

# CENTER FOR DRUG EVALUATION AND RESEARCH

## *APPLICATION NUMBER:*

**21-266 / S-005, S-006**  
**: 21-267 / S-005, S-006**  
**21-630 / S-001**

## **ADMINISTRATIVE DOCUMENTS** **AND** **CORRESPONDENCE**

NDA 21-266/S-006  
NDA 21-267/S-006  
NDA 21-630/S-001

**Labeling, Clinical and Biopharmaceutics Review of Amendments to  
Supplemental Labeling Revisions (SLRs):**

**Executive Summary:**

This review describes and recommends response to amendments to pending "Changes Being Effected" (CBE) supplemental labeling submissions. The amendments propose the following changes to the pending supplements:

- Addition of information pertaining to a voriconazole-efavirenz drug interaction study to **CLINICAL PHARMACOLOGY, Drug Interactions, Two-Way Interactions, Other Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) (CYP3A4 substrates, inhibitors or CYP450 inducers).**
- Modification of the wording regarding efavirenz in Table 8 and Table 9 within **PRECAUTIONS, Drug Interactions.**

This review recommends approval of the proposed labeling changes including the amendments.

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**Product:** VFEND® (voriconazole) Tablets  
VFEND® I.V. (voriconazole) for Injection  
VFEND® (voriconazole) for Oral Suspension

**Applicant:** Pfizer, Inc.

**Materials Reviewed:**

**NDA 21-266 (Tablets):**

<u>SLR</u>	<u>Amendment Date submitted</u>	<u>Date submitted</u>	<u>Date received</u>
006	BLMarch 31, 2004	March 31, 2004	April 1, 2004
006	BLApril 21, 2004	April 21, 2004	April 21, 2004

**NDA 21-267 (Injection):**

<u>SLR</u>	<u>Amendment Date submitted</u>	<u>Date submitted</u>	<u>Date received</u>
006	BLMarch 31, 2004	March 31, 2004	April 1, 2004
006	BLApril 21, 2004	April 21, 2004	April 21, 2004

**NDA 21-630 (Oral Suspension):**

<u>SLR</u>	<u>Amendment Date submitted</u>	<u>Date submitted</u>	<u>Date received</u>
001	BLMarch 31, 2004	March 31, 2004	April 1, 2004
006	BLApril 21, 2004	April 21, 2004	April 21, 2004

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- Approved VFEND® package insert dated December 19, 2003.
- Robin Anderson's review of NDA 21-266/S-006, NDA 21-267/S-006, and NDA 21-630/S-001 dated March 24, 2004.
- Dr. Gerlie De Los Reyes's Biopharmaceutics review of NDA 21-266/S-006, NDA 21-267/S-006, and NDA 21-630/S-001 dated April 19, 2004.

**Background:**

NDA 21-266 (Tablets) and NDA 21-267 (Injection) were originally approved on May 24, 2002. The last approved labeling change for the VFEND® package insert occurred on December 19, 2003 when VFEND® for Oral Suspension was approved and incorporated into the tablet and injection label.

Supplements 006 for both the tablet and injection were submitted as Changes Being Effected. They provide for the addition of information concerning the effect of efavirenz and voriconazole on the steady state concentrations of each other to **CLINICAL PHARMACOLOGY/Drug Interactions, CONTRAINDICATIONS and PRECAUTIONS/Drug Interactions.**

Supplement 001 for the oral suspension was also submitted as CBE. This supplement provides for the addition of information concerning the effects of both ritonavir (same as NDA 21-266/S-005 and NDA 21-267/S-005) and efavirenz (same as NDA 21-266/S-006 and NDA 21-267/S-007) on steady state concentrations of voriconazole and the effect of voriconazole on the steady state concentrations of ritonavir and efavirenz to **CLINICAL PHARMACOLOGY/Drug Interactions, CONTRAINDICATIONS and PRECAUTIONS/Drug Interactions.**

Robin Anderson completed a review of these supplements on March 24, 2004. An amendment was then received on April 1, 2004 proposing additional changes regarding efavirenz. Gerlie De Los Reyes reviewed these changes and recommended revisions. The recommended revisions were emailed to Pfizer on April 20, 2004. Pfizer submitted revised draft labeling incorporating these recommendations on April 21, 2004.

**Electronic Labeling Comparison:**

The proposed package insert dated April 21, 2004 was electronically compared to the approved package insert dated December 19, 2003. The following changes were found in addition to those described in the March 24, 2004 review:

Added text = double underline  
Deleted text = ~~strikethrough~~

**1. CLINICAL PHARMACOLOGY**

- The following paragraph in **Drug Interactions, Two-Way Interactions** was modified as indicated:

**Other Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) (CYP3A4 substrates, inhibitors or CYP450 inducers):** *In vitro* studies (human liver microsomes) show that the metabolism of voriconazole may be inhibited by an NNRTI (e.g., delavirdine). The findings of a clinical voriconazole-efavirenz drug interaction study in healthy volunteers suggest that the metabolism of voriconazole may be induced by a NNRTI. This *in vivo* study also showed that voriconazole may inhibit the metabolism of a NNRTI. Although not studies *in vitro* or *in vivo*, the metabolism of voriconazole may be induced by an NNRTI, such as nevirapine. *In vitro* studies (human liver microsomes) show that voriconazole may also inhibit the metabolism of an NNRTI (e.g., delavirdine). Efavirenz and voriconazole coadministration is contraindicated (see CLINICAL PHARMACOLOGY – Drug Interactions, CONTRAINDICATIONS, PRECAUTIONS – Drug Interactions). Patients should be frequently monitored for drug toxicity during the coadministration of voriconazole and other NNRTIs (e.g. nevirapine and delavirdine) (see PRECAUTIONS – Drug Interactions).

**2. PRECAUTIONS**

- Table 8 and Table 9 in **Drug Interactions** were revised to include the voriconazole-efavirenz drug interaction study as follows:

**Table 8 Effect of Other Drugs on Voriconazole Pharmacokinetics:**

Drug/Drug Class (Mechanism of Interaction by the Drug)	Voriconazole Plasma Exposure (C <sub>max</sub> and AUC <sub>τ</sub> after 200 mg Q12h)	Recommendations for Voriconazole Dosage Adjustment/Comments
Other NNRTIs*** (CYP3A4 Inhibition or CYP450 Induction)	<p><i>In Vitro</i> Studies Demonstrate Potential for Inhibition of Voriconazole Metabolism by <u>Delavirdine and Other NNRTIs</u> (Increased Plasma Exposure)</p> <p>A Voriconazole-Efavirenz Drug Interaction Study Demonstrates the Potential for the Metabolism of Voriconazole to be Induced by <u>Efavirenz and Other NNRTIs</u> (Decreased Plasma Exposure)</p>	<p>Frequent monitoring for adverse events and toxicity related to voriconazole</p> <p>Careful assessment of voriconazole effectiveness</p>

\*Results based on *in vivo* clinical studies generally following repeat oral dosing with 200 mg Q12h voriconazole to healthy subjects

\*\*Results based on *in vivo* clinical study following repeat oral dosing with 400 mg Q12h for 1 day, then 200 mg Q12h for 8 days voriconazole to healthy subjects

\*\*\* Non-Nucleoside Reverse Transcriptase Inhibitors

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**Table 9 Effect of Voriconazole on Pharmacokinetics of Other Drugs**

<b>Drug/Drug Class (Mechanism of Interaction by Voriconazole)</b>	<b>Drug Plasma Exposure (C<sub>max</sub> and AUC)</b>	<b>Recommendations for Drug Dosage Adjustment/Comments</b>
Other NNRTIs*** (CYP3A4 Inhibition)	A Voriconazole-Efavirenz Drug Interaction Study and <del>In-Vitro</del> Studies Demonstrates the Potential for Voriconazole to Inhibit Metabolism of Other NNRTIs (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to NNRTI

\*Results based on *in vivo* clinical studies generally following repeat oral dosing with 200 mg BID voriconazole to healthy subjects

\*\*Results based on *in vivo* clinical study following repeat oral dosing with 400 mg Q12h for 1 day, then 200 mg Q12h for 8 days voriconazole to healthy subjects

\*\*\* Non-Nucleoside Reverse Transcriptase Inhibitors

**Conclusions/Recommendations:**

In her April 19, 2004 review, Dr. De Los Reyes stated the labeling changes proposed in the subsequent amendment were not acceptable. Her labeling recommendations were accepted by Pfizer. The revised labeling submitted on April 21, 2004 was found acceptable by Dr. De Los Reyes. An approval letter should be sent advising the applicant that these supplemental NDAs are approved.

Rebecca D. Saville, Pharm.D.  
Regulatory Project Manager

Gerlie De Los Reyes, Ph. D.  
Biopharmaceutics Reviewer

Sary Beidas, M.D.  
Medical Officer

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/s/

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MEDICAL OFFICER