HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VIRACEPT safely and effectively. See full prescribing information for VIRACEPT.

VIRACEPT® (nelfinavir mesylate) Tablets, for oral use
VIRACEPT® (nelfinavir mesylate) Oral Powder, for oral use
Initial U.S. Approval: 1997

----------INDICATIONS AND USAGE----------

VIRACEPT is a protease inhibitor indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. (1)

----------DOSAGE AND ADMINISTRATION----------

- See full prescribing information for administration instructions (2)
- Adults and adolescents 13 years and older (tablets): 1250 mg twice daily or 750 mg three times daily with a meal (2.1)
- Children 2 to less than 13 years (oral powder or 250 mg tablets): 45 to 55 mg/kg twice daily or 25 to 35 mg/kg three times daily with a meal. Refer to Tables 1 and 2 of the full prescribing information for specific dosing guidelines based on age and body weight (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablet: 250 mg, 625 mg nelfinavir free base (3)
- Oral Powder: 50 mg/g nelfinavir free base (3)

----------CONTRAINDICATIONS----------

- Coadministration with drugs that are highly dependent on CYP3A for clearance and which elevated concentrations are associated with serious and/or life-threatening events (4)

----------WARNINGS AND PRECAUTIONS----------

ALERT: Find out about medicines that should not be taken with VIRACEPT.

- Hepatic impairment: should not be used in patients with either moderate or severe hepatic impairment (2.4, 5.2)
- Phenylketonuria: the oral powder contains 11.2 mg phenylalanine per gram of powder (5.3)
- Diabetes mellitus/hyperglycemia: new onset or exacerbation of pre-existing diabetes mellitus and hyperglycemia reported with protease inhibitors. In some cases after treatment discontinuation, hyperglycemia persisted (5.4)
- Hemophilia: increased bleeding, including spontaneous skin hematomas and hemarthrosis reported with protease inhibitors. In more than half of the cases, protease inhibitors was continued or reintroduced (5.5)
- Fat redistribution: observed with antiretroviral therapy (5.6)
- Immune reconstitution syndrome: reported with combination antiretroviral therapy, including VIRACEPT. Patients may develop an inflammatory response to indolent or residual opportunistic infections (5.7)

----------ADVERSE REACTIONS----------

- Most common adverse reactions (≥2%) of moderate or severe intensity in adults and adolescents (13 years and older) are diarrhea, nausea, rash, and flatulence (6.1).
- Most common adverse reactions in pediatric patients (2 to less than 13 years) are diarrhea, leukopenia/neutropenia, rash, anorexia, and abdominal pain. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Co-administration of **VIRACEPT** with other **drugs** (**CYP3A** substrates) can alter the concentration of these other **drugs**, and other drugs (inhibitors and/or inducers of CYP3A or CYP2C19) may alter the concentrations of nelfinavir. The potential drug-drug concentrations must be considered prior to and during therapy (4, 7, 12.3)
- VIRACEPT should be given with food one hour after or more than 2 hours before didanosine (7)

----------USE IN SPECIFIC POPULATIONS----------

- Use during pregnancy if the potential benefit justifies the potential risk to the fetus (8.1)
- Nursing mothers: should not breast-feed their infants (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VIRACEPT in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection.

2 DOSAGE AND ADMINISTRATION

2.1 Adults and Adolescents (13 years and older)

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 [*see Dosage and Administration (2.3)*].

2.2 Pediatric Patients (2 to less than 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 swallow tablets, VIRACEPT 250 mg tablet(s) may be dissolved in a small amount of water or, VIRACEPT Oral Powder may be administered [see *Dosage and Administration (2.3)*].

The healthcare provider should assess appropriate formulation and dosage for each patient. Tables 1 and 2 provide dosing guidelines for VIRACEPT tablets and powder based on age and body weight.

Table 1:
Dosing Table for Children 2 to less than 13 years of age (tablets)

Body weight **Kg**	**Twice daily (BID)** **45 – 55 mg/kg** **≥2 years**	**Three times daily (TID)** **25 – 35 mg/kg** **≥2 years**
	Number of tablets **(250 mg)**	**Number of tablets** **(250 mg)**
10 – 12	2	1
13 – 18	3	2
19 – 20	4	2
≥21	4 – 5*	3†

* For BID dosing, the maximum dose per day is 5 tablets BID
† For TID dosing, the maximum dose per day is 3 tablets TID

Table 2:
Dosing Table for Children 2 to less than 13 years of age (powder)

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

* 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)
† Use VIRACEPT 250 mg tablet

2.3 Method of Administration

For Patients Unable to Swallow Viracept Tablets

- Place VIRACEPT tablet(s) in small amount of water.
- Once dissolved, 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.

Viracept Oral Powder

- Mix VIRACEPT Oral Powder 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 for mixing VIRACEPT Oral Powder because the combination may result in a bitter taste.
- VIRACEPT Oral Powder should not be reconstituted with water in its original container.

2.4 Hepatic Impairment

VIRACEPT can be used in patients with mild hepatic impairment without any dose adjustment. VIRACEPT should not be used in patients with either moderate or severe hepatic impairment [*see Warnings and Precautions (5.2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

VIRACEPT 250 mg Tablet: Light-blue, capsule-shaped tablets with a clear film coating engraved with “VIRACEPT” on one side and “250 mg” on the other.

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

VIRACEPT Oral Powder: Off-white powder containing 50 mg (as nelfinavir-free base) in each level scoopful (1 gram).

4 CONTRAINDICATIONS

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 and other contraindicated drugs (which may lead to reduced efficacy of nelfinavir) are listed in Table 3 [*also see Drug Interactions (7)*, Table 6].

Table 3:
Drugs That Are Contraindicated With VIRACEPT

Drug Class	**Drugs Within Class That Are Contraindicated With VIRACEPT**	**Clinical Comment**
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Potentially increased alfuzosin concentrations can result in hypotension.
Antiarrhythmics	Amiodarone, quinidine	Potential for serious and/or life-threatening cardiac arrhythmia.
Antimycobacterial Agents	Rifampin	Plasma concentrations of nelfinavir can be reduced by concomitant use of rifampin. This may lead to loss of therapeutic effect and possible development of resistance to VIRACEPT or other coadministered antiretroviral agents.
Ergot Derivatives	Dihydroergotamine, ergotamine, methylergonovine	Potential for serious and/or life threatening reactions such as ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Herbal products	St. John's wort (*Hypericum perforatum*)	Plasma concentrations of nelfinavir can be reduced by concomitant use of the herbal preparation St. John’s wort. This may lead to loss of therapeutic effect and possible development of resistance to VIRACEPT or other coadministered antiretroviral agents.
HMG-CoA Reductase Inhibitors	Lovastatin, Simvastatin	Potential for serious reactions such as myopathy including rhabdomyolysis.
Neuroleptics	Pimozide	Potential for serious and/or life threatening reactions such as cardiac arrhythmias.
PDE5 Inhibitors	Sildenafil (Revatio®) [for treatment of pulmonary arterial hypertension][a]	A safe and effective dose has not been established when used with nelfinavir. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, prolonged erection, and syncope).

Sedative/Hypnotics	Triazolam, oral midazolam	Potential for serious and/or life threatening reactions such as prolonged or increased sedation or respiratory depression.

[a] See *Drug Interactions, Table 6* for coadministration of sildenafil and tadalafil when dosed for erectile dysfunction.

5 WARNINGS AND PRECAUTIONS

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

5.1 Drug Interactions

See Table 3 for a listing of drugs that are contraindicated for use with VIRACEPT due to potentially life-threatening adverse events or potential loss of therapeutic effect [*see Contraindications (4)*]. Please refer to Table 6 for established and other potentially significant drug-drug interactions [*see Drug Interactions (7)*].

5.2 Hepatic Impairment

VIRACEPT should not be used in patients with either moderate or severe hepatic impairment (Child-Pugh B or C, score greater than or equal to 7) [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

5.3 Phenylketonurics

Viracept Oral Powder contains phenylalanine, a component of aspartame. Each gram of VIRACEPT powder contains 11.2 mg phenylalanine. Phenylalanine can be harmful to patients with phenylketonuria.

5.4 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.

5.5 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.

5.6 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.

5.7 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 jiroveci* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

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

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience: Adults and Adolescents (13 years and older)

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.

Drug-related clinical adverse experiences of moderate or severe intensity in ≥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 4.

Table 4:
Percentage of Patients with Treatment-Emergent* Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult and Adolescent Patients

	Study 511 24 weeks			**Study 542 48 weeks**	
Adverse Events	**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%

* Includes those adverse events at least possibly, probably or definitely 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 2 and 3 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 Warnings and Precautions (5.7)*].

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.

Laboratory Abnormalities

The percentage of patients with marked laboratory abnormalities in Studies 542 and 511 are presented in Table 5. 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 5:
Percentage of Patients by Treatment Group with Marked Laboratory Abnormalities* 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

* 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

6.2 Clinical Trials Experience: Pediatrics (2 to less than 13 years of age)

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.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of VIRACEPT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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.

7 DRUG INTERACTIONS

7.1 Potential for VIRACEPT to Affect Other Drugs

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 PDE5 inhibitors) may result in increased plasma concentrations of such drugs that could increase or prolong both its therapeutic and adverse effects (see Tables 3 and 6).

7.2 Potential for Other Drugs to Affect VIRACEPT

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.

7.3 Established and Other Potentially Significant Drug Interactions

Table 6 provides the effect on concentrations of VIRACEPT or concomitant drug as a result of coadministration with VIRACEPT. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 6:
Established and Other Potentially Significant Drug Interactions:
Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies
[*see Clinical Pharmacology (12.3) (Tables 12 and 13) for magnitude of interaction*]

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
HIV Antiviral Agents: Reverse Transcriptase Inhibitors		
Delavirdine	↑ nelfinavir (C_{min}) ↓ delavirdine	Concentrations of nelfinavir were increased while concentrations of delavirdine were decreased when the two agents were coadministered. Appropriate doses of the combination, with respect to safety and efficacy, have not been established.
Nevirapine	↓ nelfinavir (C_{min})	Concentrations of nelfinavir were decreased when coadministered with nevirapine. An appropriate dose of nelfinavir with respect to safety and efficacy has not been established.
Didanosine	↔ nelfinavir	There was no change in nelfinavir concentration when coadministered with didanosine. However, 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).
HIV Antiviral Agents: Protease Inhibitors		
Indinavir	↑ nelfinavir ↑ indinavir	Concentrations of both indinavir and nelfinavir were increased when the two agents were coadministered. Appropriate doses for these combinations, with respect to safety and efficacy, have not been established.
Ritonavir	↑ nelfinavir ↔ ritonavir	Concentrations of nelfinavir were increased when coadministered with ritonavir. An appropriate dose of nelfinavir for this combination, with respect to safety and efficacy, has not been established.
Saquinavir	↑ nelfinavir ↑ saquinavir	Concentrations of both saquinavir and nelfinavir were increased when the two agents were coadministered. Appropriate doses for these combinations, with respect to safety and efficacy, have not been established.
ANTICOAGULANT		
Warfarin	Warfarin	Coadministration of warfarin and VIRACEPT may affect concentrations of warfarin. It is recommended that the INR (international normalized ratio) be monitored carefully during treatment with VIRACEPT, especially when commencing therapy.
ANTICONVULSANTS		
Carbamazepine Phenobarbital Phenytoin	↓ nelfinavir ↓ phenytoin	Concentrations of nelfinavir may be decreased. VIRACEPT may not be effective due to decreased nelfinavir plasma concentrations in patients taking these agents concomitantly. Phenytoin plasma/serum concentrations should be monitored; phenytoin dose may require adjustment to compensate for altered phenytoin concentration.
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.

ANTIGOUT		
Colchicine	↑ colchicines	Patients with renal or hepatic impairment should not be given colchicine with VIRACEPT due to the risk of colchicine toxicity. Treatment of gout flares – co- administration of colchicine in patients on VIRACEPT: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days. Prophylaxis of gout-flares – coadministration of colchicine in patients on VIRACEPT: If the original colchicine regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original colchicine regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. Treatment of familial Mediterranean fever (FMF)– coadministration of colchicine in patients on VIRACEPT: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
ANTIMYCOBACTERIAL		
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.
ENDOTHELIN RECEPTOR ANTAGONIST		
Bosentan	↑ bosentan	Concentrations of bosentan may be increased when coadministered with VIRACEPT. Coadministration of bosentan in patients on VIRACEPT or coadministration of VIRACEPT in patients on bosentan: Start at or adjust bosentan to 62.5 mg once daily or every other day based upon individual tolerability.
HMG-CoA REDUCTASE INHIBITORS		
Atorvastatin Rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Titrate atorvastatin dose carefully and use the lowest necessary dose; do not exceed atorvastatin 40 mg/day.
IMMUNOSUPPRESSANTS		
Cyclosporine Tacrolimus Sirolimus	↑ immuno-suppressants ↑ nelfinavir	Concentrations of these immunosuppressants and nelfinavir may be increased by coadministration of these agents with nelfinavir.
INHALED BETA AGONIST		
Salmeterol	↑ salmeterol	Concurrent administration of salmeterol with VIRACEPT is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
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.
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.
NARCOTIC ANALGESIC		
Methadone	↓ methadone	Concentrations of methadone were decreased when coadministered

		with VIRACEPT. Dosage of methadone may need to be increased when coadministered with VIRACEPT.
HORMONAL CONTRACEPTIVES		
Ethinyl estradiol Norethindrone	↓ ethinyl estradiol ↓ norethindrone	Concentrations of ethinyl estradiol and norethindrone were decreased when coadministered with VIRACEPT. Alternative or additional contraceptive measures should be used when oral contraceptives containing ethinyl estradiol or norethindrone and VIRACEPT are coadministered.
PDE5 INHIBITORS		
Sildenafil Vardenafil Tadalafil	↑ PDE5 Inhibitors	Concomitant use of PDE5 inhibitors and VIRACEPT should be undertaken with caution. May result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances, and priapism. Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH): • Use of sildenafil (REVATIO) is contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) [*see Contraindications (4)*]. • The following dose adjustments are recommended for use of tadalafil (ADCIRCA™) with VIRACEPT: Coadministration of ADCIRCA in patients on VIRACEPT or coadministration of VIRACEPT in patients on ADCIRCA: Start at or adjust ADCIRCA to 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Use of PDE5 inhibitors for erectile dysfunction: Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg in 24 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours, is recommended. Use with increased monitoring for adverse events.
PROTON PUMP INHIBITORS		
Omeprazole	↓ nelfinavir	Omeprazole decreases the plasma concentrations of nelfinavir. Concomitant use of proton pump inhibitors and VIRACEPT may lead to a loss of virologic response and development of resistance.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

VIRACEPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women taking VIRACEPT.

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.

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.

8.3 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**.

8.4 Pediatric Use

The safety, tolerability, pharmacokinetic profile and efficacy of VIRACEPT were evaluated in HIV infected pediatric patients from 2 to 13 years of age in multicenter clinical trials, Study 556 and PACTG 337 [*see Clinical Pharmacology (12.3) and Clinical Studies (14.3)]*. 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 Dosage and Administration (2.2), Adverse Reactions (6.2), and Clinical Pharmacology (12.3)*]. The pharmacokinetic profile, safety and antiviral activity of VIRACEPT in adolescent patients 13 years and older is supported by data from the adult clinical trials where some trials allowed enrolment of subjects 13 years and older. Thus, the data for adolescents and adults were analyzed collectively [*see Adverse Reactions (6.1)*].

8.5 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.

8.6 Hepatic Impairment

VIRACEPT should not be used in patients with either moderate or severe hepatic impairment (Child-Pugh B or C, score greater than or equal to 7) [see *Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*]. No dose adjustment of VIRACEPT is necessary for patients with mild hepatic impairment (Child-Pugh A, score 5-6).

8.7 Renal Impairment

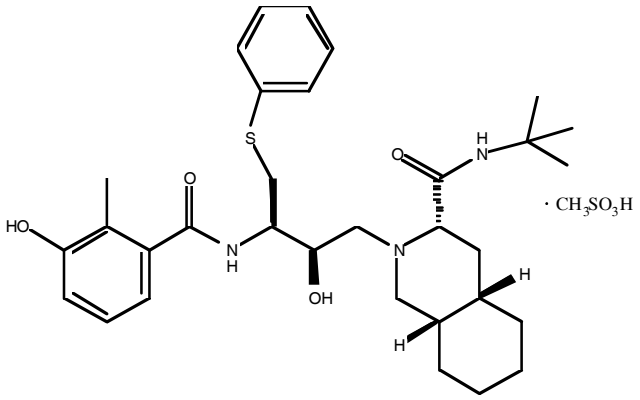
The safety and efficacy of VIRACEPT have not been established in patients with renal impairment.

10 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.

11 DESCRIPTION

VIRACEPT® (nelfinavir mesylate) is an inhibitor of the human immunodeficiency virus type 1 (HIV-1) 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**), 3α,4aβ,8aβ]]-*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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nelfinavir is an inhibitor of the HIV-1 protease [*see Microbiology (12.4)*].

12.2 Pharmacodynamics

Effects on Electrocardiogram

The effect of Viracept at the recommended dose of 1250 mg twice daily on the QTcF interval administered with a low fat meal (20% fat) was evaluated in a randomized, placebo and active (moxifloxacin 400 mg once daily) controlled, crossover study in 66 healthy subjects. The maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline-correction was below 10 milliseconds, the threshold of clinical concern. This finding was unchanged when a single supratherapeutic dose of Viracept 3125 mg was administered following a 3-day administration of Viracept 1250 mg twice daily. The exposure at 3125 mg was 1.4-fold that at 1250 mg. The dose of 3125 mg in this study did not achieve the anticipated exposures in patients taking a high fat meal (50% fat) or with concomitant administration of drugs that could increase nelfinavir exposure [see Pharmacokinetics (12.3)].

No subject in any group had an increase in QTcF of ≥60 milliseconds from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 milliseconds.

12.3 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 7.

Table 7:
Summary of a Pharmacokinetic Study in HIV-positive Patients With Multiple Dosing of 1250 mg (Five 250 mg Tablets) BID for 28 Days and 750 mg (Three 250 mg Tablets) 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. In HIV-1 infected subjects (N=21) receiving multiple doses of 1250 mg BID under fed conditions, the 625 mg formulation was bioequivalent to the 250 mg formulation based on similarity in steady state exposure (C_{max} and AUC).

Table 8 shows the summary of the steady state pharmacokinetic parameters (mean ± SD) of nelfinavir after multiple dose administration of 1250 mg BID (2 x 625 mg tablets) to HIV-infected patients (N=21) for 14 days.

Table 8:
Summary of the Steady State Pharmacokinetic Parameters (Mean ± SD) of Nelfinavir After Multiple Dose Administration of 1250 mg BID (2 x 625 mg Tablets) to HIV-infected Patients (N=21) for 14 Days.

Regimen	AUC_{12} mg·h/L	C_{max} mg/L	C_{min} mg/L
1250 mg BID	35.3 (16.4)	4.7 (1.9)	1.5 (1.0)

AUC_{12}: Steady state AUC
C_{max}: Maximum plasma concentration at steady state
C_{min}: Minimum plasma concentration at steady state

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 9 and Table 10, respectively.

Table 9:
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 10:
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 ^{14}C-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 ^{14}C-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.

Specific Populations

Hepatic Impairment

The steady-state pharmacokinetics of nelfinavir (1250 mg BID for 2 weeks) was studied in HIV-seronegative subjects with mild (Child-Pugh Class A; n=6) or moderate (Child-Pugh Class B; n=6) hepatic impairment. When compared with subjects with normal hepatic function, the C_{max} and AUC of nelfinavir were not significantly different in subjects with mild hepatic impairment but were increased by 22% and 62%, respectively, in subjects with moderate hepatic impairment. The steady-state pharmacokinetics of nelfinavir has not been studied in HIV-seronegative subjects with severe hepatic impairment.

The steady-state pharmacokinetics of nelfinavir has not been studied in HIV-positive patients with any degree of hepatic impairment.

Renal Impairment

The pharmacokinetics of nelfinavir have not been studied in patients with renal impairment.

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 AUC_{24} values are summarized in Table 11.

Table 11:
Summary of Steady-state AUC_{24} of Nelfinavir in Pediatric Studies

Protocol number	Dosing regimen*	N†	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

* Protocol specified dose (actual dose range)
† 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 AUC_{24} 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 Dosage and Administration (2.2)*].

Geriatric Patients

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

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 12 summarizes the effects of nelfinavir on the geometric mean AUC, C_{max} and C_{min} of coadministered drugs. Table 13 shows the effects of coadministered drugs on the geometric mean AUC, C_{max} and C_{min} of nelfinavir.

Table 12: 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* (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†	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
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%)
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§	750 mg q8h x 7-8 days¶	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[#] >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[Þ]	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

[*] ↑ Indicates increase; ↓ Indicates decrease; ↔ Indicates no change (geometric mean exposure increased, or decreased <10%)

[†] Using the soft-gelatin capsule formulation of saquinavir 1200 mg

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

[¶] Comparable changes in rifabutin concentrations were observed with VIRACEPT 1250 mg q12h x 7 days

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

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

Table 13: 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[*] (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[†]	750 mg Single Dose	14	↑18% (↑7-↑30%)	↔	NA
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%)
Other Agents					
Phenytoin 300 mg qd x 7 days	1250 mg BID x 14 days	15	↔	↔	↓18% (↓45-↑23%)
Omeprazole 40 mg qd x 4 days administered 30 minutes before nelfinavir	1250 mg BID x 4 days	19	↓36% (↓20-↓49%)	↓37% (↓23-↓49%)	↓39% (↓15-↓57%)

NA: Not relevant for single-dose treatment

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

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

12.4 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 Cell Culture

The antiviral activity of nelfinavir 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 EC_{95} (95% effective concentration) of nelfinavir ranged from 7 to 196 nM. Drug combination studies with other HIV-1 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, emtricitabine, lamivudine, nevirapine, tenofovir, zalcitabine, or zidovudine) antiviral activity without enhanced cytotoxicity. Nelfinavir's anti-HIV activity was not antagonized by the anti-HCV drug ribavirin.

Resistance

HIV-1 isolates with reduced susceptibility to nelfinavir have been selected in cell culture. HIV-1 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 substitution 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 substitutions 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 cell culture. All 9 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-1 isolates containing the D30N substitution (n=4) and demonstrating high-level (>10-fold) nelfinavir-resistance remained susceptible (<2.5-fold resistance) to amprenavir, indinavir, lopinavir, and saquinavir in cell culture. Patient-derived recombinant HIV-1 isolates containing the L90M substitution (n=8) demonstrated moderate to high-level resistance to nelfinavir and had varying levels of susceptibility to amprenavir, indinavir, lopinavir, and saquinavir in cell culture. 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. Amino acid substitutions associated with resistance to other protease inhibitors (e.g., G48V, V82A/F/T, I84V, L90M) appeared to confer high-level cross-resistance to

nelfinavir. Following ritonavir therapy 6 of 7 clinical isolates with decreased ritonavir susceptibility (8- to 113-fold) compared to baseline also exhibited decreased susceptibility to nelfinavir (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.

Clinical Studies: There have been no controlled or comparative studies evaluating the virologic response to subsequent protease inhibitor-containing regimens in subjects 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 subjects with extensive prior antiretroviral experience with reverse transcriptase inhibitors (mean 2.9) who had received nelfinavir 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 nelfinavir failure (median 48 weeks). Sequence analysis of HIV-1 isolates prior to switch demonstrated a D30N or an L90M substitution in 18 and 6 subjects, respectively. Subjects remained on therapy for a mean of 48 weeks (range 40 to 56 weeks) where 17 (65%) and 13 (50%) of the 26 subjects were treatment responders with HIV-1 RNA below the assay limit of detection (<500 HIV-1 RNA copies/mL, Chiron bDNA) at 24 and 48 weeks, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

Description of Clinical Studies

The efficacy of VIRACEPT is based on analyses of multiple clinical studies in HIV-1 infected antiretroviral treatment-naïve and experienced adult patients. In the adult clinical studies described below, efficacy was evaluated by the percent of patients with plasma HIV RNA <400 copies/mL (Studies 511 and 542), <500 copies/mL (Study ACTG 364), or <50 copies/mL (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 study's definition of virologic failure.

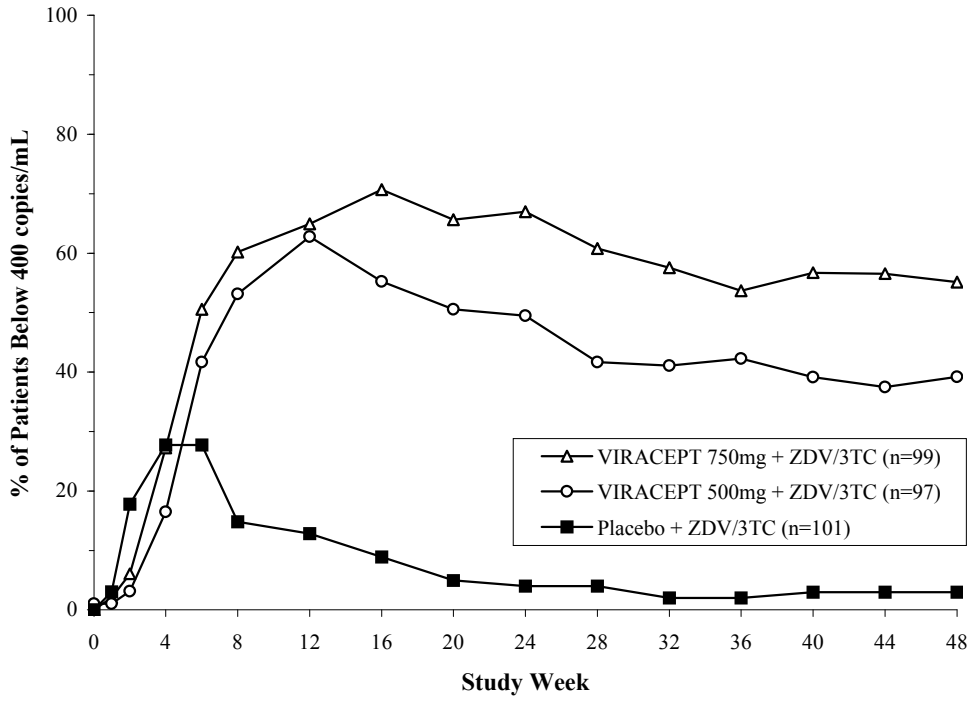
14.1 Studies in Antiretroviral Treatment Naïve Adult Patients

<u>Study 511: VIRACEPT + zidovudine + lamivudine versus zidovudine + lamivudine</u>

Study 511 is 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 naïve HIV-1 infected patients. The median age was 35 years [range 21 to 63]; 89% were male and 78% were Caucasian. Mean baseline CD4 cell count was 288 cells/mm^3 and mean baseline plasma HIV RNA was 5.21 log_{10} copies/mL (160,394 copies/mL). The proportion of patients with plasma HIV RNA <400 copies/mL at Week 48 was 86%, as summarized in Figure 1. The mean change in CD4 cell count at Week 48 was 207.6 cells/mm^3.

Figure 1

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



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

Study 542 is a, 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/mm^3 and mean baseline plasma HIV RNA was 5.0 $\log_{10}$ 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/mm^3 at 24 weeks and approximately 200 cells/mm^3 at 48 weeks.

The percent of patients with HIV RNA <400 copies/mL and the outcomes of patients through 48 weeks of treatment are summarized in Table 14.

Table 14:
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-1 RNA <400 copies/mL	198 (61%)	111 (58%)
HIV-1 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 (6)*].
*** 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-naïve 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/mm^3 and mean baseline plasma HIV RNA was 4.8 $\log_{10}$ 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.

14.2 Studies in Antiretroviral Treatment Experienced Adult 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/mm^3 and mean baseline plasma HIV RNA was 3.9 $\log_{10}$ 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.

14.3 Studies in Pediatric Patients

The pharmacokinetic profile, safety and antiviral activity of VIRACEPT in pediatric patients 2 years of age up to 13 years were evaluated in 2 randomized studies.

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/mm^3 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/mm^3. 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.

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 11 [*see Clinical Pharmacology (12.3)*].

The pharmacokinetic profile, safety and antiviral activity of VIRACEPT in adolescent patients 13 years and older is supported by data from the adult clinical trials where some trials allowed enrolment of subjects 13 years and older. Thus, the data for adolescents and adults were analyzed collectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

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 scoop …….NDC 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.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

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**.

- Instruction for Use

For optimal absorption, patients should be advised to take VIRACEPT with food.

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

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.

Adult or pediatric patients unable to swallow the tablets may dissolve the tablets in a small amount of water:

- Place VIRACEPT tablet(s) in small amount of water
- Once dissolved, 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 unable to swallow tablets can also use the powder formulation:

- Mix VIRACEPT Oral Powder 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 for mixing VIRACEPT Oral Powder because the combination may result in a bitter taste.
- VIRACEPT Oral Powder should not be reconstituted with water in its original container.

- Drug Interactions

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, or other PDE5 inhibitors, and nelfinavir should be advised that they may be at an increased risk of PDE5 inhibitor-associated adverse events including hypotension, visual changes, and prolonged penile erection, and should promptly report any symptoms to their doctor.

- Hepatic Impairment

Patients should be informed that VIRACEPT should not be used if there is moderate or severe hepatic impairment.

- Phenylketonuria

Physicians should alert patients with phenylketonuria that VIRACEPT Oral Powder contains phenylalanine

- Fat Redistribution

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

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.

- General Information

VIRACEPT is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using VIRACEPT.

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

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

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 remain under the care of a physician while using VIRACEPT. 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.

VIRACEPT and Agouron are registered trademarks of Agouron Pharmaceuticals, Inc.

REVATIO is a registered trademark of Pfizer, Inc.

ADCIRCA is a trademark of Eli Lilly and Company

Please refer to www.pfizer.com for information about Viracept.

Distributed by:
ViiV Healthcare Company
Research Triangle Park, NC 27709

LAB-0174-24.0

Patient Information

VIRACEPT® (VI-ra-cept)
(nelfinavir mesylate)
TABLETS

VIRACEPT® (VI-ra-cept)
(nelfinavir mesylate)
ORAL POWDER

VIRACEPT can interact with other medicines and cause serious side effects. It is important to know the medicines that should not be taken with VIRACEPT. See the section "Who should not take VIRACEPT?"

Read this Patient Information before you start taking VIRACEPT and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is VIRACEPT?

VIRACEPT is a prescription anti-HIV medicine used with other anti-HIV medicines to treat human immunodeficiency virus (HIV-1) infection. VIRACEPT is a type of anti-HIV medicine called a protease inhibitor. HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

When used with other HIV medicines, VIRACEPT may help reduce the amount of HIV in your blood (called "viral load"). VIRACEPT may also help to increase the number of white blood cells called CD4 (T) cells, which help fight off other infections. Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your immune system. This may reduce your risk of death or infections that can happen when your immune system is weak (opportunistic infections).

It is not known if VIRACEPT is effective in children less than 2 years of age.

VIRACEPT does not cure HIV infection or AIDS, and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. You should remain under the care of a doctor when using VIRACEPT**.**

Patients must stay on continuous HIV therapy to control infection and decrease HIV-related illness

Avoiding doing things that can spread HIV-1 infection.

- **Do not share needles or other injection equipment**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Ask your healthcare provider if you have any questions on how to prevent passing HIV to other people.

Who should not take VIRACEPT?

Do not take VIRACEPT if you take any of the following medicines:

- alfuzosin (Uroxatral®)
- amiodarone (Pacerone®, Cordarone®)
- cisapride (Propulsid®, Propulsid Quicksolv®)
- ergot, including:
  - dihydroergotamine mesylate (D.H.E. 45®, Migranal®)
  - ergotamine tartrate (Cafergot®, Migergot®, Ergomar, Ergostat®, Medihaler Ergotamine, Wigraine®, Wigrettes®)
  - methylergonovine maleate (Methergine®)
- lovastatin (Advicor®, Altoprev®, Mevacor®)

- oral midazolam (Versed®)
- pimozide (Orap®)
- quinidine (Quinaglute®, Cardioquin®, Quinidex®, Quinora®)
- rifampin (Rifadin®, Rifamate®, Rifater®, Rimactane®)
- sildenafil (Revatio®) when used to treat pulmonary arterial hypertension
- simvastatin (Zocor®, Vytorin®, Simcor®)
- St. John's wort (*Hypericum perforatum*)
- triazolam (Halcion®)

Serious problems can happen if you or your child take any of these medicines with VIRACEPT.

What should I tell my healthcare provider before taking VIRACEPT?

Before taking VIRACEPT, tell your healthcare provider if you:

- have liver problems
- have kidney problems
- have phenylketonuria. VIRACEPT contains aspartame.
- have high blood sugar (diabetes)
- have hemophilia
- have any other medical condition
- are pregnant or plan to become pregnant. It is not known if VIRACEPT will harm your unborn baby.

  Pregnancy Registry. There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

- **Do not breastfeed.** We do not know if VIRACEPT can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Using VIRACEPT with certain other medicines may affect each other and cause serious side effects. VIRACEPT may affect the way other medicines work, and other medicines may affect how VIRACEPT works.

Especially tell your healthcare provider if you take:

- medicine to treat HIV
- atorvastatin (Lipitor®)
- azithromycin (Zmax®, Zithromax®)
- bosentan (Tracleer®)
- carbamazepine (Carbatrol®, Equetro®, Tegretol®)
- colchicine (Colcrys®)
- didanosine (Videx®, Videx EC). Take VIRACEPT with food one hour after or more than two hours before you take didanosine.
- estrogen-based contraceptives (birth control pills). VIRACEPT may reduce the effectiveness of estrogen-based contraceptives. During treatment with VIRACEPT, you should use a different method of birth control or a second method of birth control method along with your hormone-based birth control. Talk to your healthcare provider about what types of birth control you can use to prevent pregnancy while taking VIRACEPT.
- fluticasone (Advair Diskus®, Advair HFA®, Flovent®, Flovent HFA®, Flovent Diskus®, Flonase®, Veramyst®)
- immunosuppresnts such as cyclosporine (Gengraf®, Sandimmune®, Neoral®), tacrolimus (Prograf®), sirolimus (Rapamune®)
- methadone hydrochloride (Dolphine hydrochloride)
- midazolam administered by injection (Versed®)
- omeprazole (Prilosec®)
- phenobarbital
- phenytoin (Dilantin®, Phenytek®)
- rifabutin (Mycobutin®)
- rosuvastatin (Crestor®)
- salmeterol (Serevent®)
- sildenafil (Viagra®), vardenafil (Levitra®) or tadalafil (Cialis®), for the treatment of erectile dysfunction (ED).

- tadalafil (Adcirca™) for the lung problem pulmonary arterial hypertension (PAH)
- warfarin (Coumadin®, Jantoven®)

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take VIRACEPT?

- You should stay under a healthcare provider's care when taking VIRACEPT.
- Take VIRACEPT every day exactly as prescribed by your healthcare provider
- Do not change your dose of VIRACEPT or stop treatment without talking to your healthcare provider first.
- **Take VIRACEPT with a meal.**
- VIRACEPT is usually taken 2 or 3 times each day. Your healthcare provider will tell you how much VIRACEPT to take and when to take it.
- If your child is taking VIRACEPT, your child's healthcare provider will decide the right dose based on your child's weight.
- VIRACEPT Tablets are film-coated to help make the tablets easier to swallow.
- If you or your child are unable to swallow the tablets:
  - You may dissolve the tablets in a small amount of water. Once the tablets are dissolved, the liquid will be cloudy.
  - Mix the cloudy liquid well, and then drink it right away.
  - Rinse the glass with water and drink the water to ensure that you take the full dose of VIRACEPT.
- If you **miss a dose** of VIRACEPT, take it as soon as possible. If you skip a dose, do not double the next dose.
- If you **take too much VIRACEPT**, call your healthcare provider or go to the nearest hospital emergency room right away.
- Do not run out of VIRACEPT. Get your VIRACEPT refilled from your doctor or pharmacy before you run out.

How should VIRACEPT Oral Powder be prepared?

- You healthcare provider should tell you how much VIRACEPT Oral Powder to use.
- VIRACEPT Oral Powder comes with a scoop for measuring. Ask your healthcare provider or pharmacist for help measuring the correct amount of VIRACEPT Oral Powder.
- Do not mix VIRACEPT Oral Powder in the container that it comes in. Measure the correct amount of VIRACEPT Oral Powder into a cup.
- You may mix VIRACEPT Oral Powder with a small amount of water, milk, formula, soy formula, soy milk, or liquid dietary supplements.
- You should not mix VIRACEPT Oral Powder with acidic food or juice, such as orange juice, apple juice, or applesauce because the mixture may taste bitter.
- Your child should drink all of the mixture to be sure that the entire dose of VIRACEPT is taken.
- If your child does not take the dose right away, store in the refrigerator until you are ready to use it. Do not store a mixed dose of VIRACEPT Oral Powder for more than 6 hours.

What are the possible side effects of VIRACEPT?

VIRACEPT can cause serious side effects, including:

- **Diabetes and high blood sugar (hyperglycemia).** Some people who take protease inhibitors including VIRACEPT can get high blood sugar, develop diabetes, or your diabetes can get worse. Tell your healthcare provider if you notice an increase in thirst or urinate often while taking VIRACEPT.
- **Increased bleeding in people with hemophilia.** Some people with hemophilia have increased bleeding with protease inhibitors including VIRACEPT.
- **Changes in body fat.** These changes can happen in people who take antiretroviral therapy. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- **Changes in you immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Call your healthcare provider right away if you start having new symptoms after starting your HIV medicine.

Common side effects of VIRACEPT in adults include:

- Diarrhea. Tell your healthcare provider if you get diarrhea with VIRACEPT. You may be able to take loperamide or another non-prescription medicine to help control your diarrhea.
- nausea
- gas
- rash

Common side effects in children include:

- Diarrhea. Tell your healthcare provider if your child gets diarrhea with VIRACEPT. Your child may be able to take loperamide or another non-prescription medicine to help control your diarrhea.
- low white blood cell count (leukopenia and neutropenia)
- rash
- loss of appetite
- stomach-area (abdominal) pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of VIRACEPT. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VIRACEPT?

- Store VIRACEPT Tablets and Oral Powder at room temperature, between 59ºF to 86ºF (15ºC to 30ºC).
- Store VIRACEPT in the original container.
- Keep the container closed tightly.

Keep VIRACEPT and all medicines out of the reach of children.

General information about VIRACEPT
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VIRACEPT for a condition for which it was not prescribed. Do not give VIRACEPT to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about VIRACEPT. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about VIRACEPT that is written for health professionals.

For more information, call 1-800-438-1985.

What are the ingredients in VIRACEPT?

Active ingredient: nelfinavir mesylate

Tablet 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.

Oral powder inactive ingredients: microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hypromellose, aspartame, sucrose palmitate, and natural and artificial flavor.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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Research Triangle Park, NC 27709

Revised: April 2012

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LAB-0346-10.0