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/s/

Denise Toyer
6/27/02 03:35:03 PM
PHARMACIST

Carol Holquist
6/27/02 03:38:33 PM
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Jerry Phillips
7/2/02 07:07:02 AM
DIRECTOR

Office of Drug Safety

MEMO

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

From: Denise P. Toyer, Pharm.D.
Safety Evaluator Team Leader, Division of Medication Errors and Technical Support (HFD-400)

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support (HFD-400)

Jerry Phillips, R.Ph.
Associate Director, Office of Drug Safety (HFD-400)

CC: Eufrecina DeGuia
Project Manager, Division of Reproductive and Urologic Drug Products (HFD-580)

Date: May 23, 2002

Re: ODS Consult 01-0149-2; Nuviva (Vardenafil Hydrochloride Tablets); NDA 21-400

The Division of Medication Errors and Technical Support (DMETS) reviewed the proposed proprietary name Nuviva, on November 14, 2001 and March 29, 2002, and did not recommend use of the name (ODS consults 01-0149 and 01-0149-1). The first DMETS review of Nuviva identified two potential look-alike names that exist in the U.S. marketplace, Norvasc and Navane. These names currently cause confusion due to their similar appearance when scripted and have resulted in medication errors. During the initial assessment, DMETS reviewed an independent analysis conducted by [redacted] that Bayer submitted to support their choice of the proprietary name Nuviva. Bayer submitted a rebuttal on February 5, 2002, and requested a reconsideration of the proposed proprietary name. DMETS noted that Bayer's rebuttal had not provided a persuasive argument that minimized the Agency's concern with regard to potential medication errors due to the similarity of spelling and pronunciation of Nuviva to the currently marketed drug products, Norvasc and Navane. Bayer submitted a second [redacted] study to support the proposed name Nuviva on April 18, 2002. Bayer also submitted a proposal for a Nuviva Medication Error Risk Management Program to support the acceptability of the proprietary name. This memo will address both issues.

[redacted] Study and Analysis

The [redacted] conducted a second study to evaluate the potential for error between Nuviva and currently marketed brand/generic drug products. [redacted] reported that 100 physicians and 100 pharmacists participated in the study. The specialties of the physicians are: internal medicine/family practice/general practice/ (60), urologists (20), endocrinologists (6), cardiologists (6), diabetiologists (4), and psychologists (4). Fifty hospital and fifty retail pharmacists participated in the study. The medical professionals participated in various aspects of the four phases of the [redacted] study.

Section A – [redacted] Review: Physicians

[redacted] asked physicians to identify any currently marketed brand or established name products that potentially sound-alike or look-alike Nuviva. They also determined if Nuviva had sound-alike or look-alike properties to any medical terms or devices. The participants evaluated the proposed name for any relationship to "hyperbole or false claims." Finally, each physician (100) provided an oral and handwritten interpretation of the following Nuviva prescription.

Nuviva 10 mg
Dipense#6
1 tab 30 minutes prior to sexual intercourse PRN

Although [redacted] indicates that 100 physicians were asked to participate in this phase of the study, the response rate was only 34%. [redacted] notes that this is an acceptable response rate for a survey of this type. However, there are limitations in the predictive value of these studies, primarily due to the sample size. It is not indicative as to what will occur once the drug is widely prescribed. Although the physician response rate for this study is slightly higher than the first [redacted] study (34% vs. 29%) DMETS notes that this study asked physicians, instead of pharmacists, to identify any Nuviva sound-alike or look-alike products. Physicians do not usually interpret prescriptions and thus the section would have been more effective if pharmacists had been included. This issue is also dependent upon the specialty of the physician. However, [redacted] did not provide any medical specialty information on the respondents. [redacted] also notes that *ten* respondents implied the name had an association with "new life" or "life-changing." If the response rate was only 34%, then approximately one-third of the respondents felt that the name implied some type of misleading connotation.

Section B – Handwritten and Verbal Analysis: Pharmacists

[redacted] provided one hundred pharmacists with a verbal and written prescription (see above sample) for Nuviva. The objective of this phase is to determine if any of the sample Nuviva prescriptions would be interpreted as a currently marketed brand or established name product.

As noted with the physician response rate, [redacted] indicates that the response rate in this portion of the study was 39% which was slightly lower than the rate found in the initial study (40%). However, [redacted] also indicates that '100 respondents' correctly identified the test name in both the verbal and handwritten sections of the study. DMETS is unclear how 100 respondents in the verbal and 100 respondents in the handwritten section is equivalent to a response rate of 39% especially if only 100 pharmacists participated in the study. Furthermore, DMETS' concern involved name confusion in handwritten prescriptions and not verbal prescriptions. [redacted] data do not provide separate response rates for the verbal or handwritten

sections. Thus, DMETS is unable to determine how many responses were attributed to handwritten Nuviva prescriptions. Moreover, two hundred sample prescriptions were collected from the physicians (i.e., 100 verbal and 100 written). Each of the one hundred pharmacists would have received two sample prescriptions to review. This methodology introduces bias because the participating pharmacists would have exposure to the drug name before evaluation of the second sample.

DMETS' review of the 100 written sample Nuviva prescriptions revealed that the majority of these prescriptions were very clearly written and some were printed instead of scripted. The signatura (*1 tab 30 minutes prior to sexual intercourse PRN)* for these prescriptions contained the indication of use for the proposed product. Most prescriptions do not contain information pertaining to the indication of the prescribed medication. Additionally, it is highly unlikely that pharmacists would misinterpret a prescription as Norvasc or Navane when the sample contained the aforementioned signatura.

Section C – Computer-Assisted Analysis

— conducted a "comprehensive search of medical references" to identify brand and established name products that may sound-alike or look-alike the proposed name Nuviva. Forty-six names were identified—including Navane and Norvasc. — analyzed the names using ——— database and using a "Phonological and Orthographical Similarity Analysis." The "Phonological and Orthographical Similarity Analysis" identifies a threshold of similarity between Nuviva and the forty-six products identified during the search of the medical references. The objective of this analysis is to identify the 'similarity between the proposed proprietary name and any sound-alike or look-alike product.'

DMETS disagrees with — statement that "Results from the Comparative Analysis show infrequent overlap in product profiles among purportedly similar drug names." Specifically, we refer to Navane and Norvasc, which have overlapping strengths, and may have overlapping dosing intervals (i.e., once daily). These product profile similarities increase the likelihood of confusion.

Section D - Pharmacists' Analysis – ———

'Five actively practicing retail and hospital pharmacists' evaluated all of the data obtained during this study and determined that based on their experience the risk of name confusion between Norvasc and Navane with Nuviva is minimal. Therefore, the review board's review was favorable for Nuviva.

Although — indicates that the reviewing pharmacists had 'expertise' in adverse event monitoring and risk management, the submission does not contain specific information on the credentials of the pharmacists on the ———. Moreover, the —' indicates that none of the '100 verbal or 100 handwritten prescriptions for Nuviva' resulted in other brand names, specifically Norvasc and Navane. As noted earlier all of the sample prescriptions included the indication for use. The probability of pharmacists interpreting these prescriptions as Norvasc or Navane would be extremely low. Additionally, DMETS' is unsure how many pharmacists actually responded. Section B contains DMETS' concerns pertaining to the inconsistencies in the response rate and respondents. DMETS' March 31, 2002 review addressed all of the points raised by the — as potential factors that would decrease the risk of potential medication errors due to name confusion (e.g., # of tablets dispensed, indication, physical appearance). Thus, DMETS disagrees with the — conclusion that the potential for confusion between Nuviva and Norvasc or Navane is 'presumably low.'

Nuviva Medication Error Risk Management Program

The overall strategy of the risk management program is to raise "awareness about the potential for medication errors due to confusion from handwritten look-alike" products. Nuviva, Norvasc, and Navane will be one of the examples used to highlight the potential for name confusion. Thus, the program is not a risk management program for Nuviva. Moreover, the tactics for decreasing medication errors in both the pharmacy and clinician categories are general in nature. For example, pharmacists will be reminded of "specific steps that should be followed to prevent medication errors e.g. check the name (brand and generic) dosage form strength, and instructions for use." These steps are Standard Operating Procedures in pharmacies. The 'steps' may be effective reminders, however it is unlikely that they will decrease the number of medication errors due to name confusion between Nuviva, Norvasc, and Navane. Bayer plans to target physician with a program including similar 'steps.'

Sponsors have used similar education programs for other products. In fact, Navane and Norvasc were part of an education program to help decrease the number of potential medication errors due to name confusion. Despite the implementation of the program, the Agency continues to receive medication errors due to name confusion.

Bayer has developed a clinician awareness program targeted to decrease the number of medication errors due to name confusion. However, DMETS does not feel that this program will help to alleviate our concerns about the potential of name confusion between the proposed proprietary name Nuviva and Norvasc or Navane.

In summary, this study has not provided a persuasive argument to diminish our concerns with potential confusion between Nuviva, Norvasc, and Navane. As concluded in our previous reviews, DMETS does not recommend the use of the proprietary name Nuviva.

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/s/

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5/23/02 08:26:40 AM
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Jerry Phillips
5/23/02 02:18:49 PM
DIRECTOR

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: June 25, 2001	DUE DATE: December 12, 2001	OPDRA CONSULT #: 01-0149

TO: Daniel Shames
Acting Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Eufrecina Deguia
Project Manager
HFD-580

PRODUCT NAME:	**NDA SPONSOR:**
Nuviva (Vardenafil Hydrochloride Tablets) 5 mg, 10 mg and 20 mg **NDA #:** 21-400	Bayer Corporation Pharmaceutical Division

SAFETY EVALUATOR: Carol Holquist, R. Ph.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-5800), OPDRA conducted a review of the proposed proprietary name " Nuviva" to determine the potential for confusion with approved proprietary and established names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name, "Nuviva". DDMAC is also concerned with the promotional aspect of the name (see section IIA of review). In addition, OPDRA recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

Jerry Phillips, RPh	Martin Himmel, MD
Associate Director for Medication Error Prevention	Deputy Director
Office of Post-Marketing Drug Risk Assessment	Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242	Center for Drug Evaluation and Research
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Office of Postmarketing Drug Risk Assessment (OPDRA)
HFD-400; Parklawn Building Room 15B-32
FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 14, 2001

NDA NUMBER: 21-400

NAME OF DRUG: Nuviva
(Vardenafil Hydrochloride Tablets) 5 mg, 10 mg and 20 mg

NDA SPONSOR: Bayer Corporation
Pharmaceutical Division

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for reassessment of the proposed proprietary name Nuviva. OPDRA also reviewed the unit-dose and container labels, carton and insert labeling.

Additionally, the sponsor submitted an independent analysis of the proposed name that was conducted by [redacted]. These findings were submitted to OPDRA for review and comment as well.

PRODUCT INFORMATION

Nuviva contains the active ingredient vardenafil hydrochloride, which is a highly selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Nuviva is an oral therapy for the improvement of erectile function in men with erectile dysfunction. The recommended starting dose of Nuviva is 10 mg taken 25 to 60 minutes before sexual activity. The recommended dose frequency is a maximum of once per day as desired. The dose may be increased to a maximum recommended dose of 20 mg or decreased to 5 mg based on efficacy and tolerability. A maximum dose of 5 mg should not be exceeded when used in combination with potent cytochrome P450 3A4 inhibitors, ketoconazole, itraconazole, indinavir, and ritonavir. Concomitant use of these products can produce elevated plasma levels of vardenafil. However, a maximum dose of 10 mg should not be exceeded when use in combination with the cytochrome P450 3A4 inhibitor, erythromycin. Consistent with the effects of PDE5 inhibition of the nitric oxide/cyclic guanosine monophosphate pathway, PDE5 inhibitors may potentiate the hypotensive effects of nitrates, and therefore co-administration of vardenafil with nitrates and nitric oxide donors is contraindicated. Nuviva will be supplied as a tablet in the following strengths, 5 mg, 10 mg and 20 mg.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to "Nuviva" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted prescription analysis studies, involving health care practitioners within FDA.. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name Nuviva. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Nuviva. These products are listed in table 1 (see page four), along with the dosage forms available and usual dosage.

DDMAC has concerns with the promotional aspects of the name indicating "new life". DDMAC believes "new life" could be considered an exaggerated claim. Moreover, Pfizer Pharmaceuticals Group submitted a letter to OPDRA on October 22, 2001, in which they objected to the promotional aspect of the name as well. Pfizer is concerned that Nuviva "is an illegitimate attempt by Bayer to associate in the minds of physicians and patients its new product with an overstated efficacy claim to bring "new life" to a patient's erectile function".

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[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

[4] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[5] WWW location http://tess.uspto.gov/bin/gate.exe?f=tess&state=k0n826.1.1

[6] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

TABLE 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Nuviva	Vardenafil Tablets 5 mg, 10 mg and 20 mg	10 mg once daily up to a maximum of 20 mg daily.	
Nivia	OTC Emollient Cream	Use as directed.	S/A and L/A per OPDRA
Sustiva	Efavirenz Capsule 50 mg, 100 mg, and 200 mg	600 mg once daily.	S/A and L/A per OPDRA
Renova	Tretinoin Cream 0.05%	Apply once daily in the evening.	L/A per OPDRA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
***NOTE: This review contains proprietary and confidential information that should not be released to the public. ***

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

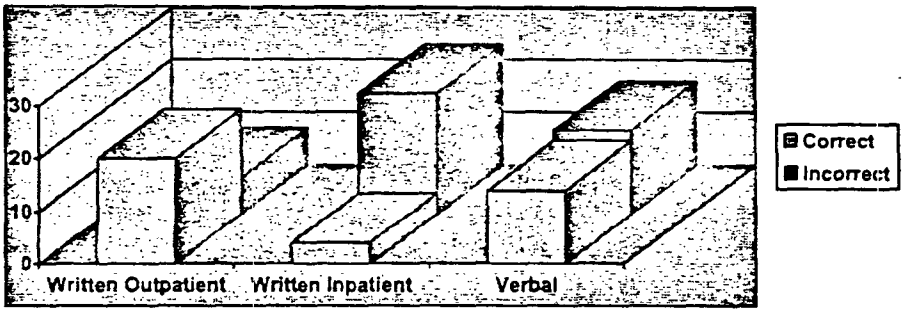
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Nuviva with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 116 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Nuviva. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient: Nuviva 10 mg UD #15	Nuviva 10 mg use as directed. #15
Inpatient: D/C Nuviva	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Nuviva" response	Other response
Written: Outpatient	39	27 (69 %)	20 (74 %)	7 (26 %)
Inpatient	38	27 (71 %)	4 (15 %)	23 (85%)
Verbal: Outpatient	39	30 (77 %)	14 (47 %)	16 (53 %)
Total:	116	84 (72 %)	38 (45 %)	46 (55 %)



Among participants in the written prescription studies, 30 of 54 respondents (56%) interpreted the name incorrectly. *Two* currently marketed products Norvir and Sustiva, were misinterpreted for Nuviva on the inpatient order. The remaining incorrect responses were misspelled variations of "Nuviva". The most common responses included a misinterpretation of the first "v" in Nuviva as either an "r" or "s", as seven guessed Nuriva and four Nusiva. Additionally, four respondents interpreted Nuviva as Noviva, misinterpreting the "u" as and "o". Other responses included Nuvida, Niviva, Nuuva, Nusara, Nuva, Nuliva, Nuria, Nuiva and Nuvina.

Among verbal prescription study respondents, 16 of 30 (53 %) interpreted the name incorrectly. The incorrect interpretations were phonetic variations of "Nuviva". Interpretations included: Nuveeva, Neuwava, Neuveva, Neuviva, Noviva and Niriva.

C. STUDY SUBMITTED BY THE APPLICANT

Bayer Pharmaceutical, requested the ——— to evaluate the proposed proprietary name, Nuviva. The objectives of the ——— study were to identify and evaluate the potential for error between Nuviva and brand name/generic drugs currently available to physicians and pharmacists. In addition, to evaluate the potential for patient harm with the brand name Nuviva based on practitioner review. ——— reported a total of 160 medical professionals participated in the study The breakdown is as follows: Sixty family practitioners/internal medicine specialists/general practitioners, twenty urologists, six endocrinologists, four diabetologists, six cardiologists, four psychologists, and sixty pharmacists from retail and hospitals. These medical professionals participated in the following four phases of research:

♦ Phase 1: "Real-world" prescribing. A physician's oral and handwritten communication of the *name itself* is captured as a sound file and graphic image. One hundred physicians participate in this phase. There is no description of the sampling of physician specialty utilized in this phase.

OPDRA does not believe this phase is reflective of "real world" prescribing. In the "real-world" the product strength, dosage form, and directions for use are generally included on the prescription. Moreover, variables such as accents, writing styles, speed of communication, lack of clarity and settings are also factors in "real-world" prescribing.

♦ Phase 2: Prescription Interpretation Study - The physician's oral and handwritten communications of the name are forwarded on-line to pharmacists. Twenty pharmacists (10 retail and 10 hospital) participated in this phase and evaluate one hundred prescriptions. However, it is unclear how many samples each pharmacist is asked to evaluate. The objective is to identify if any of the responses are brand/generic drug names. The [redacted] reported no miscommunication of the name in this phase.

♦ Phase 3: [redacted] Review (Sound-Alike and Look-Alike Similarity). One hundred physicians and 40 pharmacists (20 retail and 20 hospital) are provided the name without any supporting information and are requested to identify similar brand/generic drug names. The same practitioners are given the sound-alike/look-alike names identified by the group along with the product profile of Nuviva. The respondents were asked to select from a prepared list any aspects of the product profile that could potentially result in patient safety issues if an error were to occur by way of prescribing or dispensing the comparison drug. The choices were as follows: potential patient harm, identical formulation, identical dosage, identical frequency, identical dispensing environment, and not applicable. The drug name is also evaluated for "hyperbole" or "name claim issues".

Seventeen (17) sound-alike/look-alike names were identified in this phase of the study. The top five names identified as sound-alikes were Sustiva (7), Nevirapine (2), Neutrogena (1), Norinyl (1), and Norvir (1). The top five names identified as look-likes were Nubain (2), Sustiva (2), Navane (1), Nedocromil (1), and Neupogen (1). Norvasc (1) and Norvir (1) were also identified in the top ten as potential look-alike names. **It is worthwhile to note that two of the names identified (Sustiva and Norvir) were names that respondents had interpreted Nuviva as in the studies conducted by OPDRA.** Any name identified in this phase, no matter how low its frequency, may have a significant public health impact when used by the general population of practitioners.

The second portion of this phase is to identify aspects of the profile that could potentially result in patient safety issues. The following product profile was disseminated:

Product Profile for improvement of erectile function:

Indication:	Improvement of erectile function
Formulation:	Oral -- film coated tablet
Dosage:	5 mg, 10 mg and 20 mg
Frequency:	PRN
Distribution:	Retail

There are several confounding factors that can influence the probability of an error and lead to the administration of the wrong drug product. Same indication, formulation, dosage, frequency and product distribution are only a fraction of these factors. The degree of similarity between the sound and look alike potential of the names, overlapping strengths, similar population of prescribers, etc. are also important factors in assessing the possibility of product confusion. The product profile that was distributed to the study participants was inaccurate and incomplete. The ——— stated the frequency as prn. However, the recommended dose frequency is a maximum of once per day as desired. The dosage was also expressed in such a manner that is not representative to the usual dosage described in the insert. All the available strengths are listed rather than the usual dosage of 10 mg. In addition, four of the six precepts ask for identical information (i.e., formulation, dosage, frequency, dispensing environment). This can be misleading and lead to a lower reported number of similar characteristics. For example, if the suspect product is not available as an "oral – film coated tablet" or not available in every strength of the proposed drug product, the potential for harm would be scored as zero. However, the two dosage forms could overlap meaning "oral", the dosage could be "one tablet, capsule etc" and could possibly have at least one overlapping strength. Depending on how — defined "potential harm", there can be a substantial variation in the interpretation of this term by the respondents as well. OPDRA questions the validity of the study results based on the methodological limitations and incompleteness of the product profile. In addition, the study participants are not experts in reviewing medication errors and would not be sensitized to all factors that can potentially cause errors.

During the evaluation of the proposed proprietary name for hyperbole issues, respondents were asked to identify any misleading connotations, exaggerations, or other hyperbole implied by the proposed proprietary name. Two percent of those surveyed stated the name "suggests it elevates new life" or "implies new life". Other responses included "implies it stops the aging process, suggests a vitamin and suggests regrowth or a cellular stimulant".

♦ Phase 4: A panel of pharmacists ———

—— conducted a safety review of the drug names listed by the respondents. All of the proprietary names that were evaluated by the panel were considered to have a minimal chance of confusion due to fundamental differences in the product profiles. Generally, one would assume that based on these differences the potential for medication errors would be low. However, post-marketing experience has clearly demonstrated repeatedly that differences in product profiles such as those mentioned in the panel may not *always* eliminate the potential for error. The —— panel and —— also failed to point out the clinical consequences a patient could endure if Nuviva were administered inadvertently for any of the products identified.

OPDRA believes the following three names that were forwarded to the panel have the greatest potential to cause a medication error due to name confusion with Nuviva: Sustiva, Navane, and Norvasc.

D. SAFETY EVALUATOR RISK ASSESSMENT

***NOTE: This review contains proprietary and confidential information that should not be released to the public.

In reviewing the proprietary name, Nuviva, the primary concerns raised by the OPDRA expert panel were related to three potential sound-alike/look-alike names that already exist in the US marketplace, Nivia, Sustiva, and Renova. [redacted] was also identified as a potential sound-alike name. [redacted]
Additionally, Sustiva, was identified as a potential sound-alike/look-alike name in the study submitted by the sponsor. OPDRA is also concerned about two additional names, Norvasc and Navane, that were also identified as potential look-alike products in the same study.

OPDRA conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that *Nuviva* could be confused with *Sustiva* as *one respondent* (2 %) misinterpreted Nuviva as Sustiva. Another marketed product, *Norvir*, was also interpreted for Nuviva. Although there are limitations to the predictive value of this study, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

Nuviva and *Sustiva* may look and sound similar according to the expert panel. Nuviva and Sustiva both contain the same number of syllables and end in the same suffix "iva". Because of these similarities when spoken, the two names have a slight rhyming quality. When scripted, an "n" and "s" can appear similar. However, the "ti" in the middle of the name (see below) somewhat distinguishes Sustiva. Sustiva is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI). It is available as a capsule for oral administration containing either 50 mg, 100 mg, or 200 mg of the active ingredient efavirenz. Nuviva is available as a 5 mg, 10 mg or 20 mg tablet for oral administration. Both Sustiva and Nuviva share an overlapping dosing interval of once daily. Despite these similarities, the recommended daily dose of Sustiva is 600 mg. To achieve this dosage it would require administration of anywhere from 3 to 12 capsules dependent on the strength dispensed. Additionally, Sustiva is not indicated as a monotherapy agent. Although the names are similar, the clinical context of use, differences in patient population, and daily dosage decreases the potential for confusion. Sustiva was a name that was identified as a potential sound-alike/look-alike product in the independent study conducted by the [redacted] submitted by the sponsor. As part of their analysis, the name was forwarded to the [redacted] for review and comment. The [redacted] panel stated there is

some resemblance between Nuviva and Sustiva and that the similarity may be increased if Nuviva is pronounced differently or with an accent, thereby raising the possibility for confusion based on name alone. However, based on the differences in indication for use, dosage strengths, daily dosage and different starting letters the chance of error is minimized. We concur with this assessment.

Sustiva *Nuviva*

Renova was identified by the expert panel to have potential for look-alike confusion with *Nuviva*. Renova contains the active ingredient tretinoin and is indicated for the reduction of skin wrinkles. It is available as a 0.05% cream for topical administration. Nuviva and Renova share and overlapping dosing interval of once daily. However, despite this similarity the two have no other commonalties. Additionally, post-marketing experience has not demonstrated medication errors between solid oral dosage forms and topical drug products. Therefore, based on the numerous product differences, the potential for confusion between Renova and Nuviva is low.

According to the Expert Panel, *Nivia* can look and sound similar to *Nuviva*. Nuviva and Nivia sound and look similar because they begin with "N" and end in similar sounding suffixes "via" and "iva". Additionally, the two differ by one letter. However, Nivia is available as an OTC emollient cream. Post-marketing experience has not demonstrated medication errors between solid oral dosage forms and topical drug products. The differences in dosage forms, directions for use, and dispensing environments significantly decreases the potential for confusion between these two drug products.

Norvir was not identified by the panel as a potential look-alike. However, one respondent interpreted *Nuviva* as *Norvir* from the written inpatient order. Additionally, *Norvir* was identified as a potential sound-alike/look-alike in the study submitted by the sponsor. —— is another name that was not identified by the Expert Panel. However, it was uncovered as another potential sound-alike/look-alike name during an independent search conducted by the reviewer. —— —— —— These products are listed in table 2 (see page 10), along with the dosage forms available and usual dosages.

TABLE 2'

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Nuviva	Vardenafil Tablets 5 mg, 10 mg and 20 mg	10 mg once daily up to a maximum of 20 mg daily	
Norvir	Ritonavir Capsules 100 mg and Ritonavir Oral Solution 80 mg/mL	600 mg twice daily	L/A per Study Participant

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
***NOTE: This review contains proprietary and confidential information that should not be released to the public. ***

— and *Nuviva* can sound and look similar. —— and Nuviva both contain three syllables and end in the same suffix "iva". Both products are dosed once daily as well. However, Although the names are similar, the clinical context of use and differences in patient population (male vs. female) decreases the potential for confusion.

Norvir is an inhibitor of HIV protease indicated in combination with other antiretroviral agents for the treatment of HIV-infection. The recommended dosage of ritonavir is 600 mg twice daily by mouth. If saquinavir and ritonavir are used in combination, the dosage of saquinavir should be reduced to 400 mg twice daily. *Norvir* is available as a 100 mg capsule and 80 mg/mL oral solution. Although, Norvir was misinterpreted by one respondent on the inpatient order when scripted as D/C Nuviva, the differences in the indications of use, dosing interval and patient population would decrease the potential for product confusion. The —— panel stated there is some similarity between the names. Although the endings are different, the potentially similar appearance of the "Viva" ending of the test name for "VIR" of Norvir raises some concern for misperception in handwritten prescriptions. The chance of error is minimized by substantial differences between the drugs, according to indication, product dose, dosage strength, daily dosage, and directions for use. Furthermore, Norvir is for HIV/AIDS and these medications are usually prescribed in combinations of at least 3 different drugs, unlike the test drug that is to be taken alone. We concur with this analysis.

Norvasc and *Navane* were two additional products identified as potential look-alike names in the studies conducted by the ——— for the sponsor. OPDRA is also concerned with these names posing a significant problem, as there is current confusion in the marketplace between Norvasc and Navane due to their similar appearance when scripted.

Navane and *Nuviva* appear similar when scripted (see below). 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). ——— eviewed 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 —— sites 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 among 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.

Navane *Nuviva*

Norvasc and *Nuviva* can also look similar when scripted (see below). The names contain a similar number of characters (6 vs. 7). Norvasc and Nuviva are both available in 5 mg and 10 mg strengths and share an overlapping dosing interval of once daily. The —— panel stated that although the endings are different, the potentially similar appearance of the "viva" ending of the test name and the "vasc" of Norvasc raises some concern for misperception in handwritten prescriptions. The panel also noted the overlap between the drugs dosage forms and strengths. The panel also stated that if error occurred with Norvasc, the most commonly reported adverse effects include fatigue, edema, flushing, palpitations, GI upset, or drowsiness. Given that some of these effects are common with those of the test drug, this could make it less likely that a medication error would be detected, or more likely that severe effects might occur if the highest dose of Norvasc were taken. Moreover, NORVASC is indicated for the treatment of hypertension and therefore misadministration of this drug may result in a hypotensive crisis in a normotensive patient. These commonalties increase the potential for a medication error occurrence.

Norvasc *Nuviva*

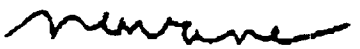
2 pages redacted from this section of the approval package consisted of draft labeling

IV. COMMENTS TO THE SPONSOR

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 confusion currently in the market place between Norvasc and Navane due to their similar appearance when scripted.

Navane and *Nuviva* appear similar when scripted (see below). 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 — sites 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 among 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.

Navane



Nuviva

Norvasc and *Nuviva* can also look similar when scripted (see below). The names contain a similar number of characters (6 vs. 7). Norvasc and Nuviva are both available in 5 mg and 10 mg strengths and share an overlapping dosing interval of once daily. The —— panel stated that although the endings are different, the potentially similar appearance of the "viva" ending of the test name and the "vasc" of Norvasc raises some concern for misperception in handwritten prescriptions. The panel also noted the overlap between the drugs dosage forms and strengths. The panel also stated that if error occurred with Norvasc, the most commonly reported adverse effects include fatigue, edema, flushing, palpitations, GI upset, or drowsiness. Given that some of these effects are common with those of the test drug, this could make it less likely that a medication error would be detected, or more likely that severe effects might occur if the highest dose of Norvasc were taken. Moreover, NORVASC is indicated for the treatment of hypertension and therefore misadministration of this drug may result in a hypotensive crisis in a normotensive patient. These commonalties increase the potential for a medication error occurrence.

Norvasc *Nuviva*

In addition, we provide the following recommendation on labeling revisions that may minimize potential user error:

1 pages redacted from this section of the approval package consisted of draft labeling

V. RECOMMENDATIONS

1. OPDRA does not recommend the use of the proprietary name, "Nuviva". DDMAC is also concerned with the promotional aspect of the name (see section IIA of review).

2. OPDRA recommends implementation of the above labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3231.

/S/

Carol Holquist, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

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

/s/

Carol Holquist
12/13/01 08:48:48 AM
PHARMACIST

Jerry Phillips
12/13/01 09:27:23 AM
DIRECTOR

Martin Himmel
12/17/01 12:58:27 PM
MEDICAL OFFICER

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED:	**DUE DATE:**	**ODS CONSULT #:** 01-0149-01
February 12, 2001	March 31, 2002	

TO: Daniel Shames, MD
Acting Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Eufrecina Deguia
Project Manager
HFD-580

PRODUCT NAME:	**NDA SPONSOR:**
Nuviva (Vardenafil Hydrochloride Tablets) 5 mg, 10 mg, and 20 mg **NDA : 21-400**	Bayer Corporation Pharmaceutical Division

SAFETY EVALUATOR: Kevin Dermanoski RPh

SUMMARY: The Division of Reproductive and Urologic Drug Products (HFD-580) submitted a request, on June 25, 2001, for a proprietary name review of Nuviva. The submission included an independent analysis of Nuviva conducted by the ——— Based on the information provided, DMETS did not recommend use of the proprietary name Nuviva (OPDRA consult 01-0149). Bayer submitted a rebuttal to support the proposed name Nuviva on February 5, 2002 and requested a reconsideration of the acceptability of the proposed proprietary name.

DMETS RECOMMENDATION: After review of the information submitted by the sponsor, the Division of Medication Errors and Technical Support (DMETS), does not recommend the use of the name "Nuviva."

/S/

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Phone: (301) 827-3242
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/S/

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 29, 2002

NDA 21-400

NAME OF DRUG: Nuviva
(Vardenafil Hydrochloride Tablets) 5 mg, 10 mg, and 20 mg

NDA HOLDER: Bayer Corporation
Pharmaceutical Division

I. INTRODUCTION:

Bayer requested a reconsideration of the acceptability of the proposed proprietary name Nuviva. The Division of Medication Errors and Technical Support (DMETS) previously reviewed the proposed proprietary name, Nuviva, on November 14, 2001, and did not recommend use of the name (OPDRA consult 01-0149). Bayer submitted a rebuttal to support the proposed name Nuviva on February 5, 2002. Bayer targeted their response to the following three categories:

- Interpretation of Prescription Analysis and Differentiation
- Medical Risk Assessment
- Does the Name Nuviva Sound Promotional

PRODUCT INFORMATION

Nuviva contains the active ingredient vardenafil hydrochloride, which is a highly selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Nuviva is an oral therapy for the improvement of erectile function in men with erectile dysfunction. The recommended starting dose of Nuviva is 10 mg taken 25 to 60 minutes before sexual activity. The recommended dose frequency is a maximum of once per day as desired. The dose may be increased to a maximum recommended dose of 20 mg or decreased to 5 mg based on efficacy and tolerability. A maximum dose of 5 mg should not be exceeded when used in combination with potent cytochrome P450 3A4 inhibitors ketoconazole, itraconazole, indinavir, and ritonavir. Concomitant

use of these products can produce elevated plasma levels of vardenafil. However, a maximum dose of 10 mg should not be exceeded when use in combination with the cytochrome P450 3A4 inhibitor, erythromycin. Consistent with the effects of PDE5 inhibition of the nitric oxide/cyclic guanosine monophosphate pathway, PDE5 inhibitors may potentiate the hypotensive effects of nitrates, and therefore co-administration of vardenafil with nitrates and nitric oxide donors is contraindicated. Nuviva will be supplied as 5 mg, 10 mg and 20 mg tablets.

II. RISK ASSESSMENT:

The initial DMETS safety assessment of Nuviva identified several sound-alike/look-alike names. Additionally, Bayer submitted an independent analysis conducted by ——— to support their choice of the proprietary name Nuviva. This analysis was reviewed by DMETS and considered in the initial assessment as well. Upon completion of the original safety assessment DMETS concluded Nuviva was unacceptable. DMETS believed the products having the greatest potential for confusion with Nuviva were Norvasc and Navane.

Additionally, Bayer stated in their rebuttal that DMETS was also concerned with the sound-alike/look-alike characteristics of Sustiva. DMETS and ——— both identified this product as a potential concern. However, 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, we will not address comments pertaining to Sustiva.

A. Interpretation of Prescription Analysis and Differentiation

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

DMET'S RESPONSE

There are several confounding factors that can influence the probability of an error and lead to the administration of the wrong drug product. A product's dosage interval is only one factor. 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. However, medication errors between these two products are well documented.

Nuviva may not always be prescribed on a prn basis, but could also be prescribed once daily as well. This once a day 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.

DMETS RESPONSE

The sponsor provided "average number of tablets" dispensed for typical Nuviva, Norvasc, or Navane prescriptions. However, they are not representative of the norm. Most prescriptions are written for a one-month or 30-day supply or multiples thereof.

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. However, prescriptions 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 meaning a dispensed amount of 7 to 14 units.

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

DMETS RESPONSE

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.). Moreover, medication errors due to sound-alike or look-alike name confusion generally occur upon initial receipt of the prescription. Practitioners cognitively misinterpret the drug product then proceed to dispense, transcribe, or administer the incorrect product because this is what was intended to be ordered. If the prescription has been cognitively misinterpreted, differences in physical characteristics would not prompt the practitioner that an error has occurred.

4. **All four products are for different indications.**

DMETS RESPONSE

Generally, indications of use are not present on a prescription.

The sponsor states that pharmacies provide information to patients that list indication and method of use. Bayer believes this information would serve as a mechanism that would note disparities between a product's intended use and the product provided. This drug information can be helpful if it is effectively utilized by the patient. If a patient is knowledgeable of their medication, receipt of incorrect information could prevent the actual administration of the wrong drug. For example, drug information provided to the patient would be reflective of the drug dispensed and not the intended drug. A knowledgeable patient would notice this discrepancy and notify the pharmacist. However, the error has still occurred because the incorrect drug was dispensed even though not administered.

Unfortunately, not all pharmacies provide these services. Furthermore, in pharmacies that offer these services, many patients do not take advantage of this beneficial information. For example, when an information brochure [redacted], is dispensed with a prescription there is no guarantee that a patient is able to read the information, chooses to read the information, or understands the information that is provided.

5. **Nuviva is prescribed only for men.**

DMETS RESPONSE

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 cannot be overlooked. Once this misinterpretation has occurred the practitioner is unlikely to correct the error based on the sex of the patient.

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

DMETS RESPONSE

DMETS agrees with the ——— conclusion regarding Sustiva.

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

DMETS RESPONSE

The previous response (Statement #6) addresses DMETS conclusion pertaining to Sustiva.

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 practitioner's handwriting trail-off." However, the dotted '' is not always a distinguishing characteristic when the name is scripted. Practitioners may not dot the 'i' or in cases where duplicate or carbon copies of prescriptions are used the dotted 'i' may not be evident.

Navane and Nuviva appear similar when scripted (see below). 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). As a part of the ——— analysis, ——— ; 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." DMETS feels that 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. In fact both Navane and Nuviva may initially be started and maintained at 10 mg tential for medication errors.

Nuviva

8. **Norvasc does not resemble the name Nuviva.**

DMETS RESPONSE

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 (sic)." Norvasc and Nuviva can look similar when scripted (see below). The names contain a similar number of characters (6 vs. 7). Norvasc and Nuviva are both available in 5 mg and 10 mg strengths and share an overlapping dosing interval of once daily. The [redacted] panel also noted the overlap between the drugs dosage forms and strengths.

Norvasc *Nuviva*

B. Medical Risk Assessment

The sponsor's introduction to its Medical Risk Assessment, submitted February 5, 2002, includes issues that were raised and answered earlier in this document. Listed below are six "what if" medical assessments submitted by the sponsor.

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

DMETS' RESPONSE

The sponsor addresses the antihypertensive effect of Norvasc in normotensive patients. The medication error may occur in patients who are hypertensive and who are receiving other antihypertensive medications. The addition of an extra hypertensive medication to the patients' regimen could potentially be lethal. In fact if the order is written as a prn medication, a patient could potentially take 2 or more tablets within a 24-hour period. The fact that normotensive patients in the clinical trials experienced minor blood pressure decreases does not ensure that patients who take this medication in error will exhibit the same results. These patients may be taking concomitant medications that may have an additive effect on their blood pressure when taken with Norvasc. Bayer is also assuming that only six tablets will be dispensed, DMETS addressed the sponsors conclusions regarding "average prescription sizes" earlier in this document and concluded that the quantity dispensed would not necessarily prevent medication errors.

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 in response, take an additional dose of Norvasc especially if the original prescription was written to be used on a prn basis. Higher

doses of Norvasc would increase the chances of patients experiencing an acute hypotensive adverse reaction.

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

DMETS' RESPONSE

Although many patients with hypertension are managed using multi-drug therapy, some patients are managed by mono-therapy. These patients could experience increases in blood pressure if Nuviva is taken in lieu of Norvasc. These increases in blood pressure could result in potentially serious complications.

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

DMETS' RESPONSE

As noted earlier, if the patient does not receive the expected results they may assume that the dose is too low or repeat the dose particularly if the prescription was written as a "prn" medication. The sponsor states that taking Navane once daily would lessen it's pharmacological effects. Although some Navane adverse events are dose-related, patients at lower dosage ranges can experience adverse effects.

Sedation is just one potential adverse reaction to Navane. Tardive dyskinesia, neurcleptic malignant syndrome, hypotension, tachycardia and syncope are only a few of the serious adverse events that may occur with the administration of Navane. Navane could precipitate seizures in patients with prior convulsive disorders.

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

DMETS' RESPONSE

The sponsor states: *"transient interruption of Navane should not lead to worsening of the emotional conditions of the patient unless it lasts several days."* Patients taking Navane have different degrees of disease severity. The sponsor assumes that this would be a "transient interruption" based on the number of tablets dispensed. DMETS noted earlier that the quantity of tablets dispensed will not lessen the potential of adverse effects from this medication error. On the other hand, using the sponsor's example of six tablets dispensed, a patient could potentially go without Navane therapy for a minimum of one week. This timeframe is sufficient for a potential relapse to occur. However, the emotional status of the affected patient may increase this timeframe.

5. What if Sustiva is mistakenly taken instead of Nuviva?

DMETS' RESPONSE

As noted in the Risk Assessment section of this document, DMETS agrees with the conclusion regarding the risk for error between Nuviva and Sustiva, thus obviating the need for a response to this question.

6. What if Nuviva is mistakenly taken instead of Sustiva?

DMETS' RESPONSE

The previous response addresses DMETS conclusion pertaining to Sustiva.

C. Does the name Nuviva sound promotional?

DMETS' RESPONSE

The sponsor submitted a response to DDMAC's concerns regarding Nuviva sounding promotional. DDMAC is a member of the DMETS Expert Panel and thus any comments from that panel are included in DMETS proprietary name reviews. However, Bayer should direct specific comments pertaining to the promotional aspects of the name to DDMAC.

III. RECOMMENDATIONS

Bayer failed to provide a persuasive argument, which would minimize the Agency's concern with regard to potential medication errors due to the similarity of spelling and pronunciation of Nuviva to the currently marketed drug products, Norvasc and Navane. DMETS does not recommend the use of the proprietary name "Nuviva."

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion, if needed. If you have any questions or need clarification, please contact Sammie Beam, project manager, at 301-827-3242.

/S/

Kevin Dermanoski, RPh
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

/S/

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Kevin Dermanoski
3/29/02 03:30:01 PM
CSO

Carol Holquist
3/29/02 03:35:38 PM
PHARMACIST

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: June 25, 2001	**DUE DATE:** December 12, 2001	**OPDRA CONSULT #:** 01-0149

TO: Daniel Shames
Acting Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Eufrecina Deguia
Project Manager
HFD-580

PRODUCT NAME:	**NDA SPONSOR:**
Nuviva (Vardenafil Hydrochloride Tablets) 5 mg, 10 mg and 20 mg **NDA #:** 21-400	Bayer Corporation Pharmaceutical Division

SAFETY EVALUATOR: Carol Holquist, R. Ph.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-5800), OPDRA conducted a review of the proposed proprietary name " Nuviva" to determine the potential for confusion with approved proprietary and established names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name, "Nuviva". DDMAC is also concerned with the promotional aspect of the name (see section IIA of review). In addition, OPDRA recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

Jerry Phillips, RPh	Martin Himmel, MD
Associate Director for Medication Error Prevention	Deputy Director
Office of Post-Marketing Drug Risk Assessment	Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242	Center for Drug Evaluation and Research
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Office of Postmarketing Drug Risk Assessment (OPDRA)
HFD-400; Parklawn Building Room 15B-32
FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 14, 2001

NDA NUMBER: 21-400

NAME OF DRUG: Nuviva
(Vardenafil Hydrochloride Tablets) 5 mg, 10 mg and 20 mg

NDA SPONSOR: Bayer Corporation
Pharmaceutical Division

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for reassessment of the proposed proprietary name Nuviva. OPDRA also reviewed the unit-dose and container labels, carton and insert labeling.

Additionally, the sponsor submitted an independent analysis of the proposed name that was conducted by the ——— These findings were submitted to OPDRA for review and comment as well.

PRODUCT INFORMATION

Nuviva contains the active ingredient vardenafil hydrochloride, which is a highly selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Nuviva is an oral therapy for the improvement of erectile function in men with erectile dysfunction. The recommended starting dose of Nuviva is 10 mg taken 25 to 60 minutes before sexual activity. The recommended dose frequency is a maximum of once per day as desired. The dose may be increased to a maximum recommended dose of 20 mg or decreased to 5 mg based on efficacy and tolerability. A maximum dose of 5 mg should not be exceeded when used in combination with potent cytochrome P450 3A4 inhibitors, ketoconazole, itraconazole, indinavir, and ritonavir. Concomitant use of these products can produce elevated plasma levels of vardenafil. However, a maximum dose of 10 mg should not be exceeded when use in combination with the cytochrome P450 3A4 inhibitor, erythromycin. Consistent with the effects of PDE5 inhibition of the nitric oxide/cyclic guanosine monophosphate pathway, PDE5 inhibitors may potentiate the hypotensive effects of nitrates, and therefore co-administration of vardenafil with nitrates and nitric oxide donors is contraindicated. Nuviva will be supplied as a tablet in the following strengths, 5 mg, 10 mg and 20 mg.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to "Nuviva" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted prescription analysis studies, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name Nuviva. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Nuviva. These products are listed in table 1 (see page four), along with the dosage forms available and usual dosage.

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

[4] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[5] WWW location http://tess.uspto.gov/bin/gate.exe?f=tess&state=k0n826.1.1

[6] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

TABLE 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Nuviva	Vardenafil Tablets 5 mg, 10 mg and 20 mg	10 mg once daily up to a maximum of 20 mg daily.	
Nivia	OTC Emollient Cream	Use as directed.	S/A and L/A per OPDRA
Sustiva	Efavirenz Capsule 50 mg, 100 mg, and 200 mg	600 mg once daily.	S/A and L/A per OPDRA
Renova	Tretinoin Cream 0.05%	Apply once daily in the evening.	L/A per OPDRA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
***NOTE: This review contains proprietary and confidential information that should not be released to the public. ***

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

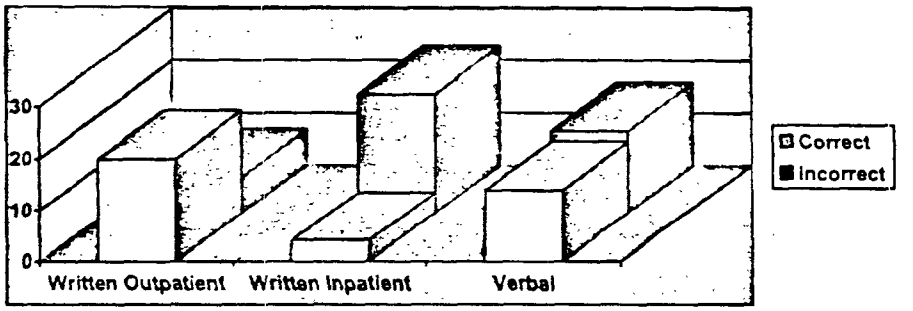
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Nuviva with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 116 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Nuviva. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient: Nuviva 10 mg UD #15	Nuviva 10 mg use as directed. #15
Inpatient: D/C Nuviva	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Nuviva" response	Other response
Written: Outpatient	39	27 (69 %)	20 (74 %)	7 (26 %)
Inpatient	38	27 (71 %)	4 (15 %)	23 (85%)
Verbal: Outpatient	39	30 (77 %)	14 (47 %)	16 (53 %)
Total:	116	84 (72 %)	38 (45 %)	46 (55 %)



Among participants in the written prescription studies, 30 of 54 respondents (56%) interpreted the name incorrectly. *Two* currently marketed products Norvir and Sustiva, were misinterpreted for Nuviva on the inpatient order. The remaining incorrect responses were misspelled variations of "Nuviva". The most common responses included a misinterpretation of the first "v" in Nuviva as either an "r" or "s", as seven guessed Nuriva and four Nusiva. Additionally, four respondents interpreted Nuviva as Noviva, misinterpreting the "u" as and "o". Other responses included Nuvida, Niviva, Nuuva, Nusara, Nuva, Nuliva, Nuria, Nuiva and Nuvina.

Among verbal prescription study respondents, 16 of 30 (53 %) interpreted the name incorrectly. The incorrect interpretations were phonetic variations of "Nuviva". Interpretations included: Nuveeva, Neuwava, Neuveva, Neuviva, Noviva and Niriva.

C. STUDY SUBMITTED BY THE APPLICANT

Bayer Pharmaceutical, requested the ——— to evaluate the proposed proprietary name, Nuviva. The objectives of the —— study were to identify and evaluate the potential for error between Nuviva and brand name/generic drugs currently available to physicians and pharmacists. In addition, to evaluate the potential for patient harm with the brand name Nuviva based on practitioner review. ——— reported a total of 160 medical professionals participated in the study The breakdown is as follows: Sixty family practitioners/internal medicine specialists/general practitioners, twenty urologists, six endocrinologists, four diabetologists, six cardiologists, four psychologists, and sixty pharmacists from retail and hospitals. These medical professionals participated in the following four phases of research:

♦ Phase 1: "Real-world" prescribing. A physician's oral and handwritten communication of the *name itself* is captured as a sound file and graphic image. One hundred physicians participate in this phase. There is no description of the sampling of physician specialty utilized in this phase.

OPDRA does not believe this phase is reflective of "real world" prescribing. In the "real-world" the product strength, dosage form, and directions for use are generally included on the prescription. Moreover, variables such as accents, writing styles, speed of communication, lack of clarity and settings are also factors in "real-world" prescribing.

♦ Phase 2: Prescription Interpretation Study - The physician's oral and handwritten communications of the name are forwarded on-line to pharmacists. Twenty pharmacists (10 retail and 10 hospital) participated in this phase and evaluate one hundred prescriptions. However, it is unclear how many samples each pharmacist is asked to evaluate. The objective is to identify if any of the responses are brand/generic drug names. The ——— reported no miscommunication of the name in this phase.

♦ Phase 3: ——— Review (Sound-Alike and Look-Alike Similarity). One hundred physicians and 40 pharmacists (20 retail and 20 hospital) are provided the name without any supporting information and are requested to identify similar brand/generic drug names. The same practitioners are given the sound-alike/look-alike names identified by the group along with the product profile of Nuviva. The respondents were asked to select from a prepared list any aspects of the product profile that could potentially result in patient safety issues if an error were to occur by way of prescribing or dispensing the comparison drug. The choices were as follows: potential patient harm, identical formulation, identical dosage, identical frequency, identical dispensing environment, and not applicable. The drug name is also evaluated for "hyperbole" or "name claim issues".

Seventeen (17) sound-alike/look-alike names were identified in this phase of the study. The top five names identified as sound-alikes were Sustiva (7), Nevirapine (2), Neutrogena (1), Norinyl (1), and Norvir (1). The top five names identified as look-likes were Nubain (2), Sustiva (2), Navane (1), Nedocromil (1), and Neupogen (1). Norvasc (1) and Norvir (1) were also identified in the top ten as potential look-alike names. **It is worthwhile to note that two of the names identified (Sustiva and Norvir) were names that respondents had interpreted Nuviva as in the studies conducted by OPDRA.** Any name identified in this phase, no matter how low its frequency, may have a significant public health impact when used by the general population of practitioners.

The second portion of this phase is to identify aspects of the profile that could potentially result in patient safety issues. The following product profile was disseminated:

Product Profile for improvement of erectile function:

Indication:	Improvement of erectile function
Formulation:	Oral – film coated tablet
Dosage:	5 mg, 10 mg and 20 mg
Frequency:	PRN
Distribution:	Retail

There are several confounding factors that can influence the probability of an error and lead to the administration of the wrong drug product. Same indication, formulation, dosage, frequency and product distribution are only a fraction of these factors. The degree of similarity between the sound and look alike potential of the names, overlapping strengths, similar population of prescribers, etc. are also important factors in assessing the possibility of product confusion. The product profile that was distributed to the study participants was inaccurate and incomplete. The ——— stated the frequency as prn. However, the recommended dose frequency is a maximum of once per day as desired. The dosage was also expressed in such a manner that is not representative to the usual dosage described in the insert. All the available strengths are listed rather than the usual dosage of 10 mg. In addition, four of the six precepts ask for identical information (i.e., formulation, dosage, frequency, dispensing environment). This can be misleading and lead to a lower reported number of similar characteristics. For example, if the suspect product is not available as an "oral – film coated tablet" or not available in every strength of the proposed drug product, the potential for harm would be scored as zero. However, the two dosage forms could overlap meaning "oral", the dosage could be "one tablet, capsule etc" and could possibly have at least one overlapping strength. Depending on how ——— defined "potential harm", there can be a substantial variation in the interpretation of this term by the respondents as well. OPDRA questions the validity of the study results based on the methodological limitations and incompleteness of the product profile. In addition, the study participants are not experts in reviewing medication errors and would not be sensitized to all factors that can potentially cause errors.

During the evaluation of the proposed proprietary name for hyperbole issues, respondents were asked to identify any misleading connotations, exaggerations, or other hyperbole implied by the proposed proprietary name. Two percent of those surveyed stated the name "suggests it elevates new life" or "implies new life". Other responses included "implies it stops the aging process, suggests a vitamin and suggests regrowth or a cellular stimulant".

♦ Phase 4: A panel of pharmacists ———

——— conducted a safety review of the drug names listed by the respondents. All of the proprietary names that were evaluated by the panel were considered to have a minimal chance of confusion due to fundamental differences in the product profiles. Generally, one would assume that based on these differences the potential for medication errors would be low. However, post-marketing experience has clearly demonstrated repeatedly that differences in product profiles such as those mentioned in the panel may not *always* eliminate the potential for error. The ———panel and ——— also failed to point out the clinical consequences a patient could endure if Nuviva were administered inadvertently for any of the products identified.

OPDRA believes the following three names that were forwarded to the panel have the greatest potential to cause a medication error due to name confusion with Nuviva: Sustiva, Navane, and Norvasc.

D. SAFETY EVALUATOR RISK ASSESSMENT

***NOTE: This review contains proprietary and confidential information that should not be released to the public.

In reviewing the proprietary name, Nuviva, the primary concerns raised by the OPDRA expert panel were related to three potential sound-alike/look-alike names that already exist in the US marketplace, Nivia, Sustiva, and Renova. [redacted] was also identified as a potential sound-alike name. [redacted]
Additionally, Sustiva, was identified as a potential sound-alike/look-alike name in the study submitted by the sponsor. OPDRA is also concerned about two additional names, Norvasc and Navane, that were also identified as potential look-alike products in the same study.

OPDRA conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that *Nuviva* could be confused with *Sustiva* as *one respondent* (2 %) misinterpreted Nuviva as Sustiva. Another marketed product, *Norvir*, was also interpreted for Nuviva. Although there are limitations to the predictive value of this study, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

Nuviva and *Sustiva* may look and sound similar according to the expert panel. Nuviva and Sustiva both contain the same number of syllables and end in the same suffix "iva". Because of these similarities when spoken, the two names have a slight rhyming quality. When scripted, an "n" and "s" can appear similar. However, the "ti" in the middle of the name (see below) somewhat distinguishes Sustiva. Sustiva is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI). It is available as a capsule for oral administration containing either 50 mg, 100 mg, or 200 mg of the active ingredient efavirenz. Nuviva is available as a 5 mg, 10 mg or 20 mg tablet for oral administration. Both Sustiva and Nuviva share an overlapping dosing interval of once daily. Despite these similarities, the recommended daily dose of Sustiva is 600 mg. To achieve this dosage it would require administration of anywhere from 3 to 12 capsules dependent on the strength dispensed. Additionally, Sustiva is not indicated as a monotherapy agent. Although the names are similar, the clinical context of use, differences in patient population, and daily dosage decreases the potential for confusion. Sustiva was a name that was identified as a potential sound-alike/look-alike product in the independent study conducted by the [redacted] submitted by the sponsor. As part of their analysis, the name was forwarded to the [redacted] for review and comment. The [redacted] panel stated there is

some resemblance between Nuviva and Sustiva and that the similarity may be increased if Nuviva is pronounced differently or with an accent, thereby raising the possibility for confusion based on name alone. However, based on the differences in indication for use, dosage strengths, daily dosage and different starting letters the chance of error is minimized. We concur with this assessment.

Sustiva *Nuviva*

Renova was identified by the expert panel to have potential for look-alike confusion with *Nuviva*. Renova contains the active ingredient tretinoin and is indicated for the reduction of skin wrinkles. It is available as a 0.05% cream for topical administration. Nuviva and Renova share and overlapping dosing interval of once daily. However, despite this similarity the two have no other commonalties. Additionally, post-marketing experience has not demonstrated medication errors between solid oral dosage forms and topical drug products. Therefore, based on the numerous product differences, the potential for confusion between Renova and Nuviva is low.

According to the Expert Panel, *Nivia* can look and sound similar to *Nuviva*. Nuviva and Nivia sound and look similar because they begin with "N" and end in similar sounding suffixes "via" and "iva". Additionally, the two differ by one letter. However, Nivia is available as an OTC emollient cream. Post-marketing experience has not demonstrated medication errors between solid oral dosage forms and topical drug products. The differences in dosage forms, directions for use, and dispensing environments significantly decreases the potential for confusion between these two drug products.

Norvir was not identified by the panel as a potential look-alike. However, one respondent interpreted *Nuviva* as *Norvir* from the written inpatient order. Additionally, *Norvir* was identified as a potential sound-alike/look-alike in the study submitted by the sponsor. — is another name that was not identified by the Expert Panel. However, it was uncovered as another potential sound-alike/look-alike name during an independent search conducted by the reviewer. — —. These products are listed in table 2 (see page 10), along with the dosage forms available and usual dosages.

TABLE 2

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Nuviva	Vardenafil Tablets 5 mg, 10 mg and 20 mg	10 mg once daily up to a maximum of 20 mg daily.	
Norvir	Ritonavir Capsules 100 mg and Ritonavir Oral Solution 80 mg/mL	600 mg twice daily	L/A per Study Participant

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
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— and *Nuviva* can sound and look similar. — and Nuviva both contain three syllables and end in the same suffix "iva". Both products are dosed once daily as well. However,

, decreases the potential for confusion.

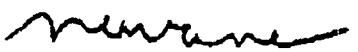
Norvir is an inhibitor of HIV protease indicated in combination with other antiretroviral agents for the treatment of HIV-infection. The recommended dosage of ritonavir is 600 mg twice daily by mouth. If saquinavir and ritonavir are used in combination, the dosage of saquinavir should be reduced to 400 mg twice daily. *Norvir* is available as a 100 mg capsule and 80 mg/mL oral solution. Although, Norvir was misinterpreted by one respondent on the inpatient order when scripted as D/C Nuviva, the differences in the indications of use, dosing interval and patient population would decrease the potential for product confusion. The — panel stated there is some similarity between the names. Although the endings are different, the potentially similar appearance of the "Viva" ending of the test name for "VIR" of Norvir raises some concern for misperception in handwritten prescriptions. The chance of error is minimized by substantial differences between the drugs, according to indication, product dose, dosage strength, daily dosage, and directions for use. Furthermore, Norvir is for HIV/AIDS and these medications are usually prescribed in combinations of at least 3 different drugs, unlike the test drug that is to be taken alone. We concur with this analysis.

Norvasc and *Navane* were two additional products identified as potential look-alike names in the studies conducted by the — for the sponsor. OPDRA is also concerned with these names posing a significant problem, as there is current confusion in the marketplace between Norvasc and Navane due to their similar appearance when scripted.

Navane and *Nuviva* appear similar when scripted (see below). 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 [redacted] sites 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 among 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.

Navane *Nuviva*



Norvasc and *Nuviva* can also look similar when scripted (see below). The names contain a similar number of characters (6 vs. 7). Norvasc and Nuviva are both available in 5 mg and 10 mg strengths and share an overlapping dosing interval of once daily. The [redacted] panel stated that although the endings are different, the potentially similar appearance of the "viva" ending of the test name and the "vasc" of Norvasc raises some concern for misperception in handwritten prescriptions. The panel also noted the overlap between the drugs dosage forms and strengths. The panel also stated that if error occurred with Norvasc, the most commonly reported adverse effects include fatigue, edema, flushing, palpitations, GI upset, or drowsiness. Given that some of these effects are common with those of the test drug, this could make it less likely that a medication error would be detected, or more likely that severe effects might occur if the highest dose of Norvasc were taken. Moreover, NORVASC is indicated for the treatment of hypertension and therefore misadministration of this drug may result in a hypotensive crisis in a normotensive patient. These commonalties increase the potential for a medication error occurrence.

Norvasc *Nuviva*

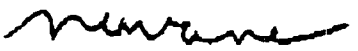
2 pages redacted from this section of the approval package consisted of draft labeling

IV. COMMENTS TO THE SPONSOR

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 confusion currently in the market place between Norvasc and Navane due to their similar appearance when scripted.

Navane and *Nuviva* appear similar when scripted (see below). 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 — sites 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 among 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.

Navane



Nuviva

Norvasc and *Nuviva* can also look similar when scripted (see below). The names contain a similar number of characters (6 vs. 7). Norvasc and Nuviva are both available in 5 mg and 10 mg strengths and share an overlapping dosing interval of once daily. The —— panel stated that although the endings are different, the potentially similar appearance of the "viva" ending of the test name and the "vasc" of Norvasc raises some concern for misperception in handwritten prescriptions. The panel also noted the overlap between the drugs dosage forms and strengths. The panel also stated that if error occurred with Norvasc, the most commonly reported adverse effects include fatigue, edema, flushing, palpitations, GI upset, or drowsiness. Given that some of these effects are common with those of the test drug, this could make it less likely that a medication error would be detected, or more likely that severe effects might occur if the highest dose of Norvasc were taken. Moreover, NORVASC is indicated for the treatment of hypertension and therefore misadministration of this drug may result in a hypotensive crisis in a normotensive patient. These commonalties increase the potential for a medication error occurrence.

Norvasc *Nuviva*

In addition, we provide the following recommendation on labeling revisions that may minimize potential user error:

1 pages redacted from this section of the approval package consisted of draft labeling

V. RECOMMENDATIONS

1. OPDRA does not recommend the use of the proprietary name, "Nuviva". DDMAC is also concerned with the promotional aspect of the name (see section IIA of review).

2. OPDRA recommends implementation of the above labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3231.

/S/

Carol Holquist, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

/S/

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/s/

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PHARMACIST

Jerry Phillips
12/13/01 09:27:23 AM
DIRECTOR

Martin Himmel
12/17/01 12:58:27 PM
MEDICAL OFFICER

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

Post-Marketing Commitments

Please refer to the commitments cited in the Approval Letter.