharmacies that offer these services, many patients do not take advantage of this information.

5. Nuviva is prescribed only for men.

   Although Nuviva is prescribed only for men, the possibility that practitioners will cognitively misinterpret the prescription because of sound-alike and/or look-alike names can not be overlooked. Once this misinterpretation has occurred, the practitioner is unlikely to correct the error based on the sex of the patient.

6. In . ——— research, the only close sound-alike was Sustiva

   DMETS agrees with the . ——— conclusion regarding Sustiva.

7. . ——— research, the only close look-alikes to Nuviva in terms of writing the names are Sustiva and Navane.

   DMETS disagrees with the sponsor's assessment of the visual similarity between Navane and Nuviva. Bayer notes that "Navane should not look like Nuviva because the dotted "i" in the center of the word would normally survive practitioners' handwriting trail-off." However, the dotted "i" is not always a distinguishing characteristic when the name is scripted. Practitioners may not dot the "i" and in cases where duplicate or carbon copies of prescriptions are used, the dotted "i" may not be evident.

DMETS believes that Navane and Nuviva appear similar when scripted. The names are both six characters in length beginning with the same letter and ending in two letters that are often undistinguishable when scripted (a and e). The two products share overlapping dosage forms, product strengths, and dosing intervals.

8. Norvasc does not resemble the name Nuviva.

The [redacted] analysis contradicts this statement. [redacted] analysis noted that "Although the endings are different, the potentially similar appearance of the "VIVA" ending of the test name for "VASC" of Norvasc raises some concern for misperception in handwritten prescriptions." DMETS believes that Norvasc and Nuviva can look similar when scripted. The names contain a similar number of characters. Norvasc and Nuviva are both available in 5 mg and 10 mg drug strengths and share an overlapping dosing interval of once daily. The [redacted] panel also noted the overlap between the drugs' dosage forms and strengths.

B. Medical risk assessment

1. What if Norvasc is mistakenly taken instead of Nuviva?

DMETS believes that the addition of an extra antihypertensive medication to the patients' regimen could potentially be problematic. In addition, not all patients may expect to achieve an erection upon their initial dose of Nuviva. A patient may believe he was prescribed too low a dose of Nuviva and may therefore take an additional dose of Norvasc, especially if the original prescription were written to be used on a prn basis. Higher doses of Norvasc would increase the chances of patients experiencing an acute hypotensive adverse event.

2. What if Nuviva is mistakenly taken instead of Norvasc?

Patients may experience an increase in blood pressure if Nuviva is taken in lieu of Norvasc.

3. What if Navane is mistakenly taken instead of Nuviva?

As noted previously, if the patient does not receive the expected results, he may assume that the dose is too low and repeat the dose, particularly if the prescription were written as a "prn" medication. Sedation is just one potential adverse reaction to Navane. Tardive dyskinesia, neuroleptic malignant syndrome, hypotension, tachycardia and syncope may occur following the administration of Navane.

4. What if Nuviva is mistakenly taken instead of Navane?

Using the sponsor's example of six tablets dispensed, a patient could potentially go without Navane therapy for one week. This timeframe is sufficient for a potential relapse to occur.

We also note that if Nuviva were taken instead of Norvasc or Navane by a nitrate-taking patient, life threatening hypotension might ensue.

If you have any questions, please call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-400
Bayer Corporation
Attention: Gautam Shah, Ph.D.
Deputy Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Dr. Shah:

Please refer to your September 24, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for vardenafil hydrochloride.

We have completed the review of the tradename section of your submission and in consultation with Office of Post-Marketing Drug Risk Assessment (OPDRA) have the following comments:

OPDRA does not recommend the use of the proprietary name, Nuviva. The primary concerns are related to two potential look-alike names that already exist in the US marketplace, Norvasc and Navane. OPDRA is concerned that these names pose a significant problem as there is already confusion between Norvasc and Navane due to their similar appearance when scripted.

Navane and *Nuviva* appear similar when scripted. The names are both six characters in length beginning with the same letter and ending in two letters that are often undistinguishable when scripted (a and e). The two products share overlapping dosage forms, product strengths (5 mg, 10 mg and 20 mg), and dosing intervals (once daily). —— reviewed this name and stated "there is some similarity between the names, more so with respect to letter construction than sound. However, the test name has a different number of syllables and a different ending than Navane, which should help to distinguish them." This would only help to distinguish them on a verbal prescription and not a written one. —— also stated that the chance of confusion is minimized by the fact that Navane has other dosage forms (besides oral), different starting dosage, different maintenance dosage and different frequency of administration. The fact that Navane is available in other dosage forms is not a distinguishing factor. If a prescription is written for the oral dosage form, that is what will be dispensed, not an injection or oral concentrate. The two do have different starting dosages. However, the maintenance dose can overlap (20 mg daily). The maximum dose —— cites in the review is for milder conditions and not the usual optimal dose of 20 to 30 mg daily. Furthermore, the frequency of administration is the same, once daily. These similar characteristics have the potential to increase the likelihood of confusion between the two products. Patients administered Navane rather than Nuviva are at risk for developing Tardive Dyskinesia, Neuroleptic Malignant Syndrome, convulsions, and other CNS effects such as restlessness, agitation and insomnia.

If you have any questions, please call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Daniel Shames, M.D.
Acting Division Director
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames.
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-400

Bayer Pharmaceutical Division
Attention: Gautam Shah, Ph.D.
Deputy Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear Dr. Shah:

We received your January 17, 2002 correspondence on January 18, 2002 requesting a meeting to discuss your proposed tradename for your pending NDA. We have reviewed and considered your request and have concluded that the meeting is inappropriate at this time.

The Division has not made a final recommendation on the tradename "NUVIVA" and would encourage you to submit an additional tradename for the Office Post-Marketing Drug Risk Assessment to review. We also encourage you to submit any additional information to support the use of the tradename "NUVIVA".

If you disagree with our decision, you may discuss the matter with Jennifer Mercier, Regulatory Project Manager, at (301) 827-4260. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at http://www.fda.gov/cder/guidance/2740fnl.htm.

Sincerely,

/S/

Daniel Shames, M.D.
Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-400

ACKNOWLEDGEMENT LETTER

Bayer Corporation
Attention: Gautam Shah, Ph.D.
400 Morgan Lane
West Haven, CT 06516-4175

Dear Dr. Shah:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Nuviva (vardenafil HCL) tablet
Review Priority Classification:	Standard (S)
Date of Application:	September 24, 2001
Date of Receipt:	September 24, 2001
Our Reference Number:	NDA 21-400

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 23, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be July 24, 2002, and the secondary user fee goal date will be September 24, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the

division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble, R.N., B.S.N.
Chief Regulatory Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Terri F. Rumble
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