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/s/

George Benson
8/19/03 06:19:53 PM
MEDICAL OFFICER

Donna Griebel
8/19/03 07:01:27 PM
MEDICAL OFFICER

I concur with Dr. George Benson, MD's review and
agree with his recommendation for approval of vardenafil
for the treatment of erectile dysfunction, as well
as his recommendations for labeling and phase 4
commitments .

Deputy Division Director's Memorandum

From: Donna J. Griebel, M. D.
Deputy Director, DRUDP

To: Florence Houn, MD
Director, ODE III

Regarding: Rationale for Regulatory Action of NDA 21-400

Date Submitted: February 7, 2003

Memorandum completed: August 19, 2003

Sponsor: Bayer Corporation

Drug: Trade: Levitra

Generic: vardenafil HCl

Drug Class: Phosphodiesterase type 5 (PDE5) inhibitor

Route and Administration: One 10 mg tablet by mouth daily

Dosage Form: Tablet

Strength: 2.5mg, 5 mg, 10 mg, 20 mg

Proposed Indication: Treatment of erectile dysfunction

Related INDs:

1.0 Background

NDA 21-400 was initially submitted on September 24, 2001. An approvable action was taken on July 23, 2003. The approvable letter divided the deficiencies into general and dose specific deficiencies.

The general deficiencies that needed to be addressed for approval of the drug at any dose were two-fold: 1) Conduct clinical studies that characterize the vardenafil plasma concentration-response relationship for QTc interval prolongation and evaluate the degree of QTc prolongation at plasma concentrations following maximal potential interaction between vardenafil and CYP 3A4 inhibitors. 2) Provide data from drug-drug interaction studies to support labeling for concomitant use of vardenafil at the maximal to-be-marketed dosage strength and an alpha-blocker used for BPH. The letter stated that the QT studies-requested should have certain attributes for approval. These included a randomized and double-blinded design, with a placebo control, enrollment of sufficient patient numbers to provide reliable results, doses adequate to evaluate degree of QTc prolongation at therapeutic and suprathreshold concentrations, and evaluate concentrations achieved with maximal interaction between vardenafil and CYP 3A4 inhibitors. Inclusion of an active control was encouraged.

The dose-specific deficiencies included two deficiencies for the proposed 20 mg dose and one for the proposed 2.5 mg dose. To address the 20 mg dose deficiencies the applicant was told in the letter that they must conduct a study in patients treated with vardenafil 20 mg or higher with co-administration of nitrates at various times following the dose to determine at what point after vardenafil dosing there is no apparent blood pressure interaction. In addition the applicant was told that the pharmacodynamic interaction of the maximum to be marketed dose, 20 mg, must be assessed with aspirin, given that vardenafil could affect phosphodiesterase type 5 in platelets. With regard to the low dose, 2.5 mg, the applicant was told they needed to submit chemistry, manufacturing and controls information for this dose form.

2.0 NDA Data and Analyses

This NDA was deemed approvable by the Division of Reproductive and Urologic Drug Products during the initial review cycle because the data from four major randomized, controlled trials conducted in men with erectile dysfunction demonstrated that vardenafil was effective. Two of the trials were conducted in a general erectile dysfunction population and two enrolled specific populations with erectile dysfunction – patients with diabetes mellitus in one and patients who had undergone radical prostatectomy in the other. The primary endpoints evaluated in these studies were all clinically relevant and included the Erectile Function Domain of the International Index of Erectile Function Questionnaire (IIEF), the Sexual Encounter Profile Question 2 (Were you able to insert your penis into your partner's vagina?) and the Sexual Encounter Profile 3 (Did your erection last long enough for you to have successful intercourse?). Vardenafil was statistically significantly superior to placebo on all endpoints in all four trials. The safety data submitted in the application supported an approvable action, but additional data was requested to define the potential for significant drug drug interactions, and to clarify the drug's potential impact of QT interval prolongation.

2.1 *QT Prolongation*

Although the initial NDA included QT interval assessments, and the data from those initial studies suggested that vardenafil had an impact on QT, the DRUDP believed that this important safety issue had not been adequately studied. In response to the approvable letter, the sponsor designed and conducted a double-blind, randomized, single dose, 6-way crossover, period balanced study in healthy adult males. Each subject was evaluated in 6 separate periods on two doses of vardenafil (10 and 80 mg), placebo, an active control (moxifloxacin), and two sildenafil dose levels. The analysis plan specified that the primary endpoint of the study would be assessed using the Fridericia correction formula. The sponsor also presented the data utilizing an individual correction methodology. Because vardenafil increases heart rate, and change in heart rate is known to affect QT interval, the validity of the various QT correction methodologies presented in the NDA (Fridericia and individual correction methodology) were the focus of extensive FDA review. The changes in QTc interval in both doses are similar to that

observed with the active control moxifloxacin with the different correction methods, and are shown in the table below. No Torsade de Pointes was observed in the study.

Drug/Dose	QT Uncorrected (msec)	Fridericia QT Correction (msec)	Individual QT Correction (msec)
Vardenafil 10 mg	-2 (-4, 0)	8 (6, 9)	4 (3, 6)
Vardenafil 80 mg	-2 (-4, 0)	10 (8, 11)	6 (4, 7)
Moxifloxacin* 400 mg	3 (1, 5)	8 (6, 9)	7 (5, 8)

* Active control (drug known to prolong QT)

The QT prolongation issues raised by these data were discussed in a Cardiovascular and Renal Drug Products Advisory Committee on May 29, 2003. The committee indicated a verbal consensus that no single correction methodology that had been presented was more valid than the other. Although the members of the committee voted that the QTc changes observed in the trial were not clinically relevant, individual members expressed their concern regarding the need to know more regarding combining medications with the degree of QT interval prolongation observed in these trial, and administering them to patients who are at greater risk for having prolonged QT interval due to underlying medical conditions. Individual committee members also expressed their belief, however, that studies designed to answer the questions in the latter group would be difficult to pass IRB review because of the potential risk to the patients. Members of the committee also stated that the post-marketing data for sildenafil presented in the FDA review and by Pfizer in the open public hearing gave them reassurance regarding the cardiac safety of vardenafil. The DRUDP review team pointed out in their briefing document for the advisory committee meeting that Torsade de Pointes can be difficult to capture in the post-marketing setting, where the patients using the drug would not be expected to be monitored like they would in an inpatient setting.

2.2 *Alpha-blocker interaction*

In response to the deficiency in the approvable letter, the sponsor designed and conducted two drug interaction studies of vardenafil combined with alpha blockers. One study evaluated vardenafil 10mg and 20 mg administered with terazosin 10 mg, and the other evaluated vardenafil (at the same doses) administered with tamsulosin. In both studies two dose intervals were evaluated, administration of the drugs to coincide C_{max} , and administration after a dose interval that would allow an assessment with separation of

C_{max} of the drugs. For the terazosin study, those time intervals were simultaneous administration (both drugs have a T_{max} of approximately 1-2 hours) and after a six hour dose interval between the drugs. In the tamsulosin study, the two times of administration were vardenafil administration 4 hours post tamsulosin (tamsulosin T_{max} is approximately 6 hours) and vardenafil administration 10 hours after tamsulosin.

Both studies were relatively small in size, and in both studies there were patients that experienced clinically relevant decreases in standing systolic blood pressure. In the terazosin study, the simultaneous administration portion of the trial was terminated early because a significant proportion of subjects dropped their standing systolic pressure. Six of eight of the subjects on vardenafil 10mg and 2/9 patients on vardenafil 20 mg experienced a drop of standing systolic blood pressure to <85 mm Hg. 3/29 patients administered 10 mg vardenafil with a 6 hour interval from terazosin experienced a drop in systolic blood pressure to <85 mm Hg, and 7/28 treated with 20 mg vardenafil with a six hour with terazosin experienced a similar drop in blood pressure. In the tamsulosin study, a lower proportion of patients experienced a clinically relevant drop in systolic blood pressure, but the study was small and there were patients in both dose intervals examined that dropped their standing systolic blood pressure to <85 mm Hg – 1/24 patients treated with vardenafil 20 mg in the 6 hour dose interval segment of the study and 2/16 patients treated with vardenafil 10 mg in the 10 hour dose interval segment.

Based on these data the DRUDP review team believed that the product label should include a contraindication for concomitant use of alpha- blockers and vardenafil. During the label discussion with the applicant, the applicant indicated that their proposal that the label should include language suggesting that prescribers should consider use of a lower dose of vardenafil, 5mg, with alpha-blockers was supported by clinical trial data. The FDA requested that those data be submitted and the applicant ultimately did submit an abbreviated study report for the vardenafil 5 mg drug interaction study with alpha-blockers on August 14. The DRUDP examined the abbreviated report for this study that evaluated vardenafil 5 mg administered with either tamsulosin 0.4 mg or terazosin 5 mg and 10 mg, and did not consider these data supportive of the proposal to include guidance in the label to use a 5 mg dose of vardenafil in combination with alpha-blockers. Two of 20 patients treated with tamsulosin and vardenafil, in each of both dose intervals examined (simultaneous administration and with a 6 hour interval between doses), experienced a drop of standing systolic blood pressure. The DRUDP and the applicant concurred that the label should specifically state that the effects of administration lower doses of vardenafil with alpha blockers had not been adequately studied.

To critically examine the use of a contraindication to manage the risk of co-administration of an alpha blocker and vardenafil, the DRUDP requested that the applicant submit data on the projected number of patients that would have both conditions, erectile dysfunction and BPH. Similarly the DRUDP requested information from the Office of Drug Safety evidence for co-prescription of sildenafil and alpha blocker. The post-marketing data from sildenafil was also examined for evidence of adverse event reporting related to concomitant use.

The marketing projections provided included an estimated 19 million men with BPH of whom 1.6 million (10%) are treated with alpha blockers. Information provided indicated that approximately a third of men with BPH have erectile dysfunction as well. Approximately 13% of men with erectile dysfunction are treated, based on information provided from A report in the Annals of Internal Medicine (Bacon CG, Mittleman MA, et al. August 5 2003. Vol 139, No. 3: pages 161-168) entitled Sexual Function in Men Older than 50 Years of Age: Results from the Health Professional's Follow-up Study reported that there was an age-standardized prevalence of erectile dysfunction in the previous 3 months in a third of the study participants. Age adjusted use of alpha blockers ranged from 3% in men less than 59 years of age, to as high as 7% in men aged 70-79 was reported. Use of oral therapy for erectile dysfunction in those two age categories was reported to be 4% and 8%, respectively. Data obtained from the by the Office of Drug Safety, indicated that in their database, the total of concomitant sildenafil and alpha blocker prescriptions distributed between January 2002 and December 2002 was In an Office of Drug Safety unit evaluation of hypotension adverse events reported in the AERS database for sildenafil that included information about concomitant alpha-blockers, 49/245 reported concomitant use of the drugs. Sildenafil is labeled to reduce the dose to 25 mg when administering with alpha blocker. The members of the review team discussed these data with the Office Director and the Division Director, and reached concurrence that labeling vardenafil with a contraindication for use with alpha blockers would be appropriate for risk management.

2.3 Nitrate Interaction

In response to the deficiency in the approvable letter regarding the need for safety data on vardenafil doses 20 mg or higher with administration of nitrates at various times following the vardenafil dose to determine at what point after vardenafil dosing there is no apparent blood pressure interaction data, the sponsor designed and conducted a study that examined vardenafil 20 mg administered with sublingual nitroglycerin 1 hour, 4 hours, 8 hours and 24 hours apart. Subjects were healthy males. vardenafil 20 mg resulted in mean further reductions in systolic blood pressure beyond the effect of nitroglycerin of 9 mm Hg at the 1 and 4 hour dose intervals. Prolonging the interval still resulted in additive hypotensive effect, but to a lesser degree, approximately 2 mm Hg further decrease, but the increase in heart rate observed with this dose interval was similar to that observed with the 1 and 4 hour intervals. Additive blood pressure and heart rate changes were not observed with a 24 hour dose interval between the drugs.

Co-administration of nitrates and vardenafil was contraindicated in the label, and the data at all dose intervals was included as information for physicians treating patients who have a need for emergency nitrates, but who have a history of recent use of vardenafil.

2.4 Aspirin interaction

In response to the deficiency in the approvable letter regarding the need for safety data on vardenafil 20 mg and aspirin, the applicant conducted and submitted the data from a study that examined this potential interaction. These data resulted in labeling that stated that

there was no evidence that vardenafil further prolonged the bleeding time in patients who take aspirin.

2.5 *Vardenafil 2.5 mg Chemistry*

After reviewing the data submitted to address the deficiency regarding the need for chemistry, manufacturing and controls data to support the 2.5 mg dosage form, the FDA Chemistry review team recommended approval of this NDA.

2.6 *Other issues in the approvable letter*

The approvable letter told the sponsor to conduct a comprehensive assessment in ongoing clinical trials of the myalgia and back pain that had been observed in the earlier clinical trials. The applicant submitted data from assessment for vasculitis, rhabdomyolysis and other inflammatory processes, and no etiology of this pain could be defined.

2.7 *Pharmacology-Toxicology*

No additional pharmacology-toxicology data was submitted. The data submitted in the initial review cycle supported an approval.

2.8 *Clinical Pharmacology and Biopharmaceutics*

This NDA included multiple pharmacokinetic and pharmacodynamic studies. Based on the review of the data from these trials the review team recommended specific labeling to address drug-drug interaction and dose adjustments, as discussed in Section 3.0 below.

3.0 Risk/Benefit and Risk Management

The efficacy and clinical trial safety data were thoroughly reviewed during the initial NDA review and the clinical trial data supported the approvable action for the indication for treatment of erectile dysfunction. The data submitted in this review cycle, including an updated ISS and the specific safety trials that were conducted in response to the approvable letter also support marketing approval.

The data from the drug-drug interaction studies and the QT data supported specific labeling to inform prescribing physicians of potential risks. The clinical pharmacology data that was submitted in the NDA defined important interactions with CYP 3A4 inhibitors, the vardenafil C_{max} and AUC data from the CYP3A4 inhibition trials permitted inclusion of specific and differing dose modifications for strong and moderate CYP3A4 inhibitors. The study of the impact of vardenafil on the pharmacokinetics of protease inhibitors, allowed inclusion in the label of information regarding the impact of vardenafil on the AUC and C_{max} of ritonavir and indinavir, two drugs that are metabolized by CYP 3A4. The pharmacokinetic data for vardenafil in special populations, including patients with Childs A and B hepatic dysfunction, the elderly and patients with renal dysfunction, also permitted specific dose adjustment information in the product label.

The QT study reviewed in this review cycle was thoroughly evaluated and discussed at a Cardiovascular and Renal Drugs Advisory Committee meeting. Based on the committee discussion at that meeting, the DRUDP worked with the sponsor to include the data from the double-blind, randomized, single dose, 6-way crossover, period balanced study in healthy adult males in the label in the Pharmacodynamics Section (uncorrected QT, Fridericia correction, and individual correction methodology) of the label, and included information on QT prolongation in the Precautions section of the label, with a statement that administration of vardenafil in patients with QT prolongation and those taking Class IA and III antiarrhythmic drugs should be avoided. The Patient Package insert (PPI) also instructs patients to inform their health care provider if they have a known history of QT prolongation or are taking Class IA and III antiarrhythmic medications. Examples of those drugs were included in the PPI. The applicant also agreed in a phase 4 commitment to conduct a study to evaluate the potential for additive QT effects when vardenafil is co-administered with a drug with a similar degree of QT prolongation. This would address concerns raised at the advisory committee meeting regarding the need for clinical information to guide clinical decisions to co-administer such drugs.

As discussed in sections 2.2 and 2.3 above, co-administration of either nitrates or alpha-blockers with vardenafil was included in the label as contraindications. These contraindications were also discussed in the patient package insert. There was significant discussion with the applicant regarding the contraindication for alpha-blockers. To address the potential that health care providers might try reducing the dose of vardenafil to enable co-administration, a specific statement that there are not adequate data to support this was included in the label. The DRUDP asked the applicant to commit to a study to investigate the potential to co-administer the lowest marketed dose, 2.5 mg, with alpha-blockers. In addition, because there is a recently approved alpha blocker, new on the U.S. market, the DRUDP asked the applicant to commit to conducting a drug-drug interaction study with that specific alpha blocker, alfuzosin, to provide information to prescribers on the effects of its co-administration with vardenafil.

The applicant agreed to a phase 4 commitment to study the visual effects of vardenafil that had been mentioned in the approvable letter.

The trade name Levitra was reviewed and approved by DMETS and DDMAC.

4.0 Conclusion and Regulatory Recommendation

I recommend that vardenafil is approved for the proposed indication, "for the treatment of erectile dysfunction", with labeling as described in Section 3.0 of this review to address safety issues that were identified in the original NDA review cycle and during the review of the data submitted in response to the approvable letter.

Donna Griebel, MD
Deputy Director, DRUDP, CDER

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Donna Griebel
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MEDICAL OFFICER

MEMORANDUM

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

DATE: August 15, 2003
FROM: Florence Houn MD MPH
SUBJECT: Office Director Memo
TO: NDA 21-400 Vardenafil (Levitra) by Bayer Corp 2.5mg, 5mg, 10mg, 20mg tablets

This memo documents my decision to support the recommendations from the Division of Reproductive and Urologic Drug Products to take an approval action on the new drug application (NDA) for vardenafil, a PDE-5 inhibitor, for the treatment of erectile dysfunction. My memo acknowledges the Division's reviews that find vardenafil effective based on randomized, double-blind, placebo controlled trials. Safety can be addressed by labeling. Below I highlight my views on select topics: the alpha blocker contraindication, the omission of comparative data with Viagra on QT, and other labeling differences with Viagra.

Alpha Blocker Contraindication

On August 1, 2003 FDA sent the company a counter proposal for labeling that included a contraindication for all alpha blockers based on hypotension seen in drug-drug interaction studies of 10 and 20 mgs in healthy volunteers with terazosin and tamsulosin. A decrease of between 7 to 23 mm Hg of blood pressure was observed in these studies, which were designed by the company to be provocative (rapid dose escalation with alpha blocker and then a second testing under concomitant Cmaxs). The designs of these studies were not suggested by FDA. FDA did comment to the company that these protocols met our need for having data to evaluate the effects of alpha blockers, vardenafil, and blood pressure. If the studies showed no effect on blood pressure, this drug would have advantages over Viagra. However, the tests showed drops in blood pressure that were clinically meaningful. In response to the FDA contraindication proposal, Bayer stated it had a 5mg vardenafil study that would support their new proposal that the alpha blocker labeling be turned into a warning and patients on alpha blockers should start at 5mg. The company then submitted the data in an email to the reviewers, but not as a formal submission to the NDA. The company also submitted a new proposal on August 7th with warnings that concomitant users of alpha blockers and vardenafil start vardenafil at 5mgs based on the assumption a dose lower than 10 or 20mg would not show a hypotensive effect FDA stated that we could not assume the 5mg dose was the right starting dose without reviewing the data. By August 8th, the company stated it would agree to full contraindications, not calling for a 5 mg starting dose of vardenafil in users of alpha blockers. Both Bayer and GSK, their marketing partner, verbally stated now FDA did not need the 5mg data, given this position, and there was no need to submit the data to the NDA, which could trigger an extension of the clock.

Meanwhile, FDA revisited the use of the contraindication to determine if it was a realistic means to manage the risk. FDA obtained data from Bayer showing about 500,000 men with benign prostatic hypertrophy on alpha blockers have erectile dysfunction. Only about 70,000 of these men were prescribed ED medications.

The experience has been that if a contraindication is known at the onset of drug marketing, such as the nitrate contraindication with Viagra, there is greater compliance with the labeling than when changes are made in the post-marketing period (e.g., cisapride and contraindicating CYP 3A4 inhibitors). FDA requested use data from vardenafil's European experience with alpha blockers and these data supported low concomitant use.

Because Bayer believed that 21 CFR 314.50 (d)(vi)(b) did not apply to this situation in which a blanket contraindication of vardenafil use with alpha blockers would obviate need for further information on a dose

of a drug. FDA sent a letter on August 13, 2003 stating that, indeed, Bayer was in possession of information that may affect labeling proposed in contraindications, warnings, precautions and adverse events and that FDA now was requesting in writing, as was done on through telephone requests (August 8, 11, and 12th), they submit these data to the NDA. Even if the 5mg data did not affect contraindications (the data on preliminary review showed problem hypotensive effects with the 5 mg dose and produced results more concerning with tamsulosin than terazosin-opposite findings from the 10 and 20 mg drug interaction studies), the information is needed for labeling of effects and explaining why there is a contraindication. On a telephone call on August 14, 2003, FDA stated that the submission would not trigger an extension and the companies needed to submit the data to comply with the regulation, and they agreed to do so.

QTc Effects.

Bayer and GSK wanted QT information showing vardenafil's effect was the same as Viagra and that of the positive control, moxifloxacin. The companies also suggested these data be moved from warnings to precautions. The QT trials were not powered to make comparative claims between Viagra and vardenafil. In addition, it is an unfair and meaningless comparison, even if the trial was designed for comparative claims on QT, to allow a single comparison to Viagra only on QT without any context of effectiveness or other risk comparisons.

Other Labeling Issues

The Viagra label contains information negotiated with cardiorenal (the division that approved the drug in 1998) that urologists do not find clinically relevant to defining a drug's effectiveness for ED. Rigiscan data is not used for defining effectiveness in drug trials and as a pharmacodynamic endpoint, it does not correlate with drug effectiveness. The patient oriented question (GAQ) of "is erection improved" is subsumed by the primary study endpoint, Erectile Function Domain score. In addition, in studies of time to onset of erection, the primary endpoint did not obtain statistical difference, as did other secondary endpoints, except one. These data do not support labeling other than how the drug was administered in the pivotal clinical trials. For these reasons, DRUDP is negotiating a label for vardenafil that may differ in several ways from the label for Viagra.

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Florence Houn
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MEDICAL OFFICER

MEMORANDUM

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

DATE: July 23, 2002

FROM: Florence Houn MD MPH

SUBJECT: Office Director's Memo

TO: NDA 21-400 Levitra (vardenafil hydrochloride) Tablets by Bayer Corporation

This memo documents my concurrence with the Division of Reproductive and Urologic Drug Products' (DRUDP) recommendation to issue an approvable letter to Bayer for Levitra, indicated for erectile dysfunction. Levitra is a PDE-5 inhibitor that increases levels of cGMP that is believed to facilitate vasodilatation and smooth muscle relaxation of the corpus cavernosa, resulting in erection. The division has outlined that efficacy has been established in the 2.5, 5, 10, and 20 mg doses. It should be noted that efficacy trials included 70 % of patients with previous history of Viagra responsiveness. I stated that the division should be including all comers to these trials as the use for Levitra will likely include men who have used Viagra previously and did not respond satisfactorily and are seeking satisfactory therapeutic or improved adverse event effect. Safety has been thoroughly reviewed. There are a few major outstanding issues relating to the need for more QT data with greater multiples of exposures that are possible given that inhibition of CYP 3A4 leads to increases in Levitra levels, interaction study of alpha-blocker and Levitra, a nitrate interaction study and aspirin interaction study for the 20mg dose, chemistry and manufacturing information on the 2.5mg tablet, and further work up for backpain and myalgias and eye effects.

QT Prolongation Data Need

The need for QT data was communicated to the manufacturer in June 2002 by the division. A face to face meeting occurred July 12, 2002. The company argued that the pooled human QT data showed no signal, the in vitro data were also void of a signal for QT prolongation, and that the drug increases heart rate, making assessments for QT impossible. The division stated that none of the human studies were designed specifically for QT assessment, that studies 94, 100196, and 10006 were positive for effect (even though 100196 had EKGs performed at 2 hours, while Levitra's Cmax is 1 hour), and that there was some suggestion of dose-response. The adverse event reports include a man with ventricular tachycardia and an acute MI without a predisposing factor. Furthermore, drug interactions with inhibitors of CYP 3A4 (such as the protease inhibitors and ketoconazole) produce high increases in Cmax and AUC of Levitra. The magnitude of the interaction mandates exposure of parent vardenafil, obtained when these drugs are co-administered, must be investigated for QT effects. These inhibitors of CYP 3A4 are expected to be used in the population also using Levitra. The concern about wide spread recreational use of PDE-5 inhibitors to counteract erectile dysfunction from abuse of stimulants in men who are HIV- positive has been discussed by officials of the Centers for Disease Prevention and Control, San Francisco health department authorities, and San Francisco area gay health organizations with myself and Dr. Dan Shames earlier this year.

The manufacturer on July 16, 2002 telephoned me and stated that they wanted to amend the application to include the 2.5 mg dose in hopes of getting an approval this cycle. On July 16, 2002 Dr. Dan Shames, Director, DRUDP, contacted Dr. Douglas Throckmorton and asked that he and his primary reviewer provide us with his division's recommendation on if there are sufficient data to conclude no QT effect for the 2.5 mg dose. In an email to me and Dr. Shames on July 17, 2002, the cardiorenal primary reviewer, Dr. Norman Stockbridge, stated that after discussions with Dr. Throckmorton "I don't believe you can rule out even a 10-ms effect at 40 mg [which is the comparable dose one would achieve with 2.5 mg and CYP 3A4 inhibitors]. None of these data have the active-control assay validation we are seeking. In summary, neither of us think the proposal is encouraging." The amendment would most likely not have changed an

approvable action; however, on July 17, 2002, Ms. Mary Taylor of Bayer told Dr. Shames that no amendment would be submitted at this time.

2.5 mg Strength

It is clear from the clinical pharmacology reviews this drug has significant interactions with CYP 3A4 inhibitors. There is a 7-fold increase in Cmax for 10mg of Levitra. The AUC is increased by 16-fold. There is a clear need for lower doses of this drug for patients who are on CYP 3A4 inhibitors and take Levitra to avoid high exposures and adverse events such as hypotension, syncope, and back pain. As stated above, there is expected use of Levitra in such a population of HIV-positive men who are on protease inhibitors and who will use this drug. Contraindicating Levitra in this population in labeling would be of little practical consequence. Providing a safer dose has more impact.

20 mg Strength

I note that the reviewers are not convinced of the need for a 20 mg strength, given the comparable efficacy of 20 mg and 10 mg. The company feels that the statistical difference in one erectile function domain endpoint in a diabetic trial justifies this dose. Additional safety information is being requested on the 20 mg. A final decision about this dose can be made next cycle with the added information.

Nitrate Interaction Data Need

The company was informed during development that nitrates would be contraindicated and no further data beyond what they provided for the 10mg dose was needed. However, the division informed the company in June 2002 that nitrate interaction needed further investigation. This change in requirement is based on the increased awareness that nitrates are being given to patients who take PDE-5 inhibitors for erectile dysfunction, despite the labeled contraindication. It is part of medical practice to give nitrates for chest pain. Men who take Levitra will get chest pain, some after sexual exertion, and will be given nitrates. Review of post-marketing adverse events documents this occurrence. In addition, physicians have asked the FDA to better define the nitrate interaction with PDE-5 inhibitors. The current Viagra label states it is not known when nitrates can be safely given. This is because Pfizer had not studied the phenomena, not because there is some inherent difficulty in characterizing this profile. Data about this interaction is needed for labeling because there is a medical need for this information. Of note, the 10 mg nitrate study submitted did not have an additive nor synergistic effect on blood pressure with nitrates and Levitra. This was viewed by the cardiorenal reviewer and the urology reviewer as unusual.

Myalgias and Back Pain and Eye Effects

This adverse event appears to be dose-dependent. Etiology is unknown. Serologic work up for rheumatologic disorder is negative. As clinical trials proceed, those subjects developing back pain will continue to undergo work up.

More studies on vision are needed, but could be done post-marketing.

Aspirin Interaction Study and Alpha Blocker Interaction Study

I agree that platelet function must be studied prior to approval for the 20 mg strength because PDE-5 inhibitors act on platelets and this action cannot be related to pharmacokinetics. The case of syncope with Levitra and terazosin is noted. Formal interaction study at the highest Levitra dose the manufacturer proposes to market is required prior to approval.

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Florence Houn
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MEDICAL OFFICER

Teleconference Minutes

Date: July 3, 2002 **Time:** 2:30 – 3:15 PM **Location:** Room 17B-45

NDA 21-400 **Drug Name:** vardenafil hydrochloride

Indication: treatment of erectile dysfunction

Sponsor: Bayer Corporation

Type of Meeting: Guidance

Meeting Chair: Dr. Mark Hirsch **External Participant Lead:** Dr. Gautam Shah

Meeting Recorder: Eufrecina DeGuia

FDA Attendees:

Mark Hirsch, M.D. – Urology Team Leader, Division of Reproductive and Urologic Drug Products; DRUDP (HFD-580)

Eufrecina DeGuia – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:

Gautam Shah – Deputy Director, Regulatory Affairs

Objective: To provide the sponsor the requested feedback on the status of the Cardio-Renal consult regarding their QT data in the NDA.

Discussion and Decision Points:

As requested by the sponsor, Dr. Hirsch provided an update and noted that the following issues are still concerning and the studies have deficiencies that may preclude approval. He reiterated that although there are still some data to be investigated, the NDA appears to be leading to an Approvable (AE) action.

1. QT Study:

- As per Cardio-Renal consult, the data provided are not compelling enough to rule out the effect of vardenafil on the QT interval at doses of 40 and 80 mg. This opinion is consistent with review of the data by the DRUDP Medical Reviewer. Lack of data to rule out QT effect poses a major obstacle to approval.

2. Myalgia and Back Pain

- Dr. Hirsch would like to see the sponsor provide data on a total of 50 patients who have reported the occurrence of back pain/myalgia after taking vardenafil and perform a work up with due diligence; additional information must be collected to rule out any underlying pathology in any patient in new or ongoing trials reporting back pain or myalgia

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3. Nitroglycerin Interaction Study:

- this is a risk management question that needs to be addressed pre-approval; information must be provided on the effect of vardenafil on blood pressure when a patient, who, on emergency situations, need to be dosed with nitroglycerin; there is no such information for the 20 mg dose, although such information was submitted for the 10 mg dose.

Other Issues:

- LFT – the review is not yet fully completed; there are few cases that still cannot be attributed to any other cause except study drug.
- CPK – data submitted is convincing that there is probably no direct effect on CPK
- Sildenafil Exclusion Criteria – can be worked on the label
- Restricting patients, 65 years and older to 10 mg only dose; this is a recommendation from the Biopharm reviewer and will be presented at the upcoming briefing with the Office of Pharmacology and Biopharmaceutics (OCPB); sponsor's argument regarding safety data in population >65 years old is very reasonable

Action Items:

- meeting minutes will be sent to the sponsor within 30 days

/s/

Signature, minutes preparer

See appended electronic signature page

/s/

Concurrence, Chair

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/s/

Mark S. Hirsch
7/29/02 01:33:58 PM

Meeting Minutes

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cc:

NDA Arch:

HFD-580/DeGuia/Hirsch

drafted: DeGuia/070802

concurrences:Hirsch072402

final: DeGuia072402

MEETING MINUTES

Teleconference Minutes

Date: June 13, 2002 **Time:** 9:00 – 10:00 AM **Location:** Room 17B-45

NDA 21-400 **Drug Name:** vardenafil hydrochloride

Indication: treatment of erectile dysfunction

Sponsor: Bayer Corporation

Type of Meeting: Guidance

Meeting Chair: Dr. Mark Hirsch **External Participant Lead:** Dr. Gautam Shah

Meeting Recorder: Eufrecina DeGuia

FDA Attendees:

Mark Hirsch, M.D. – Urology Team Leader, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)

George Benson, M.D. – Medical Reviewer, DRUDP (HFD-580)

Eufrecina DeGuia – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:

Gautam Shah – Deputy Director, Regulatory Affairs

Friedrich Jekat, M.D. – Director, Drug Safety Evaluation

Paul McCarthy, M.D. – Vice President, US Medical Sciences

Pavur Sundaresan, M.D., Ph.D. – Director, Clinical Pharmacology

Thomas Segerson, M.D. – Global Clinical Project Leader

Mary Taylor, MPH – Vice President, Regulatory Affairs

Marc Thibonnier, M.D. – Director, US Medical

Arthur Mazzu, Ph.D. – Deputy Director, Clinical Pharmacology

Objective: To provide the sponsor another feedback regarding the status of the review, import permit and the pending tradename review.

Discussion and Decision Points:

As requested by the sponsor, Dr. Hirsch provided another update and noted that the following issues are still under review. He also reiterated that decisions are not final for there are still six weeks left before the PDUFA goal date of July 24, 2002.

Tradename: Nuviva is still found unacceptable after the submission of _____ and Medication Error Risk Management Program; study is flawed and does not provide convincing argument

- Additional tradenames were submitted – Dr. Hirsch noted that _____ and _____ are likely not acceptable and that the sponsor should pick one top candidate name for review

Import Permit: Office of Regulatory Affairs (ORA) has the authority to grant or deny permits. The NDA review is still on-going and no final decision has been made regarding the approvability or non-

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approvability of the product. The Division refused to send ORA a note stating that approval was "imminent."

Issues under review:

1. QT issues – with the reporting of some cardiovascular events in this NDA (including but not limited to palpitations, tachycardia, syncope and MI) and because of postmarketing Adverse Events (AE) reports with a related compound, rigorous analysis of QT interval is required
 - in Bayer QT trials, 9 have been reviewed; none appear adequately designed to assess QT; two of the studies did not include a placebo control group and in two, EKGs were taken 2.5 hours post-dosing which potentially miss C_{max}
 - only 5 patients were studied at the maximum dose of 80 mg
 - pre-clinical data is not concerning
 - can't rule out the effect of vardenafil on the QT interval at doses of 40 and 80 mg
 - sponsor should show no evidence of QT effect at high exposures (at least 80 mg) in light of vardenafil's potential for interaction with other drugs like ketoconazole, indinavir and erythromycin
2. Nitroglycerin Interaction:
 - Design of study 100304 is acceptable and the conclusion is valid; however, it provides data for 10 mg only and not 20 mg and the sponsor is asking for the approval of 20 mg dose;
 - The sponsor was asked what should be told to a patient or physician after taking vardenafil and then requiring nitroglycerin; this is a risk management question that needs to be addressed pre-approval
3. Interaction with ketoconazole, indinavir and erythromycin – at this time, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) recommends contraindicating ketoconazole and protease inhibitors in the label
4. OCPB recommends that patients 65 years and older be limited to a maximum dose of 10 mg.
5. Ophthalmology consult is still pending but it is unlikely that any issues in this consult would preclude approval.
6. In three of four pivotal trials, CPK abnormalities are concerning; there is a mean increase in CPK in drug group over placebo. The sponsor should summarize data for this issue and provide an argument as to its clinical relevance.
7. Cases of elevated LFTs were seen at higher doses (40 mg BID); in one case, a patient was hospitalized for observation. The sponsor should summarize the data for this issue and provide an argument as to its clinical relevance.
8. Clinical Significant AEs – clinically significant AEs that were cardiovascular in nature were reported in several trials; even if there only few cases, drug relatedness needs to be ruled out; each case is being reviewed separately with emphasis on temporal relationship to drug accounting tablet and diary counts.

9. Myalgia and Back Pain – effect is seen at 40 mg BID and 40 mg QID but it does not seem to be a problem at 5, 10 and 20 mg doses; what happens at higher exposures should be taken into consideration; the sponsor should provide an argument for lack of clinical safety concern for this issue
10. A “history of unresponsiveness to sildenafil” was an exclusion criterion in Trials 100249, 100250 and 100285; the sponsor should comment on whether this criterion confounds the efficacy results.

Action Items:

- meeting minutes will be sent to the sponsor within 30 days

/s/

Signature, minutes preparer

See appended */s/* signature page

Concurrence, Chair

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Mark S. Hirsch
7/14/02 05:31:56 PM

Teleconference Minutes

Date: May 22, 2002 **Time:** 3:00 – 3:30 PM **Location:** Room 17B-45

NDA 21-400 **Drug Name:** vardenafil hydrochloride

Indication: treatment of erectile dysfunction

Sponsor: Bayer Corporation

Type of Meeting: Guidance

Meeting Chair: Dr. Daniel Shames **External Participant Lead:** Dr. Gautam Shah

Meeting Recorder: Eufrecina DeGuia

FDA Attendees:

Daniel Shames, M.D. – Acting Director, Division of Reproductive and Urologic Drug Products;
DRUDP (HFD-580)

Margaret Kober, R.Ph. – Chief Project Management Staff, DRUDP (HFD-580)

Eufrecina DeGuia – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:

Gautam Shah – Deputy Director, Regulatory Affairs

Nancy Bryan – Vice President, Men's Health Marketing

Paul McCarthy, M.D. – Vice President, Medical Sciences

Lawrence Posner – Head, Global Regulatory Affairs

Objective: To provide the sponsor some feedback regarding the status of the review, import permit and the pending tradename review.

Discussion and Decision Points:

As requested by the sponsor, Dr. Shames provided an update and noted that the following issues are under review:

1. Dose Issue:
 - 5, 10, and 20 mg doses are all more efficacious than placebo and are highly statistically significant
 - 20 mg is marginally more efficacious than 10 mg in the diabetic study; the only statistically significant difference for 20 mg over 10 mg was the ED Domain of the IIEF in the diabetic study
 - none of the pivotal studies was designed to specifically compare the 10 and 20 mg doses
2. QT Prolongation:
 - there is no evidence so far to rule out QT problems
 - QT data have been sent to Division of Cardio-Renal Drugs for consultation; review is pending
 - there's little data at 80 mg; most data is at 40 mg

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- there is no positive control arm
 - there's a question as to timing of conducting EKG in relationship to C_{max}
3. Nitrate Interaction:
 - Dose of vardenafil studied was 10 mg; no data on 20 mg
 4. Myalgia and Back Pain seen at higher doses
 - back pain is not a concern in the controlled clinical trials in doses of 20 mg
 5. Drug – Drug Interaction:
 - the Division is looking aggressively into the effect of vardenafil in patients taking protease inhibitors
 6. Ophthalmology Consult
 - Ophthalmology consult is pending
 7. Analysis of clinically significant adverse events in pivotal trials and extensions are underway.
 8. Tradename Review:
 - Nuviva is still unacceptable; a new tradename proposal should be submitted
 9. Import Permit:
 - any problems regarding import permits should be discussed with the Office of Regulatory Affairs

Action Items:

- meeting minutes will be sent to the sponsor within 30 days

/s/

Signature, minutes preparer

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/s/

Concurrence, Chair

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/s/

Daniel A. Shames
6/20/02 05:12:12 PM

Teleconference Minutes

Date: April 29, 2002 **Time:** 5:00 p.m. – 5:15 p.m. **Location:** Parklawn; 17B-45

NDA 21-400 **Drug:** Vardenafil hydrochloride Tablet

Sponsor: Bayer

Indication: Erectile Dysfunction

Type of Meeting: Information Request

Meeting Chair: David Lin, Ph.D.

External Lead: Gautam Shah, Ph.D.

Meeting Recorder: Eufrecina DeGuia

FDA Attendees

David Lin, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ Division of Reproductive and Urologic Drug products, DRUDP (HFD-580)

Eufrecina DeGuia, Project Manager, DRUDP (HFD-580)

External Attendees:

Gautam Shaw, Ph.D., Deputy Director, Regulatory Affairs

Meeting Objectives:

A follow-up to a T-con between Jila Boal, Review Chemist and the sponsor to clarify whether the drug product tablets are “debossed” or “embossed”.

Background:

During a previous guidance T-con held on November 30, 2000 for IND [redacted] the issue of whether the drug product tablet is debossed or embossed was discussed. The sponsor indicated that although Bayer calls the process “embossing”, the tablet may actually be debossed.

Discussion:

- this T-con was held as a follow-up to the Review Chemist’s request to clarify whether the commercial product is indeed a debossed tablet. The NDA as submitted indicates that the product is “embossed” with the “Bayer” cross and the dosage strength. The sponsor stated that the tablet is “debossed”.

Decisions reached:

- in lieu of the sponsor submitting an amendment, the minutes of this T-con provides the sponsor’s concurrence that the drug product is a “debossed” tablet.

Action Items:

- the Review Chemist will refer to these meeting minutes for the review of the NDA
- Meeting minutes from this teleconference will be conveyed to the sponsor within 30 days

|S|

Minutes Preparer:

|S|

Meeting Chair

cc:
Original NDA 21-400
HFD-580/Div. Files
Concurrence: DeGuia, , Lin,
Drafted by: Lin, 5.2.02
final: Lin,

MEETING MINUTES

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David T. Lin
5/14/02 04:58:40 PM
CHEMIST

Teleconference Minutes

Date: April 18, 2002

Time: 3:00 – 4:00 PM

Location: Room 17B-45

NDA 21-400

Drug Name: Nuviva (vardenafil hydrochloride)

Indication: treatment of erectile dysfunction

Sponsor: Bayer Corporation

Type of Meeting: Guidance

Meeting Chair: Dr. Mark Hirsch, M.D.

External Participant Lead: Gautam Shah

Meeting Recorder: Eufrecina DeGuia

FDA Attendees:

Mark Hirsch, M.D. – Urology Team Leader, Division of Reproductive and Urologic Drug Products; DRUDP (HFD-580)

George Benson, M.D. – Medical Reviewer, DRUDP (HFD-580)

Margaret Kober – Acting, Chief Project Management Staff, DRUDP (HFD-580)

Eufrecina DeGuia – Regulatory Project Manager, DRUDP (HFD-580)

Carol Holquist, R.Ph. – Deputy Director, Division of Medication Error and Technical Support (DMETS) HFD-400

Jerry Phillips, R.Ph. – Associate Director, DMETS (HFD-400)

Denise Toyer, R.Ph., M.P.H. – Team Leader, DMETS (HFD-400)

Kevin Dermanoski, R.Ph. – Safety Evaluator, DMETS (HFD-400)

External Participants:

Gautam Shah – Deputy Director, Regulatory Affairs

Nancy Bryan – Vice President, Men's Health Marketing

Karen Dawes – Senior Vice President, Marketing

Paul McCarthy, M.D. – Vice President, Medical Sciences

Lawrence Posner – Head, Global Regulatory Affairs

Amy Straub, Ph.D. – Deputy Director, Project Management

Marc Thibonnier, M.D. – Director, Medical Sciences

Marc vanUnen, Deputy Director, Men's Health Marketing

Objective: To discuss the previous comments and recommendations regarding the proposed proprietary name.

Background: This NDA was submitted on September 24, 2001 for the treatment of erectile dysfunction indication. DRUDP submitted a request to Office of Post-Marketing and Drug Risk Assessment (OPDRA) on June 25, 2001 for a proprietary name review of Nuviva. The submission included an independent analysis of Nuviva conducted _____ . Based on the information provided, OPDRA did not recommend the proprietary name Nuviva due to concerns related to

two look-alike names that already exist in the marketplace, Norvasc and Navane. The sponsor was informed of this decision on January 9, 2002 and was advised to submit another proprietary name proposal. Bayer submitted a rebuttal and additional information to support the original proprietary name on February 5, 2002. This submission was consulted out to OPDRA, now DMETS, for re-assessment and review. The second review from DMETS still does not recommend the use of the proprietary name Nuviva due to safety concerns. A teleconference was held on April 3, 2002, and a regulatory letter was sent on April 11, 2002 outlining the DMETS comments

Discussion Points:

- Bayer noted that the proposed proprietary name Nuviva will be used internationally; different U.S. and international names may be confusing; the Division responded that drugs are often marketed with different proprietary names overseas
- sponsor has pursued the research of tradenames with due diligence and cannot come up with another proprietary name to replace Nuviva; the Division acknowledges the sponsor's effort in this regard
- sponsor believes that another impediment to medication error would be the substantial price differential which would alert pharmacists and patients alike; DMETS does not agree with this thought because they believe that there are several confounding factors that can influence the probability of error
- the sponsor acknowledges potential safety concerns but is willing to commit to post-marketing risk management (i.e., the use of first databank system that covers 95% of pharmacies to alert pharmacies regarding medication errors)
- additionally, the sponsor commits to launch public health campaign and conduct other measures that the Agency deem appropriate

Decisions Reached:

- DMETS will review the second Study faxed on April 18, 2002; all aspects will be considered
- Bayer will submit a proposal for Nuviva Medication Error Risk Management Program for review and comment
- sponsor will submit all of the 100 actual hand-written scripts by physicians for evaluation

Action Items:

- meeting minutes will be sent to the sponsor within 30 days

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Signature, minutes preparer

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Concurrence, Chair

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Mark S. Hirsch
5/14/02 04:12:19 PM

Teleconference Minutes

Date: April 3, 2002 **Time:** 11:00 – 11:30 PM **Location:** Room 17B-45

NDA 21-400 **Drug Name:** Nuviva (vardenafil hydrochloride)

Indication: treatment of erectile dysfunction

Sponsor: Bayer Corporation

Type of Meeting: Guidance

Meeting Chair: Dr. Mark Hirsch, M.D.

External Participant Lead: Gautam Shah

Meeting Recorder: Eufrecina DeGuia

FDA Attendees:

Mark Hirsch, M.D. – Urology Team Leader, Division of Reproductive and Urologic Drug Products; DRUDP (HFD-580)

George Benson, M.D. – Medical Reviewer, DRUDP (HFD-580)

Eufrecina DeGuia – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:

Gautam Shah – Deputy Director, Regulatory Affairs

Mary Taylor, MPH – Vice President, Regulatory Affairs

Nancy Bryan – Vice President, Men's Health Marketing

Paul McCarthy, M.D. – Vice President, Medical Sciences

Marc Thibonnier, M.D. – Director, Medical Sciences

Marc vanUnen, Deputy Director, Men's Health Marketing

Objective: To provide comments and recommendations regarding the review of the proprietary name Nuviva.

Background: This NDA was submitted on September 24, 2001 for the treatment of erectile dysfunction indication. DRUDP submitted a request to Office of Post-Marketing and Drug Risk Assessment (OPDRA) on June 25, 2001 for a proprietary name review of Nuviva. The submission included an independent analysis of Nuviva conducted _____ Based on the information provided, OPDRA did not recommend the proprietary name Nuviva due to concerns related to two look-alike names that already exist in the marketplace, Norvasc and Navane. The sponsor was informed of this decision on January 9, 2002 and was advised to submit another proprietary name proposal. Bayer decided to submit instead a rebuttal and additional information to support the proprietary name on February 5, 2002. The submission was again consulted out to OPDRA, now Division of Medication Error and Technical Support (DMETS), for re-assessment and review. The second review from DMETS still does not recommend the use of the proprietary name Nuviva due to safety concerns.

Decisions Reached:

The following comments from DMETS were conveyed to the sponsor:

1. 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 _____

_____ 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.

2. 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.

3. 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.

4. 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.).

5. 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.

6. 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 gender of the patient.

7. In _____, the only close sound-alike was Sustiva

DMETS agrees with the _____ conclusion regarding Sustiva.

8. In _____ 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.

9. Norvasc does not resemble the name Nuviva.

The _____ component of the _____ analysis contradicts this statement. _____ 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 _____ panel also noted the overlap between the drugs' dosage forms and strengths.

10. 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.

11. 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.

12. 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.

13. 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.

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

Action Items:

- comments from the first and second proprietary name reviews from DMETS will be sent to the sponsor via regulatory letter
- Project Manager will schedule a teleconference between DRUDP (and DMETS) and Bayer to further discuss DMETS comments.

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Signature, minutes preparer

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Concurrence, Chair

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Mark S. Hirsch
5/14/02 04:08:22 PM

Meeting Minutes

Date: May 2, 2001 **Time:** 10:00am -11:30 p.m. **Location:** Parklawn; CR-"C"

IND: **Drug:** BAY 38-9456

Sponsor: Bayer

Indication: Erectile Dysfunction

Type of Meeting: Pre-NDA

Meeting Chair: Susan Allen, M.D., M.P.H.

Meeting Recorder: Dornette Spell-LeSane, NP-C, M.H.A

FDA Attendees

Susan Allen, M.D., M.P.H., Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Daniel Shames, M.D., Deputy Director, DRUDP (HFD-580)

Mark Hirsch, M.D., Medical Team Leader, DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

David Lin, Ph.D., Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Dhruba Chatterjee, Ph.D., Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Michael Welch, Ph.D., Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Ashok Batra, M.D., Medical Officer, DRUDP (HFD-580)

Dornette Spell-LeSane, NP-C, Project Manager, DRUDP (HFD-580)

External Attendees:

Bill Baker, MS, Associate Director, Submission Support Services

Wolfgang Barth, Director, Global Project Management,

Carl E. Calcagni, R.Ph., Vice President, Regulatory Affairs

Margaret Foley, Regulatory Compliance Associate, Regulatory Affairs

Dennis Haggerty, Ph.D., Chemical Development

Friedrich Jekat, M.D., Director, Toxicology

Sharon Kawam, J.D., Associate Director, Project Management

Arthur Mazzu, Ph.D., Deputy Director, Clinical Pharmacology

Thomas Segerson, M.D., Global Clinical Project Leader

Gautam Shah, Ph.D., Deputy Director, Regulatory Affairs

JoAnn Shapiro, M.S., Associate Director, Statistics

Pavur Sundaresan, M.D., Ph.D., Director, Clinical Pharmacology

Terry Taylor, M.D., Global Clinical Strategist

Marc Thibonnier, M.D., Director, Medical Sciences

Meeting Objectives: To discuss the sponsors plan to submit an NDA

Background:

Vardenafil, BAY 38-9456, is a PDE 5 inhibitor under development by the sponsor for the indication of male erectile dysfunction. A Pre-IND meeting was held October 7, 1998, and an EOP2 meeting was held March 17, 2000. On March 14, 2001, the Sponsor submitted a request for a Pre-NDA meeting. The meeting package was submitted April 4, 2001, and contained 6 points for discussion. The sponsor plans to submit an NDA to the Division by the end of September 2001. A trademark has not been identified.

Discussion:

- the sponsor presented a slide entitled "Estimated Long –Term Safety Exposure in NDA Submission"
 - sponsor reported on the number of patient exposures to be available at the time of the NDA submission
 - approximately 800 patients with at least 6 months exposure will be available at the time of filing
 - approximately 225 patients with at least one year exposure will be available at the time of the 4-month safety update
 - DRUDP reported that from Study 100199 the patient population by exclusion criteria were healthier and therefore the study may not support approval

- The sponsor presented slide entitled "Plan for Integrated Efficacy Data Pools"
 - sponsor plans to submit individual study reports and an ISE
 - DRUDP stated that the proposed pooling of efficacy data is exploratory as opposed to individual reports which would provide stand alone data
 - DRUDP stated that stand alone data of the pivotal trial using individual study reports may be adequate to support possible efficacy
 - sponsor states that the analysis plan and the data for subgroups will be provided in table format; the plan to provide subgroup data analysis is acceptable

- The sponsor presented a slide entitled "Plan for Integrated Safety Pool"
 - Study 100199 could represent a different population from those that are followed in other studies
 - sponsor should justify that Study 100199 should be submitted as part of the pool for safety
 - DRUDP is not comfortable with the sponsor pooling the data from Study 100199 with other safety studies given the exclusion criteria that is provided in Study 100199

Question #1

Are the proposed clinical pharmacology studies including interaction studies, provided in summary in the briefing package, acceptable for an NDA submission?

Answer:

- *Yes, the PK studies and the drug interaction studies proposed are acceptable*
- *If sponsor conducts interaction studies note that M_1 is a metabolic inhibitor that accounts for 37% exposure of the parent drug; this M_1 exposure should be addressed in the drug interaction studies*
- *M_1 is characterized in-vivo but not in-vitro for interaction potential*
- *C_{max} is comparable to parent drug*

Question #2

Are the following items acceptable for submission in the 4-month safety update:

a) The final report for the 10125 One-Year safety Study

Answer:

- *Yes, this is acceptable;*
- *1-year data must be submitted at the time of the 4-month safety update*
- *three months before the 10-month due date, the Division will be requesting follow-up information (an additional safety updates) before an action will be taken on the NDA; additional safety data will be required at that time*

b) The final toxicology report of the 2-year carcinogenicity study?

Answer:

- *Yes, this is acceptable*

c) The final safety analysis of study 10152, open label 6-months 20-mg safety study if required?

Answer:

- *all required safety information should be submitted with the 4-month safety update*

Question #3a

Are the responses provided to the Division's August 29, 2000, request for information acceptable?

1) Use of Bonferroni versus Bonferroni-Holm?

Answer:

- *the proposed use of the Bonferroni method for confidence interval estimation would be acceptable*

2) Following all patients until planned end of study, regardless of whether the patient discontinued study medication?

Answer:

- *the proposed follow-up plan is acceptable*
- *the Sponsor stated that they will analyze both intent to treat and evaluable subject populations; the last-observation-carried-forward procedure will be applied to missing data*

3) Approaches for assessing the impact of missing data?

Answer:

- *the sponsor plans to address the sensitivity of the missing data assumptions in their analyses; this will largely be a review issue*

4) Clarification of sample size?

Answer:

- *the Sponsor's Nov 9, 2000 reply to the sample size questions is satisfactory*

5) Presentation of efficacy and safety results by ethnic origin and age?

Answer:

- *the Sponsor plans to present these subgroup analyses in their ISS and ISE*

Question #3b

Are the modifications to the statistical analysis plan acceptable?

Answer:

- *the modified statistical analysis plans were not submitted to the IND for review*
- *on April 27, 2001, the Sponsor submitted protocols for studies 10128, 10232 and 10152 and the requested rationale for the modifications to the statistical analysis plans*
- *the Sponsor was asked to further clarify the statistical analysis plan in regard to modeling procedure and the prespecification of covariates*
- *the Sponsor had been informed that the use of a generalized estimating equations (GEE) approach would be problematic as a primary efficacy analysis and that analysis of covariance (ANCOVA) methods could be used*
- *the Sponsor stated that ANCOVA methods would be used for the IIEF variables including the primary variable EF domain score*
- *the Agency indicated that the use of ANCOVA for analysis of categorical outcomes from individual IIEF questions may not be appropriate; distributional assumptions should be examined*
- *the Sponsor was asked to clarify in their submission the chronology of protocol changes with respect to clinical trial timelines and data unblinding (from time of submission of amendments to the IND)*

Question #4

Is providing narratives in the submission for the following adverse events acceptable?

- a) Death
- b) serious AE's occurring after treatment
- c) AE's leading to premature discontinuation
- d) visual adverse events and
- e) specific cardiovascular/hemodynamic events not captured in the above

Answer:

- *All serious adverse events (SAE's) should be reported*

Question #5

Does the Division agree with the format of the following:

- a) a summary of which studies will be included in each of the safety pools?

Answer:

- *justification is needed for inclusion of Study 100199 in the pooled data.*

- b) Sample tables of AE's, labs, etc.

Answer:

- *sponsor states that data contained in the tables provided in the meeting package does not reflect actual data, but rather is an example of how AE data will be presented in the application*
- *DRUDP recommends sponsor include vasodilation, flushing, rhinitis, dyspepsia, and sinusitis as reportable adverse events and should be included in the adverse event tables*
- *sponsor should include serum LFT's that are >5x and >10x the upper limit of normal in the lab tables*

c) A list of specific adverse events to be summarized by subgroup?

Answer:

- *cerebral vascular accident or stroke should be broken down by category (i.e. thrombotic, hemorrhagic etc.) and summarized by subgroup*

d) The subgroups that will be explored for these specific adverse events?

Answer:

- *in addition please add smoking history and pulmonary disease to the subgroup analysis ie, chronic COPD*

Question #6 Chemistry manufacturing and Controls

Does the Division agree that _____ is the starting material for the synthesis of Bay 38-9456?
(On April 27, 2001, the sponsor provided additional information on the synthetic methodology of the proposed starting material)

Answer:

- *sponsor confirmed: _____ as the starting material for synthesis of Bay 38-9456*
- *DRUDP stated that based on the information provided, the proposed starting material does not meet the criteria in the February 1987 guideline for "Supporting Documentation for the Manufacture of Drug Substances"*
- *the drug substance does not appear to be commercially available*
- *the compound is not well defined in the chemical literature*
- *sponsor may consider finding commercial sources of starting material and obtain COA*
- *sponsor presented slide describing the process of synthesis from the starting material*
- *_____ chemical steps are involved in process, the _____ steps then follow*
- *sponsor stated that the guidelines numbered 8 & 9 were followed in an effort to satisfy the criteria for starting material*

- *DRUDP's recommendations are based on the limited information as provided in the IND*
- *sponsor should plan for a change in control strategy (which must be provided at the time of the NDA submission)*
- *if in the future, the sponsor obtains outside suppliers or change synthetic methodology the NDA would need to be supplemented*
- *sponsor stated that if any changes regarding the supplier or the methodology in which the starting material is produced, equivalency using the impurity profile for _____ would be demonstrated*
- *DRUDP finds starting material to be acceptable, standards relative to change needs to be established*

Additional DRUDP comments:

- *sponsor should define vasodilation; all investigator terms which were categorized into the term "vasodilation" should also be provided*
- *sponsor should address drug interactions utilizing the highest dose of the drug product*
- *stability data for embossed tablets should be provided*
- *Financial Disclosure information should be provided in the NDA submission following the Guidance For Industry entitled "Financial Disclosure By Clinical Investigators" (see attachment 1)*

- *the Guidance For Industry regarding submission of NDA's using the electronic format should be followed; special requested format items (statistical tables, biopharm documents) should be submitted as desk copies and archival copies should be submitted to the Electronic Document Room*

Decisions Reached:

1. DRUDP confirmed that studies 249, 199, 128, 232, 250, and 285 are the major trials to support efficacy and for which study reports will be provided.
2. DRUDP finds starting material to be acceptable, standards relative to change needs to be established.
3. Sponsor agrees if any changes do occur with starting material, sponsor would demonstrate equivalency using impurity profile for _____
4. Sponsor agrees to submit accelerated data at the time of the NDA submission to support the use of the embossed tablets.
5. Sponsor agrees to submit narratives for all SAE's.
6. A second safety update should be provided 3 months before the 10-month PDUFA goal date.
7. Information provided by the sponsor would appear to support filing of a NDA. A final assessment of filability will be made after the application is submitted.

Action Items:

1. Sponsor may request a teleconference to discuss treadmill studies, chemistry issues or to further obtain guidance for electronic submissions.
2. Meeting minutes to be conveyed to the sponsor within 30 days.

IS/

Minutes Preparer:

IS/

Meeting Chair

Attachment 1

FINANCIAL DISCLOSURE INFORMATION

Sponsor should submit Tables that include the following information for each study they are presenting to support safety and efficacy of their NDA. (This information will enable the Division to perform the Financial Disclosure Review more efficiently.)

Study # XXXXXX

Site Name and Number	Number of Patients enrolled	Names of Investigators (principal and sub-investigators)	<input type="checkbox"/> Certification and/or Disclosure for each Investigator (yes/no)	<input type="checkbox"/> Disclosable Information (yes/no)

- If no information is provided by the investigator (principal or sub-investigator), then the sponsor must describe their efforts at due diligence in attempting to obtain this information, (i.e., sending certified letters, performing Internet searches, etc.).
- Any and all disclosable financial information must be elaborated upon.

For more detailed information, please refer to the **GUIDANCE FOR INDUSTRY: FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS**
(www.fda.gov/oc/guidance/financialdis.html)

IND
Pre-NDA meeting
Page 8

cc:
Original NDA
HFD-580/Div. Files
HFD-580/

Drafted by: Spell-LeSane, 5.24.01

Concurrence: Rumble, Batra, 5.25.01, Chatterjee, Lin, 5.30.01, Welch, 5.31.01, Hirsch, 6.1.01, Shames,
6.4.01, Parekh, 6.5.01, Allen, 6.6.01

Final: Spell-LeSane, 6.6.01

MEETING MINUTES

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

/s/

Dornette Spell-LeSane
6/6/01 02:41:56 PM
CSO

Susan Allen
6/6/01 04:24:30 PM
MEDICAL OFFICER

Redacted 12

pages of trade

secret and/or

confidential

commercial

information



D. Quinn

Mary E. Taylor
Vice President, Regulatory Affairs
Bayer Corporation
Pharmaceutical Division
400 Morgan Lane
West Haven, Connecticut 06516

MD-20857
2002

Dear Ms. Taylor:

Between February 25 and March 5, 2002, Mr. Anthony C. Warchut, representing the Food and Drug Administration (FDA), met with you and other Bayer representatives to review your firm's monitoring practices and procedures of clinical studies. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections of sponsors/contract research organizations/monitors, designed to ensure the proper conduct of clinical studies for submission to the FDA, and to ensure that the rights and welfare of the human subjects of those studies have been protected.

The inspection focused on Protocol #100249: "A randomized double-blind, placebo-controlled, multi-center, fixed-dose, parallel group, six month comparison study to investigate the efficacy and safety of the phosphodiesterase type V inhibitor BAY 38-9456 in males with erectile dysfunction."

From our evaluation of the inspection report and the documents submitted with the report, we conclude that Bayer Corporation Pharmaceutical Division adhered to pertinent federal regulations governing sponsor/contract research organization/monitor responsibilities for the conduct of clinical studies and the protection of human subjects.

We appreciate the cooperation shown Investigator Warchut during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact Khin Maung U, M.D., Branch Chief, Good Clinical Practice I, by letter at the address below.

Sincerely yours,

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Page 2 - Mary E. Taylor

FEI: 3003387481

Field Classification: NAI

Headquarters Classification:

1) NAI

2) VAI-no response required

3) VAI-response requested

If Headquarters classification is different, explain why:

Deficiencies noted: None - no Form FDA 483 was issued.

cc:

HFA-224

HFD-580 Doc.Rm. NDA 21-400

HFD-580 Review Div. Dir. Shamens

HFD-580 MO Benson

HFD-580 PM Deguia

HFD-45 Reading File

HFD-46 c/r/s GCP File #10581

HFD-46 Blay

HFD-47 Hajarian

HFR-NE250 DIB Kravchuk

HFR-NE250 BIMO Madigan

HFR-NE250 Field Investigator Warchut

r/d:GRH:3/22/02

O:GRH:BAYER CORPORATION NAI.DOC

Note to Review Division M.O.

Procedures and practices for monitoring Protocol #100249 in support of NDA 21-400 were adequate. No Form FDA was issued.



DeQuia

Food and Drug Administration
Rockville MD 20857

APR 2 2002

Harin Padma-Nathan, M.D.
9100 Wilshire Boulevard
East Tower, Suite 360
Beverly Hills, California 90212

Dear Dr. Padma-Nathan:

Between February 25 and March 11, 2002, Mr. Ronald L. Koller, representing the Food and Drug Administration (FDA), met with you to review the conduct of a clinical study (Protocol #100249) of the investigational drug BAY 38-9456, performed for Bayer Corporation. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Koller during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact Khin Maung U, M.D., Branch Chief, Good Clinical Practice I, by letter at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 1000306513

Field Classification: NAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

cc:

HFA-224

HFD-580 Doc.Rm. NDA 21-400

HFD-580 Review Div.Dir. Shames

HFD-580 MO Benson

HFD-580 PM Deguia

HFD-45 Reading File

HFD-46 c/r/s GCP File #4063

HFD-46 Blay

HFD-47 Hajarian

HFR-PA250 DIB Stokke

HFR-PA2565 BIMO & Field Investigator Koller

r/d:GRH:3/21/02

fi:mb:3/27/02

O:\GRH\PADMA-NATHAN NAI.DOC

Reviewer Note to Rev. Div. M.O.,

Protocol #100249

Sixty-nine (69) subjects consented, 38 subjects completed the study, 12 were lost to follow-up, 6 withdrew consent and 13 were dropped after enrollment for various reasons (abnormal labs, elevated blood pressure, lost partner, etc.). The records of 15 subjects were reviewed in depth. Electronic case report forms were compared to source documents. There was adequate documentation that all subjects enrolled did exist, and that all subjects received the assigned study medication and had clinical and laboratory parameters recorded. Study visit records, diaries and questionnaires were satisfactory. All adverse events were reported. There were no deaths or serious adverse events related to the study drug. Informed consents for all subjects were verified. Except for several minor data entry errors which were acknowledged by the C.I., no significant deviations were noted. No Form FDA 483 was issued. The data appeared acceptable.

See Medical Officer's Review (page 13)

APPEARS THIS WAY
ON ORIGINAL

Abuse liability review was not needed for this product.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-400
Levitra® (vardenafil hydrochloride) Tablets
Bayer Healthcare

NDA 21-400

Review Priority: STANDARD
Chemical Class: Type 1 (new molecular entity)

APPEARS THIS WAY
ON ORIGINAL

NDA 21-400
Levitra® (vardenafil hydrochloride) Tablets
Bayer Healthcare

User Fee Goal Date: August 19, 2003

APPEARS THIS WAY
ON ORIGINAL

NDA 21-400
Levitra® (vardenafil hydrochloride) Tablets
Bayer Healthcare

Special Programs

Not Applicable.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Bayer Corporation, Pharmaceutical Division 400 Morgan Lane West Haven, CT 06516	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER N 21-400
2. TELEPHONE NUMBER (Include Area Code) (203) 812-3051	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA)
3. PRODUCT NAME NUVIVA™ (vardenafil HCl)	6. USER FEE I.D. NUMBER 4168

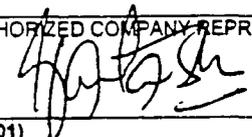
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, on reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and drug Administration CDER, HFD-84 12420 Parklawn Drive, Room 3046 and Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number
--	---	---

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE  Gautam Shah FORM FDA 3397 (3/01)	TITLE Deputy Director, Regulatory Affairs	DATE 9/24/01
--	---	-----------------

Bayer Corporation and this application are not under AIP.

APPEARS THIS WAY
ON ORIGINAL