DHHS Perinatal Panel Notice on Nelfinavir FDA-Pfizer Letter

September 11, 2007

The DHHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission wants to bring the following notice from the FDA and letter from Pfizer to your attention regarding use of Viracept (nelfinavir mesylate) in pregnant HIV-infected women. Due to potential concerns related to the presence of ethyl methane sulfonate in Viracept (nelfinavir) (see below), it is recommended that:

1. When considering the risk/benefits for use of Viracept (nelfinavir), the needs of the individual patient must always be considered.

2. Pregnant women who need to begin antiretroviral therapy or prophylaxis should not be offered regimens containing Viracept (nelfinavir) until further notice, but rather begin an alternative antiretroviral regimen.

2. Pregnant women who are currently receiving Viracept (nelfinavir) should be switched to an alternative antiretroviral regimen.

3. For pregnant women with no alternative treatment options, the risk-benefit ratio remains favorable for the continued use of Viracept (nelfinavir) in these women. In such women, the critical importance of maintaining maternal health status and preventing mother to child transmission outweighs the potential risks.

4. Alternative antiretroviral drugs for regimens are listed in Table 3 of the *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States.* The other recommended protease inhibitor for use in pregnant women is Lopinavir/ritonavir (Kaletra). Recommended alternative protease inhibitors include indinavir (boosted with ritonavir) or saquinavir (boosted with ritonavir).

The Antiretroviral Pregnancy Registry monitors the rate of birth defects in infants born to pregnant women receiving antiretroviral drugs; sufficient numbers of first trimester exposures to Viracept (nelfinavir) have been monitored to detect at least a two-fold increased risk in overall birth defects, and no such increase has been observed.

FDA Notice

Viracept (nelfinavir mesylate) is a protease inhibitor antiretroviral medicine used in combination with other anti-HIV medications to treat infection with HIV. It is approved for use in adults and in children older than 2 years of age who are infected with human immunodeficiency virus (HIV-1), the virus that causes acquired immune deficiency syndrome (AIDS).

Earlier this summer, Viracept was recalled from the European market due to high levels of a harmful substance known as ethyl methanesulfonate (EMS), a byproduct of the Viracept manufacturing process. EMS is known to be an animal carcinogen (can cause cancer), mutagen (can be harmful to DNA, the genetic material in cells), and a teratogen (can be harmful to the development of an unborn child). The level at which EMS may become carcinogenic in humans is not known.

While Roche manufactures and distributes Viracept in Europe, Pfizer manufactures and markets Viracept in the United States. The levels of EMS detected in Viracept manufactured by Pfizer are lower than the levels of EMS detected in Viracept manufactured by Roche.

The FDA and Pfizer have agreed to specific limits of exposure of EMS to allow for continued use in populations where the benefit of using Viracept outweighs the potential risk.

At this time, FDA and Pfizer consider the risks of unintended interruption of HIV treatment that may result from a recall to be greater than the risks associated with taking Pfizer manufactured Viracept.

Pfizer is issuing the following *Dear Healthcare Professional* letter to describe the current situation.

VIRACEPT® (nelfinavir mesylate) 250 mg, 625 mg tablets, and Powder for Oral Suspension

IMPORTANT INFORMATION FOR PRESCRIBERS

Dear Healthcare Professional:

The purpose of this letter is to inform you of the presence of ethyl methanesulfonate (EMS), a process-related impurity in Viracept (nelfinavir mesylate) and to provide guidance on the use of Viracept in pregnant women and pediatric patients.

In June 2007, excess levels of EMS were detected in Roche Ltd-manufactured active pharmaceutical ingredient of Viracept; subsequently Roche recalled Viracept from all their European Union (EU) markets. EMS is a process-related impurity formed during manufacture of Viracept. EMS is a potential human carcinogen (Class 2B). Data from animal studies indicate EMS is teratogenic, mutagenic and carcinogenic; however, no data from humans exists.

In response to the Roche EU recall, the Food and Drug Administration (FDA) asked Pfizer to implement a new specification to limit the presence of EMS in Pfizer-manufactured Viracept products marketed in the United States. Pfizer commenced testing all active ingredients and found levels of EMS substantially lower than those associated with the Roche EU recall. Testing

continues. Pfizer and FDA have agreed on interim and long term specifications of EMS in Viracept at levels substantially lower than those that prompted the Roche EU recall. Only product meeting the interim specifications will be released for patient use in the US. Pfizer is taking this step to balance the need to maintain the availability of Viracept as a therapeutic alternative for patients and prevent unexpected interruption of HIV-1 antiretroviral treatment with the need to minimize patient exposure to a potential carcinogen.

The agreed interim specification limits the theoretical *lifetime* increased cancer risk in adults to less than 17 cases per 100,000 exposed. The long term specification for levels of EMS limits the theoretical *lifetime* increased cancer risk in adults to less than 1 case per 100,000 exposed. Current estimates of the background incidence of cancer in the HIV population are about 20-30 cases per 1000 patient-years.

MANAGEMENT OF PEDIATRIC PATIENTS

While no data on the impact of high EMS levels in humans exist, toxicology experts generally agree that the lifetime risk associated with exposure to a carcinogen is about 3-fold greater among pediatric patients between 2 and 16 years of age and even higher among pediatric patients younger than 2 years of age; this potentially greater risk was used to determine acceptable levels of EMS in formulations used in the pediatric population. **For pediatric patients who are stable on Viracept-containing regimens, the FDA and Pfizer agree that the benefit-risk ratio remains favorable and those patients may continue to receive Viracept. Pediatric patients who need to begin HIV treatment should not start regimens containing Viracept until further notice.**

We encourage you to refer to specific **recommendations for the use of antiretroviral agents in pediatric HIV- 1 infected patients** from the United States Department of Health and Human Services (DHHS) guidelines. *[1]*

MANAGEMENT OF PREGNANT WOMEN

We currently do not have information on the ability of EMS to cross the placenta nor enter breast milk. In the Antiretroviral Pregnancy Registry involving over 6000 HIV infected pregnant women, no significant difference in the prevalence of birth defects between women who used Viracept and those who used other antiretroviral therapy was observed. Nonetheless, FDA is recommending that pregnant women limit their exposure to EMS during pregnancy. **Pregnant women who need to begin antiretroviral therapy should not be offered regimens containing Viracept until further notice. As a precautionary measure, pregnant women currently receiving Viracept should be switched to an alternative antiretroviral therapy while Pfizer and FDA work to implement the long term EMS specification for Viracept.** We encourage you to refer to specific **recommendations for the use of antiretroviral agents in pregnant HIV-1 infected patients** from the United States Department of Health and Human Services (DHHS) guidelines *[2]*, in determining an alternative treatment option.

Maintaining the health of the mother and preventing transmission of HIV to the fetus are of paramount importance. **For pregnant women with no alternative treatment options, FDA and Pfizer agree that the risk-benefit ratio remains favorable for the continued use of Viracept.**

ALL OTHER PATIENTS

There is no change in the recommended use of Viracept for all other patients. Please see enclosed full prescribing information. In considering the best treatment for patients, please be aware that many HIV antiretroviral medications are carcinogenic in animal studies. In addition, some HIV antiretroviral medications are mutagenic or are teratogenic. Despite these findings, available information shows the benefits of HIV-1 antiretroviral treatment outweigh the risks of using these products or completely stopping HIV treatment. Please see individual product labeling for additional information.

Pfizer and FDA continue to work together to define a long-term, globally harmonized, plan which appropriately limits EMS levels within Viracept while still ensuring an uninterrupted supply of the medication to patients.

Sincerely,

Michael Berelowitz MB ChB, FACP, FCP(SA)

Safety Information

VIRACEPT in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

Nelfinavir is principally metabolized by the liver; it can be used in patients with mild hepatic impairment without any dose adjustment. VIRACEPT should not be use in patients with either moderate or severe hepatic impairment.

Exercise caution when administering VIRACEPT with drugs that induce CYP3A, and with potentially toxic drugs that are metabolized by CYP3A, including those that prolong the QT interval.

In clinical studies (n>5000), the most common adverse event, diarrhea, was moderate to severe in 14% to 20% of patients.

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including VIRACEPT.

Redistribution/accumulation of body fat has been reported in patients receiving antiretroviral therapy. A causal relationship has not been established, and long-term consequences are not known at this time.

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported with protease inhibitors.

There are no adequate and well-controlled studies in pregnant women taking VIRACEPT. VIRACEPT should be used in pregnancy only if clearly needed.

VIRACEPT use is contraindicated with amiodarone, quinidine, triazolam, midazolam, ergot derivatives, and pimozide. VIRACEPT should not be coadministered with St. John's wort, simvastatin, lovastatin, rifampin, and omeprazole. Rifabutin dose should be reduced by 50%. PDE5 inhibitors should be prescribed with caution.

Increased bleeding in patients with hemophilia type A or B has been reported with protease inhibitors.

1. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. October 26, 2006; 1-126. Available at **http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf**

2. Public Health Service Taskforce: Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States. October 12, 2006; 1-65. Available at **http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf**

For additional information, see FDA's Medwatch page, titled *Questions and Answers Regarding Health Concerns and Potential Shortage of Nelfinavir* (marketed as Viracept) at
http://www.fda.gov/cder/drug/infopage/nelfinavir/qa.htm

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An archive of past list serve announcements is available on the FDA Web site at
http://www.fda.gov/oashi/aids/listserve/archive.html