



NDA 21-266/S-023
NDA 21-267/S-024
NDA 21-630/S-013

C.P. Pharmaceuticals International C.V.
c/o Pfizer, Inc.
Attention: Mr. Robert B. Clark
Vice President, U.S. Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your supplemental new drug applications dated September 7, 2007, received on September 10, 2007, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA Number	Supplement Number
VFEND [®] (voriconazole) Tablets, 50 mg and 200 mg	21-266	S-023
VFEND [®] I.V. (voriconazole) for Injection, 10 mg/mL	21-267	S-024
VFEND [®] (voriconazole) for Oral Suspension, 45 mg/mL	21-630	S-013

We acknowledge receipt of your submissions dated December 6, 2007 and March 7, 2008.

These supplemental new drug applications provide for the addition of a new contraindication with St. John's Wort, clarification of the dosage adjustment when administered with efavirenz, clarification of concomitant administration with intravenous products, and addition of pancreatic function monitoring throughout several sections of the package insert of the labeling for VFEND[®].

We have completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. The revisions to the package insert were as follows (additions noted with underline and deletions noted with ~~strikethrough~~):

1. A contraindication between voriconazole and St. John's Wort was added to the **CLINICAL PHARMACOLOGY/Drug Interactions/Effects of Other Drugs on Voriconazole** subsection of the package insert as follows:

St. John's Wort (CYP450 inducer; P-gp inducer): In an independent published study in healthy volunteers who were given multiple oral doses of St. John's Wort (300 mg LI 160 extract three times daily for 15 days) followed by a single 400 mg oral dose of voriconazole, a 59% decrease in mean voriconazole AUC_{0-∞} was observed. In contrast, coadministration of

single oral doses of St. John's Wort and voriconazole had no appreciable effect on voriconazole AUC_{0-∞}. Because long-term use of St. John's Wort could lead to reduced voriconazole exposure, concomitant use of voriconazole with St. John's Wort is contraindicated (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

2. The **CLINICAL PHARMACOLOGY/Drug Interactions/Two-Way Interactions/Efavirenz** subsection of the package insert was revised for clarification.

Significant drug interactions that may require dosage adjustment, frequent monitoring of drug levels and/or frequent monitoring of drug-related adverse events/toxicity:

Efavirenz, a non-nucleoside reverse transcriptase inhibitor (CYP450 inducer; CYP3A4 inhibitor and substrate): Standard doses of voriconazole and standard doses of efavirenz must not be coadministered (see PRECAUTIONS – Drug Interactions). Steady state efavirenz (400 mg PO QD) decreased the steady state C_{max} and AUC_τ of voriconazole (400 mg PO Q12h for 1 day, then 200 mg PO Q12h for 8 days) by an average of 61% and 77%, respectively, in healthy male subjects. Voriconazole at steady state (400 mg PO Q12h for 1 day, then 200 mg Q12h for 8 days) increased the steady state C_{max} and AUC_τ of efavirenz (400 mg PO QD for 9 days) by an average of 38% and 44%, respectively, in healthy subjects. ~~Coadministration of standard doses of voriconazole and efavirenz is contraindicated. (see CONTRAINDICATIONS, PRECAUTIONS – Drug Interactions).~~

The pharmacokinetics of adjusted doses of voriconazole and efavirenz were studied in healthy male subjects following administration of voriconazole (400 mg PO Q12h on Days 2 to 7) with efavirenz (300 mg PO Q24h on Days 1-7), relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg PO Q12h for 2 days) or efavirenz (600 mg Q24h for 9 days). ~~Coadministration of voriconazole 300 mg Q 12h with efavirenz 300 mg Q24h, decreased voriconazole AUC_τ and C_{max} by 55% (90% CI: 45%, 62%) and 36% (90% CI: 21%, 49%), respectively; efavirenz AUC_τ was equivalent and C_{max} was decreased by 14% (90% CI: 7%, 21%). Coadministration of voriconazole 400 mg Q 12h with efavirenz 300 mg Q24h, decreased voriconazole AUC_τ by 7% (90% CI: -23%, 13%) and increased C_{max} by 23% (90% CI: -1%, 53%); efavirenz AUC_τ was increased by 17% (90% CI: 6%, 29%) and C_{max} was equivalent.~~

Voriconazole may be coadministered with efavirenz if the voriconazole maintenance dose is increased to 400 mg Q12h and the efavirenz dose is decreased to 300 mg Q24h. When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored. ~~When voriconazole is coadministered with efavirenz, voriconazole maintenance dose should be increased to 400 mg Q12h and efavirenz dose should be decreased to 300 mg Q24h.~~

3. The following text was added to the last paragraph of the **CLINICAL PHARMACOLOGY/Drug Interactions/Two-Way Interactions/Other Two-Way Interactions Expected to be Significant Based on In Vitro and In Vivo Findings** subsection:

Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (CYP3A4 substrates, inhibitors or CYP450 inducers): *In vitro* studies (human liver microsomes) show that the

metabolism of voriconazole may be inhibited by a NNRTI (e.g., delavirdine). The findings of a clinical voriconazole-efavirenz drug interaction study in healthy male subjects 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 (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). Dose adjustments are required when voriconazole is co-administered with efavirenz (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS - Drug Interactions).

4. Efavirenz was removed and St. John’s Wort was added in the **CONTRAINDICATIONS** section of the package insert as follows:

~~Coadministration of standard doses of VFEND with efavirenz is contraindicated because efavirenz significantly decreases voriconazole plasma concentrations while VFEND also significantly increases efavirenz plasma concentrations. Concomitant use of adjusted doses of voriconazole and efavirenz may be administered (see CLINICAL PHARMACOLOGY – Drug Interactions, PRECAUTIONS – Drug Interactions, and DOSAGE AND ADMINISTRATION – Dosage Adjustment).~~

Coadministration of VFEND with St. John’s Wort is contraindicated (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS - Drug Interactions).

5. **Table 9. Effect of Other Drugs on Voriconazole Pharmacokinetics** of the **PRECAUTIONS** section of the package insert was revised to remove efavirenz and to add St. John’s Wort as follows:

Table 9 Effect of Other Drugs on Voriconazole Pharmacokinetics

Drug/Drug Class (Mechanism of Interaction by the Drug)	Voriconazole Plasma Exposure (C_{max} and AUC_τ after 200 mg Q12h)	Recommendations for Voriconazole Dosage Adjustment/Comments
Efavirenz** (CYP450 Induction)	Significantly Reduced	Coadministration of standard doses of efavirenz with voriconazole is contraindicated. When voriconazole is coadministered with efavirenz, voriconazole maintenance dose should be increased to 400 mg Q12h and efavirenz should be decreased to 300 mg Q24h (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION-Dosage Adjustment)
<u>St. John’s Wort (CYP450 inducer; P-gp inducer)</u>	<u>Significantly Reduced</u>	<u>Contraindicated</u>

6. **Table 10. Effect of Voriconazole on Pharmacokinetics of Other Drugs** of the **PRECAUTIONS** section of the package insert was revised as follows:

Table 10 Effect of Voriconazole on Pharmacokinetics of Other Drugs

Drug/Drug Class (Mechanism of Interaction by Voriconazole)	Drug Plasma Exposure (C _{max} and AUC _τ)	Recommendations for Drug Dosage Adjustment/Comments
Efavirenz** (CYP3A4 Inhibition)	Significantly Increased	<p>Coadministration of standard doses of efavirenz with voriconazole is contraindicated.</p> <p>When voriconazole is coadministered with efavirenz, voriconazole maintenance dose should be increased to 400 mg Q12h and efavirenz should be decreased to 300 mg Q24h (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION-Dosage Adjustment)</p>

7. The monitoring of pancreatic function was added in the **PRECAUTIONS** section of the package insert as follows:

Monitoring of Pancreatic Function

Adults and children with risk factors for acute pancreatitis (e.g., recent chemotherapy, hematopoietic stem cell transplantation [HSCT]) should be monitored for the development of pancreatitis during VFEND treatment.

8. The last paragraph of the **PRECAUTIONS/Pediatric Use** subsection of the package insert was added as follows:

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

A total of 22 patients aged 12-18 years with invasive aspergillosis were included in the therapeutic studies. Twelve out of 22 (55%) patients had successful response after treatment with a maintenance dose of voriconazole 4 mg/kg Q12h.

Sparse plasma sampling for pharmacokinetics in adolescents was conducted in the therapeutic studies (see **CLINICAL PHARMACOLOGY** - Pharmacokinetics, General Pharmacokinetic Characteristics).

There have been postmarketing reports of pancreatitis in pediatric patients.

9. Information pertaining to the concomitant use of intravenous electrolytes, blood products, and total parenteral nutrition with voriconazole IV was reorganized in the **DOSAGE AND ADMINISTRATION/Use of VFEND I.V. with other Parenteral Drug Products** subsection of the package insert as follows:

Use of Vfend I.V. with other Parenteral Drug Products

Blood products and concentrated electrolytes

VFEND I.V. must not be infused concomitantly with any blood product or short-term infusion of concentrated electrolytes, even if the two infusions are running in separate intravenous lines (or cannulas). Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of VFEND therapy (see precautions).

Intravenous solutions containing (non-concentrated) electrolytes

VFEND I.V. can be infused at the same time as other intravenous solutions containing (non-concentrated) electrolytes, but must be infused through a separate line.

Total parenteral nutrition (TPN)

VFEND I.V. can be infused at the same time as total parenteral nutrition, but must be infused in a separate line. If infused through a multiple-lumen catheter, TPN needs to be administered using a different port from the one used for VFEND I.V.

Incompatibilities:

~~VFEND I.V. must not be infused into the same line or cannula concomitantly with other drug infusions, including parenteral nutrition, e.g., Aminofusin 10% Plus.~~ Aminofusin 10% Plus is physically incompatible, with an increase in subvisible particulate matter after 24 hours of storage at 4°C.

~~Infusions of blood products must not occur simultaneously with VFEND I.V.~~

~~Infusions of total parenteral nutrition can occur simultaneously with VFEND I.V.~~

VFEND I.V. must not be diluted with 4.2% Sodium Bicarbonate Infusion. The mildly alkaline nature of this diluent caused slight degradation of VFEND after 24 hours storage at room temperature. Although refrigerated storage is recommended following reconstitution, use of this diluent is not recommended as a precautionary measure. Compatibility with other concentrations is unknown.

10. The fourth paragraph of the **DOSAGE AND ADMINISTRATION/Dosage Adjustment** subsection was revised as follows:

When voriconazole is coadministered with efavirenz, the voriconazole maintenance dose should be increased to 400 mg Q12h and the efavirenz dose should be decreased to 300 mg Q24h. When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored (see CLINICAL PHARMACOLOGY and PRECAUTIONS – Drug Interactions).

11. St. John's Wort was added to the **Patient Information** section of the package insert as follows:

Who should not take VFEND?

Do NOT take VFEND if you are taking the medicines listed below. Serious or life-threatening side effects from these medicines, or a decrease in the effect of VFEND could result if any of these medicines are taken together with VFEND. Tell your doctor right away if you are taking any of these medications:

- terfenadine (Seldane[®])
- astemizole (Hismanal[®])
- cisapride (Propulsid[®])
- pimozide (Orap[®])
- sirolimus (Rapamune[®])
- carbamazepine (Tegretol[®])
- rifampin (Rifadin[®])
- rifabutin (Mycobutin[®])
- St. John's Wort (herbal supplement)
- quinidine (like Quinaglute[®])
- ergotamine, dihydroergotamine, methysergide (Sansert[®]), bromocriptine (Parlodel[®])
- long-acting barbiturates like phenobarbital (Luminal[®])
- ritonavir (Norvir[®]) and efavirenz (Sustiva[®]) (Some doses of ritonavir and efavirenz can be taken at the same time as VFEND, but you must check with your doctor first)

12. Global editorial change from “volunteers” to “subjects.”

13. Minor editorial changes throughout the labeling.

CONTENT OF LABELING

As soon as possible, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert and text for the patient package insert). Upon receipt, we will transmit this version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions, “**SPL for approved NDA 21-266/S-023, NDA 21-267/S-024, and NDA 21-630/S-013.**”

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about these drug products (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Rebecca D. Saville, Pharm.D., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and
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/s/

Renata Albrecht
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