



NDA 20778/S-037  
NDA 20779/S-058  
NDA 21503/S-020

**SUPPLEMENT APPROVAL**

Pfizer Inc.  
Attention: Nadia Kirzecky  
Worldwide Regulatory Affairs  
235 East 42nd Street  
New York, NY 10017-5755

Dear Ms. Kirzecky:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received November 9, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Viracept<sup>®</sup> (nelfinavir mesylate) Oral Powder (NDA 20778), Tablets, 250 mg (NDA 20779), and Tablets, 625 mg (NDA 21503).

We acknowledge receipt of your January 10, 2012 e-mail communication in response to our additional non-safety labeling change request sent on December 14, 2011 via e-mail.

We also refer to our letter dated October 19, 2011, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for antiretroviral products. This information pertains to the risk of the autoimmune disorder as syndromes that can occur in the setting of immune reconstitution with the use of antiretroviral products.

In addition, we refer to non-safety labeling changes in our October 19, 2011 letter for all antiretroviral products based on recent studies demonstrating decreased transmission of HIV when HIV-infected patients or their uninfected partners take antiretroviral medication.

These supplemental new drug applications provide for revisions to the labeling for Viracept<sup>®</sup> (nelfinavir mesylate) Oral Powder, Tablets, 250 mg, and Tablets, 625 mg, consistent with our October 19, 2011 letter and December 14, 2011 e-mail request, as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~).

1. Table 9, in the **CONTRAINDICATIONS** section, was revised as follows:

<b>Drug Class</b>	<b>Drugs Within Class That Are Contraindicated With VIRACEPT</b>
Alpha 1-adrenoreceptor	Alfuzosin

antagonist	
Antiarrhythmics	Amiodarone, Quinidine
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine
HMG-CoA reductase inhibitors	<u>Lovastatin, Simvastatin</u>
Neuroleptic	Pimozide
PDE5 inhibitors	Sildenafil (REVATIO <sup>®</sup> ) [for treatment of pulmonary arterial hypertension]
Sedative/Hypnotics	Midazolam, Triazolam

2. The second paragraph of the **WARNINGS/Drug Interactions (also see PRECAUTIONS)** sub-section has been revised as follows:

Concomitant use of VIRACEPT with lovastatin or simvastatin is ~~not recommended~~ contraindicated. Caution should be exercised if HIV protease inhibitors, including VIRACEPT, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A pathway (e.g., atorvastatin). (Also see **Tables 6 and 7: Drug Interactions**). Titrate atorvastatin dose carefully and use the lowest necessary dose; do not exceed a total atorvastatin dose of 40 mg/day during coadministration with VIRACEPT.

3. The **PRECAUTIONS/Immune Reconstitution Syndrome** sub-section has been revised as follows:

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including VIRACEPT. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia(PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

4. The third paragraph of the **PRECAUTIONS/Information For Patients** sub-section was revised as follows:

~~Patients should be informed that VIRACEPT is not a cure for HIV infection and that they may continue to acquire illnesses associated with advanced HIV infection, including opportunistic infections. Patients should be told that there is currently no data demonstrating that VIRACEPT therapy can reduce the risk of transmitting HIV to others through sexual contact or blood contamination. VIRACEPT is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including~~

opportunistic infections. Patients should remain under the care of a physician when using VIRACEPT.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom ~~or other barrier method~~ to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** We do not know if VIRACEPT can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

5. Table 10 and 11, in **PRECAUTIONS/Drug Interactions** sub-section, was revised as follows:

<b>Table 10 Drugs That Should Not Be Coadministered With VIRACEPT</b>	
<b>Drug Class: Drug Name</b>	<b>Clinical Comment</b>
Alpha 1-adrenoreceptor antagonist: alfuzosin	<u>CONTRAINDICATED</u> due to <u>P</u> potentially increased alfuzosin concentrations can result in hypotension.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	<u>CONTRAINDICATED</u> due to <u>P</u> potential for serious reactions such as risk of myopathy including rhabdomyolysis.
PDE5 inhibitor: sildenafil (REVATIO) [for treatment of pulmonary arterial hypertension]	<u>CONTRAINDICATED</u> since <u>Aa</u> safe and effective dose has not been established when used with VIRACEPT. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, prolonged erection, and syncope).

<p align="center"><b>Table 11</b>  <b>Established and Other Potentially Significant Drug Interactions:</b>  <b>Alteration in Dose or Regimen May Be Recommended Based on</b>  <b>Drug Interaction Studies</b>                      (see CLINICAL PHARMACOLOGY, for Magnitude of Interaction, Tables 6 and 7)</p>		
<i>Concomitant Drug Class:</i>  <i>Drug Name</i>	<i>Effect on Concentration</i>	<b>Clinical Comment</b>
Anti-coagulant: warfarin	warfarin	Coadministration of <del>wafarin</del> warfarin and VIRACEPT may affect concentrations of warfarin. It is recommended that the INR (international normalized ratio) be monitored carefully during treatment with VIRACEPT, especially when commencing therapy.
HMG-CoA Reductase Inhibitor: atorvastatin rosuvastatin	↑ atorvastatin ↑ rosuvastatin	<del>Use lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG CoA reductase inhibitors such as pravastatin or fluvastatin in combination with VIRACEPT.</del> Titrate atorvastatin dose carefully and use the lowest necessary dose; do not exceed atorvastatin 40 mg/day.

6. The end section of package insert has been revised as follows:

LAB-0346-8.2

Revised ~~November~~February 2011

7. **Patient Prescribing Information:**

- a. The “**Does VIRACEPT cure HIV or AIDS?**” section has been revised as follows: ~~VIRACEPT is not a cure for HIV infection or AIDS. People taking VIRACEPT may still develop opportunistic infections or other conditions associated with HIV infection. Some of these conditions are pneumonia, herpes virus infections, *Mycobacterium avium* complex (MAC) infections, and Kaposi’s sarcoma. VIRACEPT does not cure HIV infection or AIDS and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. You should remain under the care of a doctor when using VIRACEPT.~~

Avoid doing things that can spread HIV-1 infection.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**

- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom ~~or other barrier method~~ to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- b. The “**Does VIRACEPT reduce the risk of passing HIV to others?**” section has been deleted.
- c. The fourth bulleted paragraph in the “**Who should not take VIRACEPT?**” section has been revised as follows:

~~If you are breast-feeding, it is very important that you speak with your healthcare provider about the best way to feed your baby. If your baby does not already have HIV, there is a chance that it can be transmitted through breast feeding. **The Centers for Disease Control and Prevention recommends that women with HIV do not breast-feed. Do not breastfeed.** We do not know if VIRACEPT can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.~~

- d. The **MEDICINES YOU SHOULD NOT TAKE WITH VIRACEPT/Do not take the following drugs because they can cause serious problems or death if taken with VIRACEPT** sub-section has been revised as follows:

- Cordarone<sup>®</sup> (amiodarone) (for irregular heartbeat)
- Orap<sup>®</sup> (pimozide) (for seizures)
- Quinidine (for irregular heartbeat), also known as Quinaglute<sup>®</sup>, Cardioquin<sup>®</sup>, Quinidex<sup>®</sup>, and others
- D.H.E. 45<sup>®</sup> Injection, Ergomar, Migranal<sup>®</sup>, Wigraine<sup>®</sup> and Cafergot<sup>®</sup> (for migraine headaches) and Methergine<sup>®</sup> (for bleeding after childbirth)
- Halcion<sup>®</sup> (triazolam) (for sleep problem)
- Versed<sup>®</sup> (midazolam) (sedative hypnotic)
- Revatio<sup>®</sup> (sildenafil) (for treatment of pulmonary arterial hypertension)
- Alfuzosin (for treatment of benign prostate enlargement)
- Mevacor<sup>®</sup> (lovastatin) (for lowering cholesterol)
- Zocor<sup>®</sup> (simvastatin) (for lowering cholesterol)

- e. The sentence after the third paragraph in the the **MEDICINES YOU SHOULD NOT TAKE WITH VIRACEPT** section has been revised as follows:

~~Do not take VIRACEPT with cholesterol lowering medicines Mevacor<sup>®</sup> (lovastatin) or Zocor<sup>®</sup> (simvastatin) because of possible serious reactions. Do not take VIRACEPT with Serevent<sup>®</sup> (salmeterol) because of possible serious reactions.~~

- f. The second sentence in the **Medicines that require dose adjustments** sub-section has been revised as follows:

There is also an increased risk of drug interactions between VIRACEPT and Lipitor<sup>®</sup> (atorvastatin), Crestor<sup>®</sup> (rosuvastatin), Pravachol<sup>®</sup> (pravastatin) and Lescol<sup>®</sup> (fluvastatin); talk to your healthcare provider before you take any of these cholesterol-reducing medicines with VIRACEPT.

- g. The end section of patient package insert has been revised as follows:  
LAB-0346-8.2  
Revised ~~November~~ February 2011

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below.

The word, "change" in the third bullet of the "**Does VIRACEPT cure HIV or AIDS?**" section should be revised to "chance" as follows:

- **Do not have any kind of sex without protection. Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the change chance of sexual contact with semen, vaginal secretions, or blood.**

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **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 Kyong Hyon, Safety Regulatory Project Manager, at (301) 796-0734.

Sincerely,

*{See appended electronic signature page}*

Kendall A. Marcus, MD  
Deputy Director for Safety  
Division of Antiviral Products  
Office Antimicrobial Products  
Center for Drug Evaluation and Research

ENCLOSURE(S):  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KENDALL A MARCUS  
02/17/2012