

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-779 / S-045

20-778 / S-024

21-503 / S-006

Trade Name: Viracept

Generic Name: (nelfinavir mesylate)

Sponsor: Pfizer Inc.

Approval Date: September 28, 2005

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APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-778/S-024
20-779/S-045
21-503/S-006

Agouron Pharmaceutical Inc., A Pfizer Company
Attention: Justine King, Regulatory Manager
US Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Ms. King:

Please refer to your supplemental new drug applications dated August 31, 2005, received September 1, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viracept (nelfinavir mesylate) 50mg/g Oral Powder, Viracept (nelfinavir mesylate) 250mg Tablets, and Viracept (nelfinavir mesylate) 625mg Tablets.

These "Changes Being Effected" supplemental new drug applications provide for the addition of drug-drug interactions and statements regarding immune reconstitution syndrome to the PRECAUTIONS section of the label.

We completed our review of these supplemental new drug applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on August 31, 2005.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Elizabeth Thompson, Regulatory Project Manager, at (301) 796-0824.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Division Director
Division of Anti-Viral Products
Center for Drug Evaluation and
Research

Enclosure: Final Printed Labeling (FPL)

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

/s/

Debra Birnkrant
9/28/2005 08:59:34 AM
NDA 21-503, 20-778, 20-779

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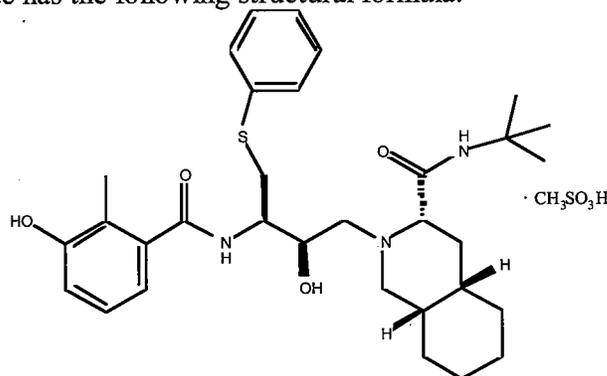
LABELING

AGOURON PHARMACEUTICALS, INC.
La Jolla, CA 92037, USA

VIRACEPT®
(nelfinavir mesylate)
TABLETS and ORAL POWDER

DESCRIPTION

VIRACEPT® (nelfinavir mesylate) is an inhibitor of the human immunodeficiency virus (HIV) protease. VIRACEPT Tablets are available for oral administration as a light blue, capsule-shaped tablet with a clear film coating in 250 mg strength (as nelfinavir free base) and as a white oval tablet with a clear film coating in 625 mg strength (as nelfinavir free base). Each tablet contains the following common inactive ingredients: calcium silicate, crospovidone, magnesium stearate, hypromellose, and triacetin. In addition, the 250 mg tablet contains FD&C blue #2 powder and the 625 mg tablet contains colloidal silicon dioxide. VIRACEPT Oral Powder is available for oral administration in a 50 mg/g strength (as nelfinavir free base) in bottles. The oral powder also contains the following inactive ingredients: microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hypromellose, aspartame, sucrose palmitate, and natural and artificial flavor. The chemical name for nelfinavir mesylate is [3*S*-[2(2*S**, 3*S**), 3 α ,4 α ,8 α]]-*N*-(1,1-dimethylethyl)decahydro-2-[2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylthio)butyl]-3-isoquinoline carboxamide monomethanesulfonate (salt) and the molecular weight is 663.90 (567.79 as the free base). Nelfinavir mesylate has the following structural formula:



Nelfinavir mesylate is a white to off-white amorphous powder, slightly soluble in water at pH ≤ 4 and freely soluble in methanol, ethanol, 2-propanol and propylene glycol.

MICROBIOLOGY

Mechanism of Action: Nelfinavir is an inhibitor of the HIV-1 protease. Inhibition of the viral protease prevents cleavage of the *gag* and *gag-pol* polyprotein resulting in the production of immature, non-infectious virus.

Antiviral Activity In Vitro: The antiviral activity of nelfinavir *in vitro* has been demonstrated in both acute and/or chronic HIV infections in lymphoblastoid cell lines, peripheral blood lymphocytes and monocytes/macrophages. Nelfinavir was found to be active against several laboratory strains and clinical isolates of HIV-1 and the HIV-2 strain ROD. The EC₉₅ (95% effective concentration) of nelfinavir ranged from 7 to 196 nM. Drug combination studies with protease inhibitors showed nelfinavir had antagonistic interactions with indinavir, additive interactions with ritonavir or saquinavir and synergistic interactions with amprenavir and lopinavir. Minimal to no cellular cytotoxicity was observed with any of these protease inhibitors alone or in combination with nelfinavir. In combination with reverse transcriptase inhibitors, nelfinavir demonstrated additive (didanosine or stavudine) to synergistic (abacavir, delavirdine, efavirenz, lamivudine, nevirapine, tenofovir, zalcitabine or zidovudine) antiviral activity *in vitro* without enhanced cytotoxicity.

Drug Resistance: HIV-1 isolates with reduced susceptibility to nelfinavir have been selected *in vitro*. HIV isolates from selected patients treated with nelfinavir alone or in combination with reverse transcriptase inhibitors were monitored for phenotypic (n=19) and genotypic (n=195, 157 of which were evaluable) changes in clinical trials over a period of 2 to 82 weeks. One or more viral protease mutations at amino acid positions 30, 35, 36, 46, 71, 77 and 88 were detected in the HIV-1 of >10% of patients with evaluable isolates. The overall incidence of the D30N mutation in the viral protease of evaluable isolates (n=157) from patients receiving nelfinavir monotherapy or nelfinavir in combination with zidovudine and lamivudine or stavudine was 54.8%. The overall incidence of other mutations associated with primary protease inhibitor resistance was 9.6% for the L90M substitution whereas substitutions at 48, 82, or 84 were not observed. Of the 19 clinical isolates for which both phenotypic and genotypic analyses were performed, 9 showed reduced susceptibility (5- to 93-fold) to nelfinavir *in vitro*. All 9 patient isolates possessed one or more mutations in the viral protease gene. Amino acid position 30 appeared to be the most frequent mutation site.

Cross-resistance: Non-clinical Studies- Patient-derived recombinant HIV isolates containing the D30N mutation (n=4) and demonstrating high-level (>10-fold) NFV-resistance remained susceptible (<2.5-fold resistance) to amprenavir, indinavir, lopinavir, and saquinavir, *in vitro*. Patient-derived recombinant HIV isolates containing the L90M mutation (n=8) demonstrated moderate to high-level resistance to NFV and had varying levels of susceptibility to amprenavir, indinavir, lopinavir, and saquinavir, *in vitro*. Most patient-derived recombinant isolates with phenotypic and genotypic evidence of reduced susceptibility (>2.5-fold) to amprenavir, indinavir, lopinavir, and/or saquinavir demonstrated high-level cross-resistance to nelfinavir, *in vitro*. Mutations associated with resistance to other PIs (e.g. G48V, V82A/F/T, I84V, L90M) appeared to confer high-level cross-resistance to NFV. Following ritonavir therapy 6 of 7 clinical isolates with decreased ritonavir susceptibility (8- to 113-fold) *in vitro* compared to baseline also exhibited decreased susceptibility to nelfinavir *in vitro* (5- to 40-fold). Cross-resistance between nelfinavir and reverse transcriptase inhibitors is unlikely because different enzyme targets are involved. Clinical isolates (n=5) with decreased susceptibility to lamivudine, nevirapine or zidovudine remain fully susceptible to nelfinavir *in vitro*.

Clinical Studies- There have been no controlled or comparative studies evaluating the virologic response to subsequent protease inhibitor-containing regimens in patients who have demonstrated loss of virologic response to a nelfinavir-containing regimen. However, virologic response was evaluated in a single-arm prospective study of 26 patients with extensive prior antiretroviral experience with reverse transcriptase inhibitors (mean 2.9) who had received VIRACEPT for a mean duration of 59.7 weeks and were switched to a ritonavir (400 mg BID)/saquinavir hard-gel (400 mg BID) containing regimen after a prolonged period of VIRACEPT failure (median 48 weeks). Sequence analysis of HIV-1 isolates prior to switch demonstrated a D30N or an L90M substitution in 18 and 6 patients, respectively. Subjects remained on therapy for a mean of 48 weeks (range 40 to 56 weeks) where 17 of 26 (65%) subjects and 13 of 26 (50%) subjects were treatment responders with HIV RNA below the assay limit of detection (<500 HIV RNA copies/mL, Chiron bDNA) at 24 and 48 weeks, respectively.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetic properties of nelfinavir were evaluated in healthy volunteers and HIV-infected patients; no substantial differences were observed between the two groups.

Absorption: Pharmacokinetic parameters of nelfinavir (area under the plasma concentration-time curve during a 24-hour period at steady-state [AUC_{24}], peak plasma concentrations [C_{max}], morning and evening trough concentrations [C_{trough}]) from a pharmacokinetic study in HIV-positive patients after multiple dosing with 1250 mg (five 250 mg tablets) twice daily (BID) for 28 days (10 patients) and 750 mg (three 250 mg tablets) three times daily (TID) for 28 days (11 patients) are summarized in Table 1.

Table 1
Summary of a Pharmacokinetic Study in HIV-positive Patients with Multiple Dosing of 1250 mg BID for 28 days and 750 mg TID for 28 days

Regimen	AUC_{24} mg.h/L	C_{max} mg/L	C_{trough} Morning mg/L	C_{trough} Afternoon or Evening mg/L
1250 mg BID	52.8 ± 15.7	4.0 ± 0.8	2.2 ± 1.3	0.7 ± 0.4
750 mg TID	43.6 ± 17.8	3.0 ± 1.6	1.4 ± 0.6	1.0 ± 0.5

data are mean ± SD

The difference between morning and afternoon or evening trough concentrations for the TID and BID regimens was also observed in healthy volunteers who were dosed at precisely 8- or 12-hour intervals.

In healthy volunteers receiving a single 1250 mg dose, the 625 mg tablet was not bioequivalent to the 250 mg tablet formulation. Under fasted conditions (n=27), the AUC and C_{max} were 34% and 24% higher, respectively, for the 625 mg tablets. In a relative bioavailability assessment under fed conditions (n=28), the AUC was 24% higher for the 625 mg tablet; the C_{max} was comparable for both formulations. (See ADVERSE REACTIONS.)

In healthy volunteers receiving a single 750 mg dose under fed conditions, nelfinavir concentrations were similar following administration of the 250 mg tablet and oral powder.

Effect of Food on Oral Absorption: Food increases nelfinavir exposure and decreases nelfinavir pharmacokinetic variability relative to the fasted state. In one study, healthy volunteers received a single dose of 1250 mg of VIRACEPT 250 mg tablets (5 tablets) under fasted or fed conditions (three different meals). In a second study, healthy volunteers received single doses of 1250 mg VIRACEPT (5 x 250 mg tablets) under fasted or fed conditions (two different fat content meals). The results from the two studies are summarized in Table 2 and Table 3, respectively.

Table 2
Increase in AUC, C_{max} and T_{max} for Nelfinavir in Fed State Relative to Fasted State Following 1250 mg VIRACEPT (5 x 250 mg tablets)

Number of Kcal	% Fat	Number of subjects	AUC fold increase	C _{max} fold increase	Increase in T _{max} (hr)
125	20	n=21	2.2	2.0	1.00
500	20	n=22	3.1	2.3	2.00
1000	50	n=23	5.2	3.3	2.00

Table 3
Increase in Nelfinavir AUC, C_{max} and T_{max} in Fed Low Fat (20%) versus High fat (50%) State Relative to Fasted State Following 1250 mg VIRACEPT (5 x 250 mg tablets)

Number of Kcal	% Fat	Number of subjects	AUC fold increase	C _{max} fold increase	Increase in T _{max} (hr)
500	20	n=22	3.1	2.5	1.8
500	50	n=22	5.1	3.8	2.1

Nelfinavir exposure can be increased by increasing the calorie or fat content in meals taken with VIRACEPT.

A food effect study has not been conducted with the 625 mg tablet. However, based on a cross-study comparison (n=26 fed vs. n=26 fasted) following single dose administration of nelfinavir 1250 mg, the magnitude of the food effect for the 625 mg nelfinavir tablet appears comparable to that of the 250 mg tablets. VIRACEPT should be taken with a meal.

Distribution: The apparent volume of distribution following oral administration of nelfinavir was 2-7 L/kg. Nelfinavir in serum is extensively protein-bound (>98%).

Metabolism: Unchanged nelfinavir comprised 82-86% of the total plasma radioactivity after a single oral 750 mg dose of ¹⁴C-nelfinavir. *In vitro*, multiple cytochrome P-450 enzymes including CYP3A and CYP2C19 are responsible for metabolism of nelfinavir. One major and several minor oxidative metabolites were found

in plasma. The major oxidative metabolite has *in vitro* antiviral activity comparable to the parent drug.

Elimination: The terminal half-life in plasma was typically 3.5 to 5 hours. The majority (87%) of an oral 750 mg dose containing ¹⁴C-nelfinavir was recovered in the feces; fecal radioactivity consisted of numerous oxidative metabolites (78%) and unchanged nelfinavir (22%). Only 1-2% of the dose was recovered in urine, of which unchanged nelfinavir was the major component.

Special Populations

Hepatic Insufficiency: The multi-dose pharmacokinetics of nelfinavir have not been studied in HIV-positive patients with hepatic insufficiency.

Renal Insufficiency: The pharmacokinetics of nelfinavir have not been studied in patients with renal insufficiency; however, less than 2% of nelfinavir is excreted in the urine, so the impact of renal impairment on nelfinavir elimination should be minimal.

Gender and Race: No significant pharmacokinetic differences have been detected between males and females. Pharmacokinetic differences due to race have not been evaluated.

Pediatrics: The pharmacokinetics of nelfinavir have been investigated in 5 studies in pediatric patients from birth to 13 years of age either receiving VIRACEPT three times or twice daily. The dosing regimens and associated AUC₂₄ values are summarized in Table 4.

Table 4
Summary of Steady-state AUC₂₄ of Nelfinavir in Pediatric Studies

Protocol no.	Dosing regimen ¹	N ²	Age	AUC ₂₄ (mg.hr/L) arithmetic mean ± SD
AG1343-524	20 (19-28) mg/kg TID	14	2-13 years	56.1 ± 29.8
PACTG-725	55 (48-60) mg/kg BID	6	3-11 years	101.8 ± 56.1
PENTA 7	40 (34-43) mg/kg TID	4	2-9 months	33.8 ± 8.9
PENTA 7	75 (55-83) mg/kg BID	12	2-9 months	37.2 ± 19.2
PACTG-353	40 (14-56) mg/kg BID	10	6 weeks	44.1 ± 27.4
			1 week	45.8 ± 32.1

¹ Protocol specified dose (actual dose range)

² N: number of subjects with evaluable pharmacokinetic results

C_{trough} values are not presented in the table because they are not available for all studies

Pharmacokinetic data are also available for 86 patients (age 2 to 12 years) who received VIRACEPT 25-35 mg/kg TID in Study AG1343-556. The pharmacokinetic data from Study AG1343-556 were more variable than data from other studies conducted in the pediatric population; the 95% confidence interval for AUC₂₄ was 9 to 121 mg.hr/L.

Overall, use of VIRACEPT in the pediatric population is associated with highly variable drug exposure. The high variability may be due to inconsistent food intake in pediatric patients. (See PRECAUTIONS: Pediatric Use, DOSAGE AND ADMINISTRATION.)

Geriatric Patients: The pharmacokinetics of nelfinavir have not been studied in patients over 65 years of age.

Drug Interactions (also see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions)

CYP3A and CYP2C19 appear to be the predominant enzymes that metabolize nelfinavir in humans. The potential ability of nelfinavir to inhibit the major human cytochrome P450 enzymes (CYP3A, CYP2C19, CYP2D6, CYP2C9, CYP1A2 and CYP2E1) has been investigated *in vitro*. Only CYP3A was inhibited at concentrations in the therapeutic range. Specific drug interaction studies were performed with nelfinavir and a number of drugs. Table 5 summarizes the effects of nelfinavir on the geometric mean AUC, C_{max} and C_{min} of coadministered drugs. Table 6 shows the effects of coadministered drugs on the geometric mean AUC, C_{max} and C_{min} of nelfinavir.

**Table 5: Drug Interactions:
Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence
of VIRACEPT**

Coadministered Drug	Nelfinavir Dose	N	% Change of Coadministered Drug Pharmacokinetic Parameters ¹ (90% CI)		
			AUC	C _{max}	C _{min}
HIV-Protease Inhibitors					
Indinavir 800 mg Single Dose	750 mg q8h x 7 days	6	↑51% (↑29-↑77%)	↓10% (↓28-↑13%)	NA
Ritonavir 500 mg Single Dose	750 mg q8h x 5 doses	10	↔	↔	NA
Saquinavir 1200 mg Single Dose ²	750 mg tid x 4 days	14	↑392% (↑291-↑521%)	↑179% (↑117-↑259%)	NA
Amprenavir 800 mg tid x 14 days	750 mg tid x 14 days	6	↔	↓14% (↓38-↑20%)	↑189% (↑52-↑448%)
Nucleoside Reverse Transcriptase Inhibitors					
Lamivudine 150 mg Single Dose	750 mg q8h x 7-10 days	11	↑10% (↑2-↑18%)	↑31% (↑9-↑56%)	NA
Stavudine 30-40 mg bid x 56 days	750 mg tid x 56 days	8	See footnote ³		
Zidovudine 200 mg Single Dose	750 mg q8h x 7-10 days	11	↓35% (↓29-↓40%)	↓31% (↓13-↓46%)	NA
Non-Nucleoside Reverse Transcriptase Inhibitors					
Efavirenz 600 mg qd x 7 days	750 mg q8h x 7 days	10	↓12% (↓31-↑12%)	↓12% (↓29-↑8%)	↓22% (↓54-↑32%)
Nevirapine 200 mg qd x 14 days ³ Followed by 200 mg bid x 14 days	750 mg tid x 36 days	23	See footnote ³		
Delavirdine 400 mg q8h x 14 days	750 mg q8h x 7 days	7	↓31% (↓57-↑10%)	↓27% (↓49-↑4%)	↓33% (↓70-↑49%)
Anti-infective Agents					
Rifabutin 150 mg qd x 8 days ⁴	750 mg q8h x 7-8 days ⁵	12	↑83% (↑72-↑96%)	↑19% (↑11-↑28%)	↑177% (↑144-↑215%)
Rifabutin 300 mg qd x 8 days	750 mg q8h x 7-8 days	10	↑207% (↑161-↑263%)	↑146% (↑118-↑178%)	↑305% (↑245-↑375%)
Azithromycin 1200 mg Single Dose	750 mg tid x 11 days	12	↑112% (↑80-↑150%)	↑136% (↑77-↑215%)	NA

HMG-CoA Reductase Inhibitors					
Atorvastatin 10 mg qd x 28 days	1250 mg bid x 14 days	15	↑74% (↑41-↑116%)	↑122% (↑68-↑193%)	↑39% (↓21-↑145%)
Simvastatin 20 mg qd x 28 days	1250 mg bid x 14 days	16	↑505% (↑393-↑643%)	↑517% (↑367-↑715%)	ND
Other Agents					
Ethinyl estradiol 35 µg qd x 15 days	750 mg q8h x 7 days	12	↓47% (↓42-↓52%)	↓28% (↓16-↓37%)	↓62% (↓57-↓67%)
Norethindrone 0.4 mg qd x 15 days	750 mg q8h x 7 days	12	↓18% (↓13-↓23%)	↔	↓46% (↓38-↓53%)
Methadone 80 mg +/- 21 mg qd ⁶ > 1 month	1250 mg bid x 8 days	13	↓47% (↓42-↓51%)	↓46% (↓42-↓49%)	↓53% (↓49-↓57%)
Phenytoin 300 mg qd x 14 days ⁷	1250 mg bid x 7 days	12	↓29% (↓17-↓39%)	↓21% (↓12-↓29%)	↓39% (↓27-↓49%)

NA: Not relevant for single-dose treatment; ND: Cannot be determined

¹ ↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change (geometric mean exposure increased or decreased < 10%)

² Using the soft-gelatin capsule formulation of saquinavir 1200 mg

³ Based on non-definitive cross-study comparison, drug plasma concentrations appeared to be unaffected by coadministration

⁴ Rifabutin 150 mg qd changes are relative to Rifabutin 300 mg qd x 8 days without coadministration with nelfinavir

⁵ Comparable changes in rifabutin concentrations were observed with VIRACEPT 1250 mg q12h x 7 days

⁶ Changes are reported for total plasma methadone; changes for the individual R-enantiomer and S-enantiomer were similar

⁷ Phenytoin exposure measures are reported for total phenytoin exposure. The effect of nelfinavir on unbound phenytoin was similar

**Table 6: Drug Interactions:
Changes in Pharmacokinetic Parameters for Nelfinavir in the Presence of the
Coadministered Drug**

Coadministered Drug	Nelfinavir Dose	N	% Change of Nelfinavir Pharmacokinetic Parameters ¹ (90% CI)		
			AUC	C _{max}	C _{min}
HIV-Protease Inhibitors					
Indinavir 800 mg q8h x 7 days	750 mg Single Dose	6	↑83% (↑42-↑137%)	↑31% (↑16-↑48%)	NA
Ritonavir 500 mg q12h x 3 doses	750 mg Single Dose	10	↑152% (↑96-↑224%)	↑44% (↑28-↑63%)	NA
Saquinavir 1200 mg tid x 4 days ²	750 mg Single Dose	14	↑18% (↑7-↑30%)	↔	NA
Amprenavir 800 mg tid x 14 days	750 mg tid x 14 days	6	See footnote ³		
Nucleoside Reverse Transcriptase Inhibitors					
Didanosine 200 mg Single Dose	750 mg Single Dose	9	↔	↔	NA
Zidovudine 200 mg + Lamivudine 150 mg Single Dose	750 mg q8h x 7-10 days	11	↔	↔	↔
Non-Nucleoside Reverse Transcriptase Inhibitors					
Efavirenz 600 mg qd x 7 days	750 mg q8h x 7 days	7	↑20% (↑8-↑34%)	↑21% (↑10-↑33%)	↔
Nevirapine 200 mg qd x 14 days Followed by 200 mg bid x 14 days	750 mg tid x 36 days	23	↔	↔	↓32% (↓50-↑5%)
Delavirdine 400 mg q8h x 7 days	750 mg q8h x 14 days	12	↑107% (↑83-↑135%)	↑88% (↑66-↑113%)	↑136% (↑103-↑175%)
Anti-infective Agents					
Ketoconazole 400 mg qd x 7 days	500 mg q8h x 5-6 days	12	↑35% (↑24-↑46%)	↑25% (↑11-↑40%)	↑14% (↓23-↑69%)
Rifabutin 150 mg qd x 8 days	750 mg q8h x 7-8 days	11	↓23% (↓14-↓31%)	↓18% (↓8-↓27%)	↓25% (↓8-↓39%)
	1250 mg q12h x 7-8 days	11	↔	↔	↓15% (↓43-↑27%)
Rifabutin 300 mg qd x 8 days	750 mg q8h x 7-8 days	10	↓32% (↓15-↓46%)	↓24% (↓10-↓36%)	↓53% (↓15-↓73%)
Rifampin 600 mg qd x 7 days	750 mg q8h x 5-6 days	12	↓83% (↓79-↓86%)	↓76% (↓69-↓82%)	↓92% (↓86-↓95%)
Azithromycin 1200 mg Single Dose	750 mg tid x 9 days	12	↓15% (↓7-↓22%)	↓10% (↓19-↑1%)	↓29% (↓19-↓38%)

HMG-CoA Reductase Inhibitors					
Atorvastatin 10 mg qd x 28 days	1250 mg bid x 14 days	15	See footnote ³		
Simvastatin 20 mg qd x 28 days	1250 mg bid x 14 days	16	See footnote ³		
Other Agents					
Methadone 80 mg +/- 21 mg qd > 1 month	1250 mg bid x 8 days	13	See footnote ³		
Phenytoin 300 mg qd x 7 days	1250 mg bid x 14 days	15	↔	↔	↓18% (↓45-↑23%)

NA: Not relevant for single-dose treatment

¹ ↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change (geometric mean exposure increased or decreased < 10%)

² Using the soft-gelatin capsule formulation of saquinavir 1200 mg

³ Based on non-definitive cross-study comparison, nelfinavir plasma concentrations appeared to be unaffected by coadministration

For information regarding clinical recommendations see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions.

INDICATIONS AND USAGE

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

Description of Studies

In the clinical studies described below, efficacy was evaluated by the percent of patients with plasma HIV RNA < 400 copies/mL (Studies 511 and 542) or < 500 copies/mL (Study ACTG 364), using the Roche RT-PCR (Amplicor) HIV-1 Monitor or < 50 copies/mL, using the Roche HIV-1 Ultrasensitive assay (Study Avanti 3). In the analysis presented in each figure, patients who terminated the study early for any reason, switched therapy due to inadequate efficacy or who had a missing HIV-RNA measurement that was either preceded or followed by a measurement above the limit of assay quantification were considered to have HIV-RNA above 400 copies/mL, above 500 copies/mL, or above 50 copies/mL at subsequent time points, depending on the assay that was used.

a. Studies in Antiretroviral Treatment Naïve Patients

Study 511: VIRACEPT + zidovudine + lamivudine versus zidovudine + lamivudine

Study 511 was a double-blind, randomized, placebo controlled trial comparing treatment with zidovudine (ZDV; 200 mg TID) and lamivudine (3TC; 150 mg BID) plus 2 doses of VIRACEPT (750 mg and 500 mg TID) to zidovudine (200 mg TID) and lamivudine (150 mg BID) alone in 297 antiretroviral naive HIV-1 infected patients (median age 35 years [range 21 to 63], 89% male and 78% Caucasian). Mean baseline CD4 cell count was 288 cells/mm³ and mean baseline plasma HIV RNA was 5.21 log₁₀ copies/mL (160,394 copies/mL). The percent of patients with plasma HIV RNA < 400 copies/mL and mean changes in CD4 cell count are summarized in Figures 1 and 2, respectively.

Figure 1

Study 511: Percentage of Patients With HIV RNA Below 400 Copies/mL

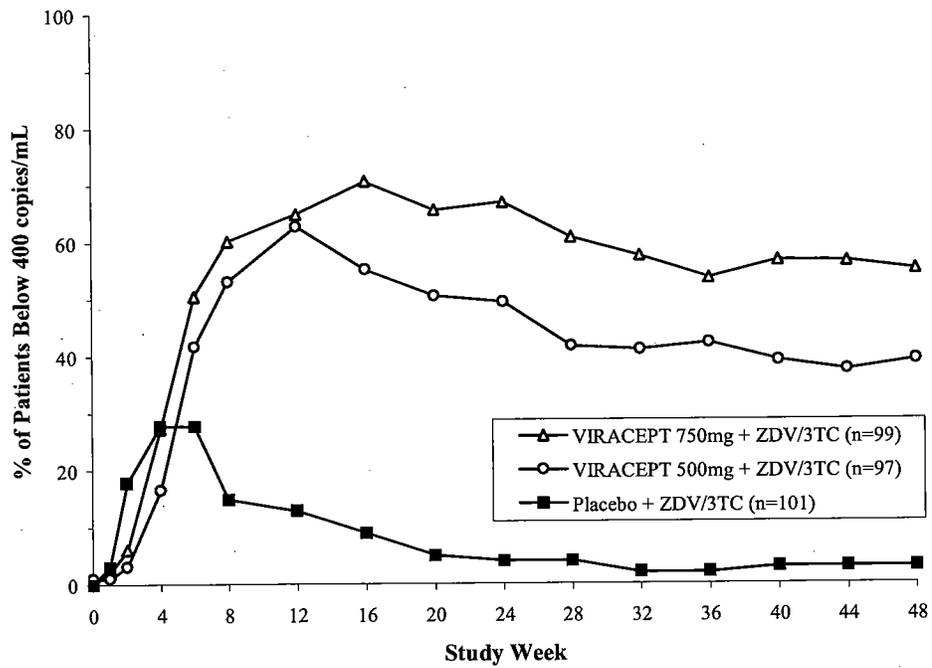
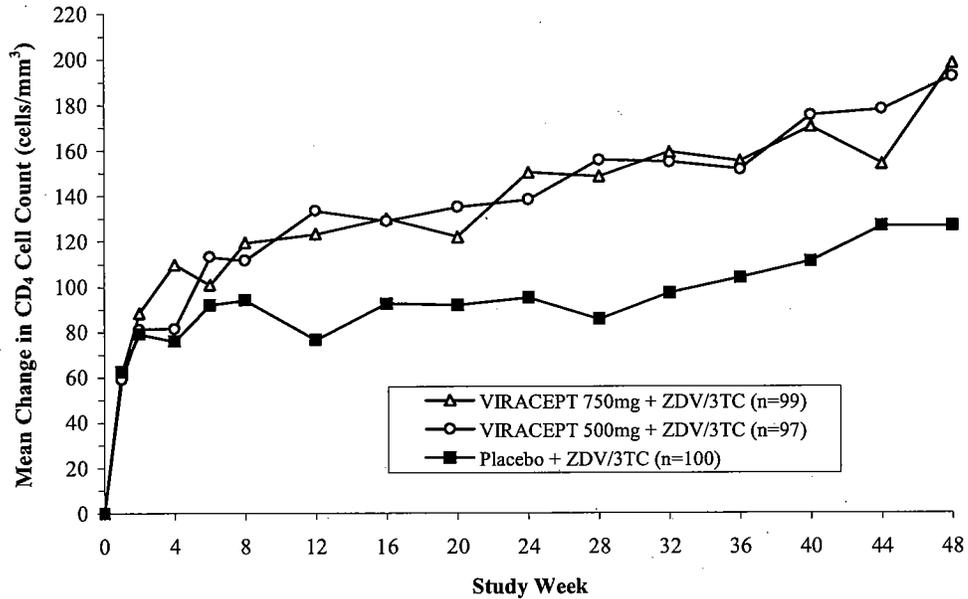


Figure 2

Study 511: Mean Change From Baseline in CD₄ Cell Counts



Study 542: VIRACEPT BID + stavudine + lamivudine compared to VIRACEPT TID + stavudine + lamivudine

Study 542 is an ongoing, randomized, open-label trial comparing the HIV RNA suppression achieved by VIRACEPT 1250 mg BID versus VIRACEPT 750 mg TID in patients also receiving stavudine (d4T; 30-40 mg BID) and lamivudine (3TC; 150 mg BID). Patients had a median age of 36 years (range 18 to 83), were 84% male, and were 91% Caucasian. Patients had received less than 6 months of therapy with nucleoside transcriptase inhibitors and were naïve to protease inhibitors. Mean baseline CD4 cell count was 296 cells/mm³ and mean baseline plasma HIV RNA was 5.0 log₁₀ copies/mL (100,706 copies/mL).

Results showed that there was no significant difference in mean CD4 cell count among treatment groups; the mean increases from baseline for the BID and TID arms were 150 cells/mm³ at 24 weeks and approximately 200 cells/mm³ at 48 weeks.

The percent of patients with HIV RNA < 400 copies/mL is summarized in Figure 3. The outcomes of patients through 48 weeks of treatment are summarized in Table 7.

Figure 3

Study 542: Percentage of Patients With HIV RNA Below 400 Copies/mL

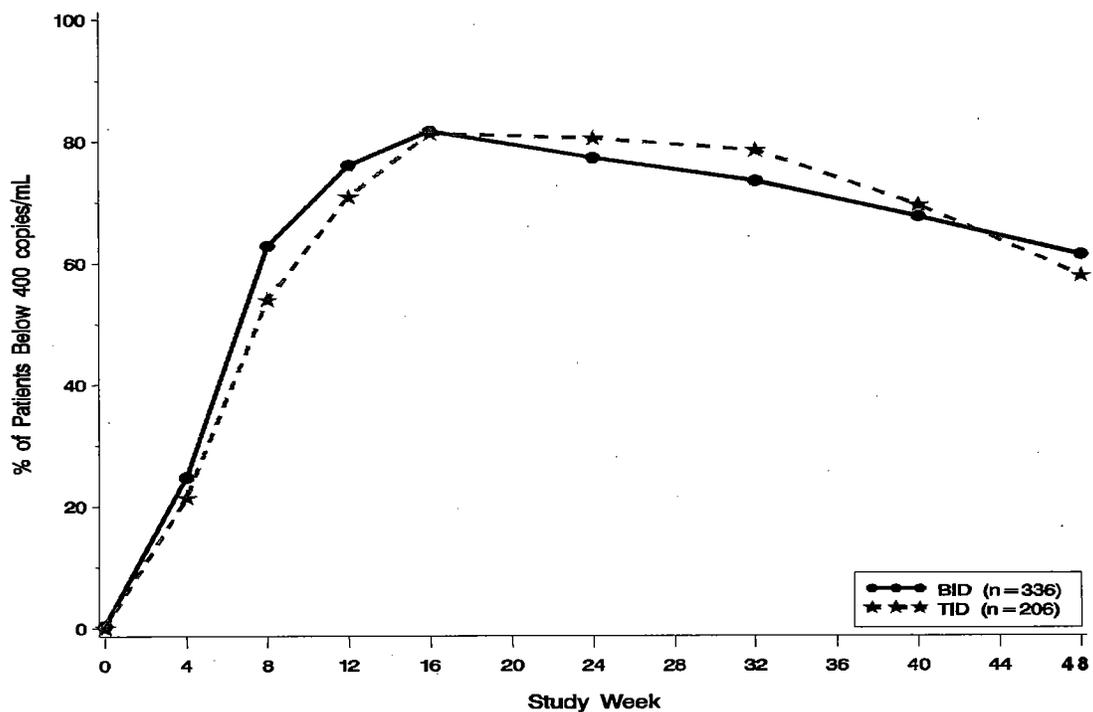


Table 7
Outcomes of Randomized Treatment Through 48 Weeks

Outcome	VIRACEPT 1250 mg BID Regimen	VIRACEPT 750 mg TID Regimen
Number of patients evaluable*	323	192
HIV RNA < 400 copies/mL	198 (61%)	111 (58%)
HIV RNA ≥ 400 copies/mL	46 (14%)	22 (11%)
Discontinued due to VIRACEPT toxicity**	9 (3%)	2 (1%)
Discontinued due to other antiretroviral agents' toxicity**	3 (1%)	3 (2%)
Others***	67 (21%)	54 (28%)

*Twelve patients in the BID arm and fourteen patients in the TID arm had not yet reached 48 weeks of therapy.

**These rates only reflect dose-limiting toxicities that were counted as the initial reason for treatment failure in the analysis (see ADVERSE REACTIONS for a description of the safety profile of these regimens).

***Consent withdrawn, lost to follow-up, intercurrent illness, noncompliance or missing data; all assumed as failures.

Study Avanti 3: VIRACEPT TID + zidovudine + lamivudine compared to zidovudine + lamivudine

Study Avanti 3 was a placebo-controlled, randomized, double-blind study designed to evaluate the safety and efficacy of VIRACEPT (750 mg TID) in combination with zidovudine (ZDV; 300 mg BID) and lamivudine (3TC; 150 mg BID) (n=53) versus placebo in combination with ZDV and 3TC (n=52) administered to antiretroviral-naive patients with HIV infection and a CD4 cell count between 150 and 500 cells/μL. Patients had a mean age of 35 (range 22-59), were 89% male, and 88% Caucasian. Mean baseline CD4 cell count was 304 cells/mm³ and mean baseline plasma HIV RNA was 4.8 log₁₀ copies/mL (57,887 copies/mL). The percent of patients with plasma HIV RNA < 50 copies/mL at 52 weeks was 54% for the VIRACEPT + ZDV + 3TC treatment group and 13% for the ZDV + 3TC treatment group.

b. Studies in Antiretroviral Treatment Experienced Patients

Study ACTG 364: VIRACEPT TID + 2NRTIs compared to efavirenz + 2NRTIs compared to VIRACEPT + efavirenz + 2NRTIs

Study ACTG 364 was a randomized, double-blind study that evaluated the combination of VIRACEPT 750 mg TID and/or efavirenz 600 mg QD with 2 NRTIs (either didanosine [ddI] + d4T, ddI + 3TC, or d4T + 3TC) in patients with prolonged prior nucleoside exposure who had completed 2 previous ACTG studies. Patients had a mean age of 41 years (range 18 to 75), were 88% male, and were 74% Caucasian. Mean baseline CD4 cell count was 389 cells/mm³ and mean baseline plasma HIV RNA was 3.9 log₁₀ copies/mL (7,954 copies/mL).

The percent of patients with plasma HIV RNA < 500 copies/mL at 48 weeks was 42%, 62%, and 72% for the VIRACEPT (n=66), EFV (n=65), and VIRACEPT + EFV (n=64) treatment groups, respectively. The 4-drug combination of VIRACEPT + EFV + 2 NRTIs was more effective in suppressing plasma HIV RNA in these patients than either 3-drug regimen.

CONTRAINDICATIONS

VIRACEPT is contraindicated in patients with clinically significant hypersensitivity to any of its components.

Coadministration of VIRACEPT is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 8.

Table 8
Drugs That Are Contraindicated With VIRACEPT

Drug Class	Drugs Within Class That Are Contraindicated With VIRACEPT
Antiarrhythmics	Amiodarone, Quinidine
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine
Neuroleptic	Pimozide
Sedative/Hypnotics	Midazolam, Triazolam

WARNINGS

ALERT: Find out about medicines that should not be taken with VIRACEPT. This statement is included on the product's bottle label.

Drug Interactions (also see PRECAUTIONS)

Nelfinavir is an inhibitor of the CYP3A enzyme. Coadministration of VIRACEPT and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects. Caution should be exercised when inhibitors of CYP3A, including VIRACEPT, are coadministered with drugs that are metabolized by CYP3A and that prolong the QT interval. (See ADVERSE REACTIONS: Post-Marketing Experience.) Nelfinavir is metabolized by CYP3A and CYP2C19. Coadministration of VIRACEPT and drugs that induce CYP3A

or CYP2C19 may decrease nelfinavir plasma concentrations and reduce its therapeutic effect. Coadministration of VIRACEPT and drugs that inhibit CYP3A or CYP2C19 may increase nelfinavir plasma concentrations. (Also see **PRECAUTIONS: Table 9: Drugs That Should Not Be Coadministered With VIRACEPT, Table 10: Established and Other Potentially Significant Drug Interactions.**)

Concomitant use of VIRACEPT with lovastatin or simvastatin is not recommended. 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 5 and 6: Drug Interactions**). The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including VIRACEPT, are used in combination with these drugs.

Particular caution should be used when prescribing sildenafil in patients receiving protease inhibitors, including VIRACEPT. Coadministration of a protease inhibitor with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism. (See **PRECAUTIONS, Drug Interactions and Information for Patients, and the complete prescribing information for sildenafil.**)

Concomitant use of St. John's wort (*hypericum perforatum*) or St. John's wort containing products and VIRACEPT is not recommended. Coadministration of St. John's wort with protease inhibitors, including VIRACEPT, is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of VIRACEPT and lead to loss of virologic response and possible resistance to VIRACEPT or to the class of protease inhibitors.

Patients with Phenylketonuria

Patients with Phenylketonuria: VIRACEPT Oral Powder contains 11.2 mg phenylalanine per gram of powder.

Diabetes mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

PRECAUTIONS

General

Nelfinavir is principally metabolized by the liver. Therefore, caution should be exercised when administering this drug to patients with hepatic impairment.

Resistance/Cross Resistance

HIV cross-resistance between protease inhibitors has been observed. (See MICROBIOLOGY.)

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has not been established.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome

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.

Information For Patients

"A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with VIRACEPT.** A Patient Package Insert (PPI) for VIRACEPT is available for patient information."

For optimal absorption, patients should be advised to take VIRACEPT with food (see CLINICAL PHARMACOLOGY: Pharmacokinetics and DOSAGE AND ADMINISTRATION).

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.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should be advised to take VIRACEPT and other concomitant antiretroviral therapy every day as

prescribed. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of VIRACEPT is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

Patients should be informed that VIRACEPT Tablets are film-coated and that this film-coating is intended to make the tablets easier to swallow.

The most frequent adverse event associated with VIRACEPT is diarrhea, which can usually be controlled with non-prescription drugs, such as loperamide, which slow gastrointestinal motility.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time.

VIRACEPT may interact with some drugs, therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Patients receiving oral contraceptives should be instructed that alternate or additional contraceptive measures should be used during therapy with VIRACEPT.

Patients receiving sildenafil and nelfinavir should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and prolonged penile erection, and should promptly report any symptoms to their doctor.

Drug Interactions (Also see CONTRAINDICATIONS, WARNINGS, CLINICAL PHARMACOLOGY: Drug Interactions)

Nelfinavir is an inhibitor of CYP3A. Coadministration of VIRACEPT and drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and sildenafil) may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse effects. (See Tables 9 and 10). Nelfinavir is metabolized by CYP3A and CYP2C19. Coadministration of VIRACEPT and drugs that induce CYP3A or CYP2C19, such as rifampin, may decrease nelfinavir plasma concentrations and reduce its therapeutic effect. Coadministration of VIRACEPT and drugs that inhibit CYP3A or CYP2C19 may increase nelfinavir plasma concentrations.

Drug interaction studies reveal no clinically significant drug interactions between nelfinavir and didanosine, lamivudine, stavudine, zidovudine, efavirenz, nevirapine, or ketoconazole and no dose adjustments are needed. In the case of didanosine, it is recommended that didanosine be administered on an empty stomach; therefore, nelfinavir should be administered with food one hour after or more than 2 hours before didanosine.

Based on known metabolic profiles, clinically significant drug interactions are not expected between VIRACEPT and dapsone, trimethoprim/sulfamethoxazole, or itraconazole.

Table 9
Drugs That Should Not Be Coadministered
With VIRACEPT

Drug Class: Drug Name	Clinical Comment
Antiarrhythmics: amiodarone, quinidine	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	May lead to loss of virologic response and possible resistance to VIRACEPT or other coadministered antiretroviral agents.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to VIRACEPT or other coadministered antiretroviral agents.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as prolonged or increased sedation or respiratory depression.

<p align="center">Table 10 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies (see CLINICAL PHARMACOLOGY, for Magnitude of Interaction, Tables 5 and 6)</p>		
Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
HIV-Antiviral Agents		
Protease Inhibitors: indinavir ritonavir saquinavir	↑ nelfinavir ↑ indinavir ↑ nelfinavir ↑ saquinavir	Appropriate doses for these combinations, with respect to safety and efficacy, have not been established.
Non-nucleoside Reverse Transcriptase Inhibitors: delavirdine nevirapine	↑ nelfinavir ↓ delavirdine ↓ nelfinavir (C _{min})	Appropriate doses for these combinations, with respect to safety and efficacy, have not been established.
Nucleoside Reverse Transcriptase Inhibitor: didanosine		It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after VIRACEPT (given with food).
Other Agents		
Anti-Convulsants: carbamazepine phenobarbital	↓ nelfinavir	May decrease nelfinavir plasma concentrations. VIRACEPT may not be effective due to decreased nelfinavir plasma concentrations in patients taking these agents concomitantly.
Anti-Convulsant: phenytoin	↓ phenytoin	Phenytoin plasma/serum concentrations should be monitored; phenytoin dose may require adjustment to compensate for altered phenytoin concentration.

Anti-Mycobacterial: rifabutin	↑ rifabutin ↓ nelfinavir (750 mg TID) ↔ nelfinavir (1250 mg BID)	It is recommended that the dose of rifabutin be reduced to one-half the usual dose when administered with VIRACEPT; 1250 mg BID is the preferred dose of VIRACEPT when coadministered with rifabutin.
Erectile Dysfunction Agent: sildenafil	↑ sildenafil	Sildenafil should not exceed a maximum single dose of 25 mg in a 48 hour period.
HMG-CoA Reductase Inhibitor: atorvastatin	↑ atorvastatin	Use lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with VIRACEPT.
Immuno-suppressants: cyclosporine tacrolimus sirolimus	↑ immuno-suppressants	Plasma concentrations may be increased by VIRACEPT.
Narcotic Analgesic: methadone	↓ methadone	Dosage of methadone may need to be increased when coadministered with VIRACEPT.
Oral Contraceptive: ethinyl estradiol	↓ ethinyl estradiol	Alternative or additional contraceptive measures should be used when oral contraceptives and VIRACEPT are coadministered.
Macrolide Antibiotic: azithromycin	↑ azithromycin	Dose adjustment of azithromycin is not recommended, but close monitoring for known side effects such as liver enzyme abnormalities and hearing impairment is warranted.
Inhaled/nasal steroid: Fluticasone	↑ fluticasone	Concomitant use of fluticasone propionate and VIRACEPT may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.
Antidepressant: trazodone	↑ trazodone	Concomitant use of trazodone and VIRACEPT may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as VIRACEPT, the combination should be used with caution and a lower dose of trazodone should be considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies in mice and rats were conducted with nelfinavir at oral doses up to 1000 mg/kg/day. No evidence of a tumorigenic effect was noted in mice at systemic exposures (C_{max}) up to 9-fold those measured in humans at the recommended therapeutic dose (750 mg TID or 1250 mg BID). In rats, thyroid follicular cell adenomas and carcinomas were increased in males at 300 mg/kg/day and higher and in females at 1000 mg/kg/day. Systemic exposures (C_{max}) at 300 and 1000 mg/kg/day were 1- to 3-fold, respectively, those measured in humans at the recommended therapeutic dose. Repeated administration of nelfinavir to rats produced effects consistent with hepatic microsomal enzyme induction and increased thyroid hormone deposition; these effects predispose rats, but not humans, to thyroid follicular cell neoplasms. Nelfinavir showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* genetic toxicology assays. These studies included bacterial mutation assays in *S. typhimurium* and *E. coli*, a mouse lymphoma tyrosine kinase assay, a chromosomal aberration assay in human lymphocytes, and an *in vivo* mouse bone marrow micronucleus assay.

Nelfinavir produced no effects on either male or female mating and fertility or embryo survival in rats at systemic exposures comparable to the human therapeutic exposure.

Pregnancy - Pregnancy Category B

There were no effects on fetal development or maternal toxicity when nelfinavir was administered to pregnant rats at systemic exposures (AUC) comparable to human exposure. Administration of nelfinavir to pregnant rabbits resulted in no fetal development effects up to a dose at which a slight decrease in maternal body weight was observed; however, even at the highest dose evaluated, systemic exposure in rabbits was significantly lower than human exposure. Additional studies in rats indicated that exposure to nelfinavir in females from mid-pregnancy through lactation had no effect on the survival, growth, and development of the offspring to weaning. Subsequent reproductive performance of these offspring was also not affected by maternal exposure to nelfinavir. However, there are no adequate and well-controlled studies in pregnant women taking VIRACEPT. Because animal reproduction studies are not always predictive of human response, VIRACEPT should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: (APR): To monitor maternal-fetal outcomes of pregnant women exposed to VIRACEPT and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling (800) 258-4263.

Nursing Mothers

The Centers for Disease Control and Prevention recommends that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats have demonstrated that nelfinavir is excreted in milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in

nursing infants, **mothers should be instructed not to breast-feed if they are receiving VIRACEPT.**

Pediatric Use

The safety and effectiveness of VIRACEPT have been established in patients from 2 to 13 years of age. The use of VIRACEPT in these age groups is supported by evidence from adequate and well-controlled studies of VIRACEPT in adults and pharmacokinetic studies and studies supporting activity in pediatric patients. In patients less than 2 years of age, VIRACEPT was found to be safe at the doses studied, but a reliably effective dose could not be established (see CLINICAL PHARMACOLOGY: Special Populations, ADVERSE REACTIONS: Pediatric Population, and DOSAGE AND ADMINISTRATION: Pediatric Patients).

The following issues should be considered when initiating VIRACEPT in pediatric patients:

- In pediatric patients ≥ 2 years of age receiving VIRACEPT as part of triple combination antiretroviral therapy in randomized studies, the proportion of patients achieving a HIV RNA level <400 copies/mL through 48 weeks ranged from 26% to 42%.
- Response rates in children <2 years of age appeared to be poorer than those in patients ≥ 2 years of age in some studies.
- Highly variable drug exposure remains a significant problem in the use of VIRACEPT in pediatric patients. Unpredictable drug exposure may be exacerbated in pediatric patients because of increased clearance compared to adults and difficulties with compliance and adequate food intake with dosing. Pharmacokinetic results from the pediatric studies are reported in Table 4 (see CLINICAL PHARMACOLOGY, Special Populations).

Study 556 was a randomized, double-blind, placebo-controlled trial with VIRACEPT or placebo coadministered with ZDV and ddI in 141 HIV-positive children who had received minimal antiretroviral therapy. The mean age of the children was 3.9 years. Ninety four (67%) children were between 2-12 years, and 47 (33%) were < 2 years of age. The mean baseline HIV RNA value was 5.0 log for all patients and the mean CD4 cell count was 886 cells/mm³ for all patients. The efficacy of VIRACEPT measured by HIV RNA <400 at 48 weeks in children ≥ 2 years of age was 26% compared to 2% of placebo patients ($p=0.0008$). In the children < 2 years of age, only 1 of 27 and 2 of 20 maintained an undetectable HIV RNA level at 48 weeks for placebo and VIRACEPT patients, respectively.

PACTG 377 was an open-label study that randomized 181 HIV treatment-experienced pediatric patients to receive: d4T+NVP+RTV, d4T+3TC+NFV, or d4T+3TC+NVP+NFV

with NFV given on a TID schedule. The median age was 5.9 years and 46% were male. At baseline the median HIV RNA was 4.4 log and median CD4 cell count was 690 cells/mm³. Substudy PACTG 725 evaluated d4T+3TC+NFV with NFV given on a BID schedule. The proportion of patients with detectable viral load at baseline achieving HIV RNA <400 copies/mL at 48 weeks was: 41% for d4T+NVP+RTV, 42% for d4T+3TC+NFV, 30% for d4T+NVP+NFV, and 52% for d4T+3TC+NVP+NFV. No significant clinical differences were identified between patients receiving VIRACEPT in BID or TID schedules.

VIRACEPT has been evaluated in 2 studies of young infants. The PENTA 7 study was an open-label study to evaluate the toxicity, tolerability, pharmacokinetics, and activity of NFV+d4T+ddI in 20 HIV-infected infants less than 12 weeks of age. PACTG 353 evaluated the pharmacokinetics and safety of VIRACEPT in infants born to HIV-infected women receiving NFV as part of combination therapy during pregnancy.

Geriatric Use

Clinical studies of VIRACEPT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

The safety of VIRACEPT was studied in over 5000 patients who received drug either alone or in combination with nucleoside analogues. The majority of adverse events were of mild intensity. The most frequently reported adverse event among patients receiving VIRACEPT was diarrhea, which was generally of mild to moderate intensity. The frequency of nelfinavir-associated diarrhea may be increased in patients receiving the 625 mg tablet because of the increased bioavailability of this formulation.

Drug-related clinical adverse experiences of moderate or severe intensity in $\geq 2\%$ of patients treated with VIRACEPT coadministered with d4T and 3TC (Study 542) for up to 48 weeks or with ZDV plus 3TC (Study 511) for up to 24 weeks are presented in Table 11.

Table 11**Percentage of Patients with Treatment-Emergent¹ Adverse Events of Moderate or Severe Intensity Reported in > 2% of Patients**

Adverse Events	Study 511 24 weeks			Study 542 48 weeks	
	Placebo + ZDV/3TC (n=101)	500 mg TID VIRACEPT + ZDV/3TC (n=97)	750 mg TID VIRACEPT + ZDV/3TC (n=100)	1250 mg BID VIRACEPT + d4T/3TC (n=344)	750 mg TID VIRACEPT + d4T/3TC (n=210)
Digestive System					
Diarrhea	3%	14%	20%	20%	15%
Nausea	4%	3%	7%	3%	3%
Flatulence	0	5%	2%	1%	1%
Skin/Appendages					
Rash	1%	1%	3%	2%	1%

¹ Includes those adverse events at least possibly related to study drug or of unknown relationship and excludes concurrent HIV conditions

Adverse events occurring in less than 2% of patients receiving VIRACEPT in all phase II/III clinical trials and considered at least possibly related or of unknown relationship to treatment and of at least moderate severity are listed below.

Body as a Whole: abdominal pain, accidental injury, allergic reaction, asthenia, back pain, fever, headache, malaise, pain, and redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).

Digestive System: anorexia, dyspepsia, epigastric pain, gastrointestinal bleeding, hepatitis, mouth ulceration, pancreatitis and vomiting.

Hemic/Lymphatic System: anemia, leukopenia and thrombocytopenia.

Metabolic/Nutritional System: increases in alkaline phosphatase, amylase, creatine phosphokinase, lactic dehydrogenase, SGOT, SGPT and gamma glutamyl transpeptidase; hyperlipemia, hyperuricemia, hyperglycemia, hypoglycemia, dehydration, and liver function tests abnormal.

Musculoskeletal System: arthralgia, arthritis, cramps, myalgia, myasthenia and myopathy.

Nervous System: anxiety, depression, dizziness, emotional lability, hyperkinesia, insomnia, migraine, paresthesia, seizures, sleep disorder, somnolence and suicide ideation.

Respiratory System: dyspnea, pharyngitis, rhinitis, and sinusitis.

Skin/Appendages: dermatitis, folliculitis, fungal dermatitis, maculopapular rash, pruritus, sweating, and urticaria.

Special Senses: acute iritis and eye disorder.

Urogenital System: kidney calculus, sexual dysfunction and urine abnormality.

Post-Marketing Experience

The following additional adverse experiences have been reported from postmarketing surveillance as at least possibly related or of unknown relationship to VIRACEPT:

Body as a Whole: hypersensitivity reactions (including bronchospasm, moderate to severe rash, fever and edema).

Cardiovascular System: QTc prolongation, torsades de pointes.

Digestive System: jaundice.

Metabolic/Nutritional System: bilirubinemia, metabolic acidosis.

Laboratory Abnormalities

The percentage of patients with marked laboratory abnormalities in Studies 542 and 511 are presented in Table 12. Marked laboratory abnormalities are defined as a Grade 3 or 4 abnormality in a patient with a normal baseline value or a Grade 4 abnormality in a patient with a Grade 1 abnormality at baseline.

Table 12

Percentage of Patients by Treatment Group With Marked Laboratory Abnormalities¹ in > 2% of Patients

	Study 511			Study 542	
	Placebo + ZDV/3TC (n=101)	500 mg TID VIRACEPT + ZDV/3TC (n=97)	750 mg TID VIRACEPT + ZDV/3TC (n=100)	1250 mg BID VIRACEPT + d4T/3TC (n=344)	750 mg TID VIRACEPT + d4T/3TC (n=210)
Hematology					
Hemoglobin	6%	3%	2%	0	0
Neutrophils	4%	3%	5%	2%	1%
Lymphocytes	1%	6%	1%	1%	0
Chemistry					
ALT (SGPT)	6%	1%	1%	2%	1%
AST (SGOT)	4%	1%	0	2%	1%
Creatine Kinase	7%	2%	2%	NA	NA

¹ Marked laboratory abnormalities are defined as a shift from Grade 0 at baseline to at least Grade 3 or from Grade 1 to Grade 4

Pediatric Population

VIRACEPT has been studied in approximately 400 pediatric patients in clinical trials from birth to 13 years of age. The adverse event profile seen during pediatric clinical trials was similar to that for adults.

The most commonly reported drug-related, treatment-emergent adverse events reported in the pediatric studies included: diarrhea, leukopenia/neutropenia, rash, anorexia and abdominal pain. Diarrhea, regardless of assigned relationship to study drug, was reported in 39% to 47% of pediatric patients receiving VIRACEPT in 2 of the larger treatment trials. Leukopenia/neutropenia was the laboratory abnormality most commonly reported as a significant event across the pediatric studies.

OVERDOSAGE

Human experience of acute overdose with VIRACEPT is limited. There is no specific antidote for overdose with VIRACEPT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. Since nelfinavir is highly protein bound, dialysis is unlikely to significantly remove drug from blood.

DOSAGE AND ADMINISTRATION

Adults: The recommended dose is 1250 mg (five 250 mg tablets or two 625 mg tablets) twice daily or 750 mg (three 250 mg tablets) three times daily. VIRACEPT should be taken with a meal. Patients unable to swallow the 250 or 625 mg tablets may dissolve the tablets in a small amount of water. Once dissolved, patients should mix the cloudy liquid well, and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure the entire dose is consumed.

Pediatric Patients (2-13 years): In children 2 years of age and older, the recommended oral dose of VIRACEPT Oral Powder or 250 mg tablets is 45 to 55 mg/kg twice daily or 25 to 35 mg/kg three times daily. All doses should be taken **with a meal**. Doses higher than the adult maximum dose of 2500 mg per day have not been studied in children. For children unable to take tablets, VIRACEPT Oral Powder may be administered. The oral powder may be mixed with a small amount of water, milk, formula, soy formula, soy milk or dietary supplements; once mixed, the entire contents must be consumed in order to obtain the full dose. If the mixture is not consumed immediately, it must be stored under refrigeration, but storage must not exceed 6 hours. Acidic food or juice (e.g., orange juice, apple juice or apple sauce) are not recommended to be used in combination with VIRACEPT, because the combination may result in a bitter taste. VIRACEPT Oral Powder should not be reconstituted with water in its original container.

The healthcare provider should assess appropriate formulation and dosage for each patient. Crushed 250 mg tablets can be used in lieu of powder. Tables 13 and 14 provide dosing guidelines for VIRACEPT tablets and powder based on age and body weight.

Table 13
Dosing Table for Children ≥ 2 years of age (tablets)

Body weight		Twice daily (BID) 45 - 55 mg/kg ≥ 2 years	Three times daily (TID) 25 - 35 mg/kg ≥ 2 years
		# of tablets (250 mg)	# of tablets (250 mg)
Kg.	Lbs.		
10 – 12	22 – 26.4	2	1
13 – 18	28.6 – 39.6	3	2
19 – 20	41.8 – 44	4	2
≥ 21	≥ 46.2	4-5 ¹	3 ²

¹ For BID dosing, the maximum dose per day is 5 tablets BID

² For TID dosing, the maximum dose per day is 3 tablets TID

Table 14
Dosing Table for Children ≥ 2 years of age (powder)

Body weight		Twice daily (BID) 45-55 mg/kg		Three times daily (TID) 25-35 mg/kg	
Kg.	Lbs.	Scoops of powder (50 mg/1 g)	Teaspoons ¹ of Powder	Scoops of powder (50 mg/1 g)	Teaspoons ¹ of Powder
9.0 to < 10.5	20 to < 23	10	2½	6	1½
10.5 to < 12	23 to < 26.5	11	2¾	7	1¾
12 to < 14	26.5 to < 31	13	3¼	8	2
14 to < 16	31 to < 35	15	3¾	9	2¼
16 to < 18	35 to < 39.5	Not recommended ²	Not recommended ²	10	2½
18 to < 23	39.5 to < 50.5	Not recommended ²	Not recommended ²	12	3
≥ 23	≥ 50.5	Not recommended ²	Not recommended ²	15	3¾

¹ If a teaspoon is used to measure VIRACEPT oral powder, 1 level teaspoon contains 200 mg of VIRACEPT (4 level scoops equals 1 level teaspoon)

² Use VIRACEPT 250 mg tablet

HOW SUPPLIED

VIRACEPT (nelfinavir mesylate) 250 mg: Light blue, capsule-shaped tablets with a clear film coating engraved with "VIRACEPT" on one side and "250 mg" on the other.

Bottles of 300, 250 mg tablets.....NDC 63010-010-30

VIRACEPT (nelfinavir mesylate) 625 mg: White oval tablet with a clear film coating engraved with "V" on one side and "625" on the other.

Bottles of 120, 625 mg tablets.....NDC 63010-027-70

VIRACEPT (nelfinavir mesylate) Oral Powder is available as a 50 mg/g off-white powder containing 50 mg (as nelfinavir free base) in each level scoopful (1 gram).

Multiple use bottles of 144 grams of powder with scoopNDC 63010-011-90

Viracept tablets and oral powder should be stored at 15° to 30°C (59° TO 86°F).
Keep container tightly closed. Dispense in original container.

Rx only

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LAB-0174-12

Revised August 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-779 / S-045

20-778 / S-024

21-503 / S-006

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration

Rockville, MD 20857

**Division of Anti-Viral Products
Consumer Safety Officer Labeling Review**

Application Numbers: 20-778/S-024
20-779/S-045
21-503/S-006

Name of Drug: Viracept® (nelfinavir mesylate) 50mg/g Oral Powder
Viracept® (nelfinavir mesylate) 250mg Tablets
Viracept® (nelfinavir mesylate) 625mg Tablets

Applicant: Agouron Pharmaceuticals Inc., A Pfizer Company
235 East 42nd Street
New York, NY 10017

Submission Date: August 31, 2005

Receipt Date: September 1, 2005

Materials Reviewed:

Supplements (S-024, S-045 and S-006) dated August 31, 2005
Final Printed Labeling acknowledged and retained March 31, 2005
Supplements (S-023, S-044 and S-003) approved June 4, 2004

Background and Summary:

On April 8, 2005, DAVDP issued a CBE Supplement Request letter to the applicant requesting all manufacturers of protease inhibitors for the treatment of HIV infection submit CBE supplements for the addition of drug-drug interactions and statements regarding immune reconstitution syndrome be added to the PRECAUTIONS section of the label. As a result, the labeling supplements (SLRs) S-024 for NDA 20-778, S-045 for NDA 20-779 and S-006 for NDA 21-503 were submitted on August 31, 2005 and received September 1, 2005. These SLRs were submitted as "Special Supplements: Changes Being Effected" and were compared to the final printed labeling submitted on March 31, 2005 in response to the June 4, 2004 approval of supplements NDA 20-778/S-023, NDA 20-779/S-044 and NDA 21-503/S-003.

Review:

1. The following subsection and statements were added under PRECAUTIONS section:

Immune Reconstitution Syndrome

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.

2. The following was added to the PRECAUTIONS, Drug Interactions section (Table 10):

Inhaled/nasal steroid: Fluticasone	↑ fluticasone	Concomitant use of fluticasone propionate and VIRACEPT may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.
Antidepressant: trazodone	↑ trazodone	Concomitant use of trazodone and VIRACEPT may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as VIRACEPT, the combination should be used with caution and a lower dose of trazodone should be considered.

3. Under PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility section: The word disposition in sentence 5 changed to deposition.

4. Under How Supplied:

The following:

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LAB-0174-11

Revised September 2004

changed to:

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LAB-0174-12

Revised August 2005

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this page is the manifestation of the electronic signature.**

/s/

Elizabeth Thompson
9/27/2005 11:56:42 AM
CSO

Virginia Behr
9/27/2005 12:40:37 PM
CSO

Conclusions:

It should be conveyed to the applicant that the “Special Supplement: Changes Being Effected” is acceptable, and an approval letter should be sent.

Elizabeth Thompson
Regulatory Project Manager

Virginia L. Behr
Chief, Project Management Staff

Attachment: annotated copy of label

Drafted: September 19, 2005/egt

Finalized: September 26, 2005/egt

Filename: V:\DAVDP\CSO\THOMPSON\NDA\207782077921503\cso
review\SLR024045006\csorev.doc