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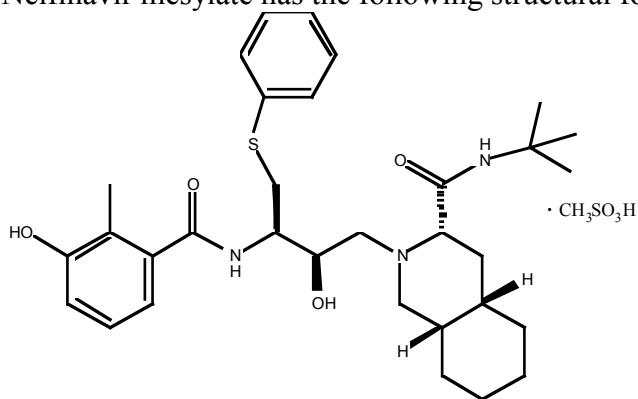
VIRACEPT®

(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, hydroxypropyl methylcellulose 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, hydroxypropyl methylcellulose, 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 β ,8 α β]]-*N*-(1,1-dimethylethyl)decahydro-2-[2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylthio)butyl]-3-isoquinoline carboxamide mono-methanesulfonate (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-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 zidovudine or lamivudine 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 (zidovudine, lamivudine, zalcitabine, abacavir, tenofovir, delavirdine, efavirenz or nevirapine) 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 saquinavir, indinavir, lopinavir and amprenavir, *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 saquinavir, indinavir, lopinavir, and amprenavir, *in vitro*. Most patient-derived recombinant isolates with phenotypic and genotypic evidence of reduced susceptibility (>2.5-fold) to lopinavir, amprenavir, saquinavir and/or indinavir 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 zidovudine therapy 6 of 7 clinical isolates with decreased zidovudine 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 zidovudine, lamivudine, or nevirapine 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 TID 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: Maximum plasma concentrations and area under the plasma concentration-time curve (AUC) were 2 to 3-fold higher under fed conditions compared to fasting. The effect of food on nelfinavir absorption was evaluated in two studies (n=14, total). The meals evaluated contained 517 to 759 Kcal, with 153 to 313 Kcal derived from fat.

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: (see PRECAUTIONS: Pediatric Use)

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 2 summarizes the effects of nelfinavir on the geometric mean AUC, C_{max} and C_{min} of coadministered drugs. Table 3 shows the effects of coadministered drugs on the geometric mean AUC, C_{max} and C_{min} of nelfinavir.

**Table 2: 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 3: 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

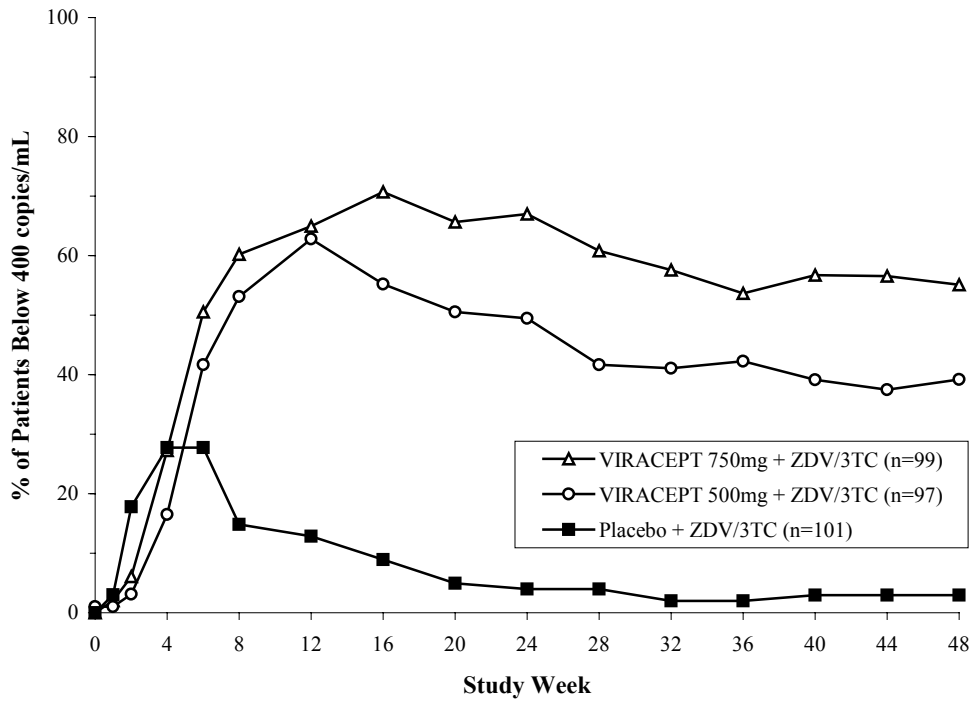
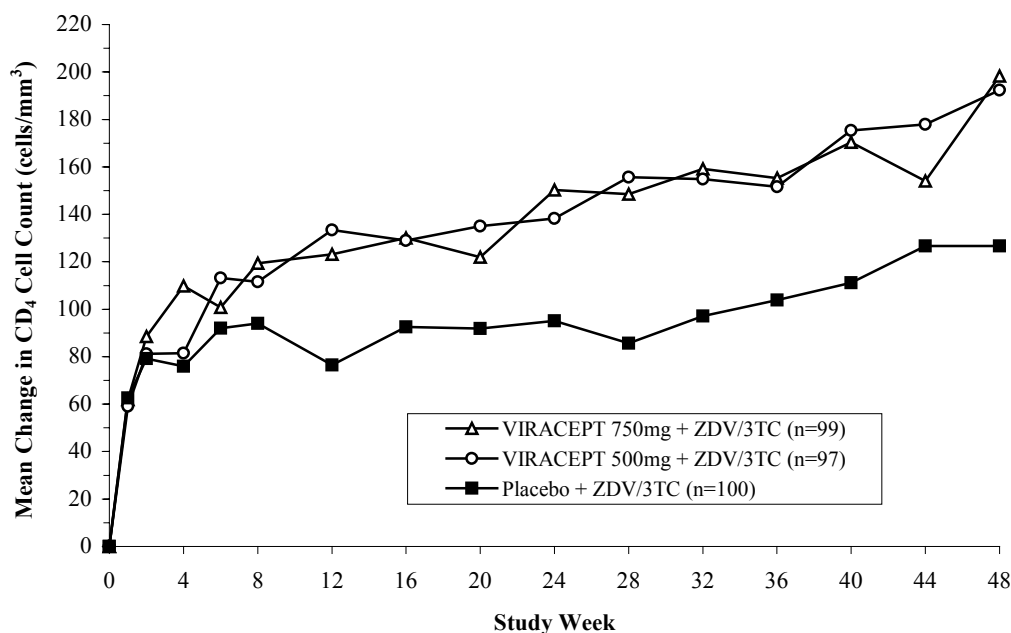


Figure 2

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 4.

Figure 3

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

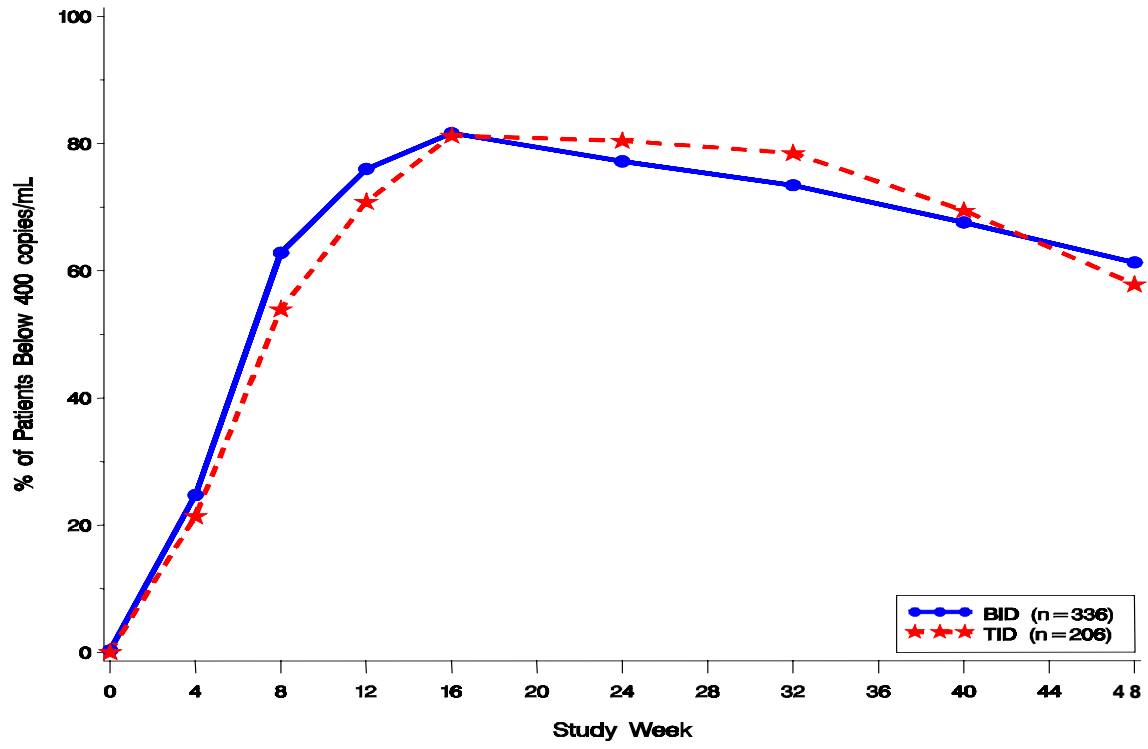


Table 4
Outcomes of Randomized Treatment Through 48 Weeks

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 have 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 5.

**Table 5
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
HMG-CoA Reductase Inhibitors	Lovastatin, Simvastatin

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 6: Drugs That Should Not Be Coadministered With VIRACEPT - Table 7: Established and Other Potentially Significant Drug Interactions With VIRACEPT.**)

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 2 and 3: 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.

Information For Patients

“A statement to patients and health care 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 6 and 7). 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 6
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	CONTRAINDICATED due to 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 7 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 2 and 3)</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		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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in rats have been conducted with nelfinavir at doses of 0, 100, 300, and 1000 mg/kg/day via oral gavage. Thyroid follicular cell adenomas and carcinomas were increased in male rats at 300 mg/kg/day and higher and in female rats at 1000 mg/kg/day. The systemic exposures (C_{max}) at 300 and 1000 mg/kg/day were 1- to 3-fold, respectively, of those measured in humans at the recommended therapeutic dose (750 mg TID or 1250 mg BID). The mechanism of nelfinavir-induced tumorigenesis in rats is unknown. However, 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. Given the lack of genotoxic activity of nelfinavir, the relevance to humans of neoplasms in nelfinavir-treated rats is not known.

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: 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

Nelfinavir was studied in one open-label, uncontrolled trial in 38 pediatric patients ranging in age from 2 to 13 years. In order to achieve plasma concentrations in pediatric patients which approximate those observed in adults, the recommended pediatric dose is 20-30 mg/kg given three times daily with a meal, not to exceed 750 mg three times a day (see DOSAGE AND ADMINISTRATION).

A similar adverse event profile was seen during the pediatric clinical trial as in adult patients. The evaluation of the antiviral activity of nelfinavir in pediatric patients is ongoing. The evaluation of the safety, effectiveness and pharmacokinetics of nelfinavir in pediatric patients below the age of 2 years is ongoing.

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 8.

Table 8
Percentage of Patients with Treatment-Emergent¹ Adverse Events of Moderate or Severe Intensity Reported in \geq 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 phosphate, 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 9. 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 9
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

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): The recommended oral dose of VIRACEPT for pediatric patients 2 to 13 years of age is 20-30 mg/kg per dose, three times daily with a meal. The pharmacokinetics of twice daily dosing of VIRACEPT in pediatric patients has not been established. 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