PRODUCT MONOGRAPH

# PR VIRACEPT®

Nelfinavir tablets,
250 mg, 625 mg
(as nelfinavir mesylate)

Nelfinavir powder,
50 mg/g
(as nelfinavir mesylate)

HIV PROTEASE INHIBITOR

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## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Oral | - film-coated tablets, 250, 625 mg nelfinavir<br>- powder, nelfinavir 50 mg/g | Not applicable. For a complete listing see Dosage Forms, Composition and Packaging section. |

### INDICATIONS AND CLINICAL USE

VIRACEPT (nelfinavir mesylate) is indicated for the treatment of HIV infection in combination with other antiretroviral agents. This indication is based on analyses of surrogate endpoints in studies of up to 48 weeks (See **CLINICAL TRIALS** for Description of Studies).

Pediatrics (<13 years of age): The safety and effectiveness of VIRACEPT have been established in patients from 2 to 13 years of age. 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. Therefore, VIRACEPT should be used in children below the age of 2 years only when the potential benefit clearly outweighs the potential risks. (see **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment – Children and DETAILED PHARMACOLOGY**)

Geriatrics (>65 years of age): Clinical studies of VIRACEPT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects (see **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment)**

## CONTRAINDICATIONS

VIRACEPT (nelfinavir mesylate) is contraindicated in patients with clinically significant hypersensitivity to any of its components. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

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 1.

**Table 1: Drugs That Are Contraindicated With VIRACEPT**

| Drug Class | Drugs Within Class That Are Contraindicated With VIRACEPT |
|---|---|
| Gastrointestinal Prokinetic | cisapride* |
| Antiarrhythmics | amiodarone, quinidine |
| Ergot Derivatives | dihydroergotamine, ergonovine, ergotamine, methylergonovine |
| Sedative/Hypnotics | midazolam, triazolam |
| HMG-CoA Reductase Inhibitors | lovastatin, simvastatin |
| Herbal Products | St. John's Wort (*hypericum perforatum*) |
| Alpha 1-adrenoceptor antagonist | alfuzosin |
| PDE-5 Inhibitors | sildenafil for treatment of pulmonary arterial hypertension |
| Antimycobacterials | rifampin |
| Antipsychotics | lurasidone<br>pimozide |

* is no longer marketed in Canada

## WARNINGS AND PRECAUTIONS

### General

VIRACEPT (nelfinavir mesylate) is an inhibitor of the P450 isoform CYP3A. *In vitro* data indicates that nelfinavir is unlikely to be an inhibitor of CYP2C19 (Ki = 68 μM or 39 mg/L). Coadministration of VIRACEPT (nelfinavir mesylate) 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 primarily metabolized by CYP3A4 may result in increased plasma concentrations of the other drug with the potential for increased toxicity (see **DRUG INTERACTIONS**).

Due to inhibition of CYP3A4 by VIRACEPT, co-administration of VIRACEPT with quetiapine may result in increased quetiapine concentrations. Serious and/or life-threatening quetiapine-related adverse reactions, including severe sedation and coma, have been reported for concomitant use of HIV protease inhibitors and quetiapine. VIRACEPT should not be used in combination with quetiapine. If coadministration is necessary, reduce the quetiapine dose and monitor for quetiapine-associated adverse reactions as recommended in the quetiapine product monograph (see **DRUG INTERACTIONS**).

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.

**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.

**Hepatic Impairment**
VIRACEPT (nelfinavir mesylate) is principally metabolized by the liver. Therefore, caution should be exercised when administering this drug to patients with hepatic impairment. (See **ACTION AND CLINICAL PHARMACOLOGY**: Hepatic Insufficiency).

Patients with hepatic impairment should not be given colchicine with VIRACEPT.

**Resistance/Cross-Resistance**
HIV cross-resistance between protease inhibitors has been observed (see **VIROLOGY**).

**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 re-introduced. A causal relationship between protease inhibitors and these events has not been established, however, the frequency of bleeding episodes should be closely monitored in patients on nelfinavir mesylate.

**Redistribution/Accumulation of Body Fat**

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

**Immune Reconstitution Syndrome**

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium Avium infection (MAC), Cytomegalovirus (CMV), Pneumocystis jirovecii (PCP) and Tuberculosis(TB)), 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.

**Special Populations**

**Pregnant Women (Pregnancy, Fertility and Reproduction)**

Clinical experience in pregnant women is lacking. Until additional data become available, VIRACEPT (nelfinavir mesylate) is not recommended for use in pregnant women.

No treatment-related effects were demonstrated in nonclinical developmental and reproductive toxicity studies when nelfinavir was administered to pregnant rats at systemic exposures (AUC) comparable to that observed in humans at the recommended therapeutic doses of VIRACEPT. Administration of nelfinavir to pregnant rabbits resulted in no fetal development effects up to a dose at which a slight maternal decrease was observed; however even at the highest dose evaluated, systemic exposure in rabbits was appreciably lower than that achieved in humans administered therapeutic doses of nelfinavir.

*Antiretroviral Pregnancy Registry:* To monitor maternal-fetal outcomes of pregnant women exposed to nelfinavir and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling (800) 258-4263 or via email at http://www.apregistry.com.

A prospective review of first trimester exposures to VIRACEPT reported that there was no increased risk (at least two-fold increase) of overall birth defects including the more common classes, cardiovascular and genitourinary systems. To date, fifteen birth defects out of 416 live births of first trimester exposure have been reported.

**Nursing Mothers**: It is recommended that HIV-infected women not breastfeed their infants under any circumstances to avoid the transmission of HIV. Studies in lactating rats have demonstrated that nelfinavir is excreted in milk. It is not known whether nelfinavir is excreted in human milk.

Mothers should be instructed not to breast-feed if they are receiving VIRACEPT because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants.

**Pediatrics:** The safety and effectiveness of VIRACEPT have been established in patients from 2 to 13 years of age. 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. Response rates in children <2 years of age appeared to be poorer than those in patients ≥ 2 years of age in some studies. Therefore, nelfinavir should be used in children below the age of 2 years only when the potential benefits clearly outweigh the potential risks.

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 (see **ADVERSE REACTIONS-Pediatric Population**, **DOSAGE AND ADMINISTRATION-Recommended Dose and Dosage Adjustment-Children** and **DETAILED PHARMACOLOGY- Special Populations**).

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

Patients with renal impairment should not be given colchicine with VIRACEPT.

**Geriatric Use:** Clinical studies of nelfinavir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects (see **DOSAGE AND ADMINISTRATION-Recommended Dose and Dosage Adjustment)**.

**Gender and Race**: No significant pharmacokinetic differences have been detected between males and females. Pharmacokinetic differences due to race have not been evaluated; however, pivotal trials have revealed no significant differences between races for efficacy or safety.

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

The safety of VIRACEPT (nelfinavir mesylate) was studied in over 5000 patients who received drug either alone or in combination with antiretroviral agents. 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.

### Clinical Trial Adverse Drug Reactions

Drug-related clinical adverse experiences of moderate or severe intensity in ≥ 2% of patients treated with VIRACEPT coadministered with d4T and lamivudine (Study 542) for up to 48 weeks or with ZDV + lamivudine (Study 511) for up to 24 weeks are presented in Table 2.

**Table 2: Percentage of Patients with Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of 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=296) | 750 mg TID VIRACEPT + d4T/3TC (n=159) |
| Body as a Whole | | | | | |
| Asthenia | 2% | 1% | 1% | 1% | 1% |
| Digestive System | | | | | |
| Diarrhea | 3% | 14% | 20% | 18% | 14% |
| Nausea | 4% | 3% | 7% | 1% | 3% |
| Flatulence | 0 | 5% | 2% | 0 | 0 |
| Skin/Appendages | | | | | |
| Rash | 1% | 1% | 3% | 2% | 2% |

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

**Less Common Clinical Trial Adverse Drug Reactions (<2%)**

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, back pain, fever, headache, malaise, pain and redistribution/accumulation of body fat (see **WARNING AND PRECAUTIONS-Redistribution/Accumulation of Body Fat**).

*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, creatinine 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.

**Abnormal Hematologic and Clinical Chemistry Findings**

The percentage of patients with marked laboratory abnormalities in Studies 542 and 511 are presented in Table 3. 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 3: Percentage of Patients by Treatment Group With Marked Laboratory Abnormalities[1] in ≥2% of Patients**

| | **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=296) | 750 mg TID VIRACEPT d4T/3TC (n=159) |
| 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% | 3% | 0 |
| AST (SGOT) | 4% | 1% | 0 | 2% | 1% |
| Creatine Kinase | 7% | 2% | 2% | -- | -- |

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

**Pediatric Population**

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

Drug-related, treatment-emergent adverse events of all grades in ≥ 2% of patients treated with VIRACEPT TID with 2 NRTIs for up to 48 weeks in two pediatric studies (Study 524 and Study 556) are presented in Table 4, by age range. In Study 524, diarrhea, leukopenia, abdominal pain and rash were the most commonly reported drug-related adverse events in pediatric patients older than 2 years of age. In the group less than 2 years of age, rash, diarrhea, anorexia and leukopenia were the most commonly reported drug-related adverse events. In Study 556, no drug-related

adverse events were reported in children less than 2 years of age; in children older than 2 years of age, two instances of Grade 2 diarrhea and one instance of Grade 4 rash were reported as drug related.

**Table 4: Number (%) of Drug-related Treatment-emergent Adverse Events Reported in > 2% Pediatric Patients**

| | **Children** | | | |
|---|---|---|---|---|
| | **Study 524 VIRACEPT 20 mg/kg TID + NRTI1** | | **Study 556 VIRACEPT 25-35 mg/kg TID + ZDV/ddI** | |
| **Body System COSTART Adverse Event Term** | **<2 Yrs n=25** | **≥2 Yrs n=39** | **<2 Yrs n=47** | **≥2 Yrs n=94** |
| Body as a whole | | | | |
| Fever | 0 (0) | 1 (3) | 0 (0) | 0 (0) |
| Pain abdomen | 0 (0) | 2 (5) | 0 (0) | 0 (0) |
| Digestive | | | | |
| Anorexia | 1 (4) | 0 (0) | 0 (0) | 0 (0) |
| Diarrhea | 1 (4) | 15 (38) | 0 (0) | 2 (2) |
| Flatulence | 0 (0) | 1 (3) | 0 (0) | 0 (0) |
| Nausea | 0 (0) | 1 (3) | 0 (0) | 0 (0) |
| Hemic and lymphatic | | | | |
| Anemia | 0 (0) | 1 (3) | 0 (0) | 0 (0) |
| Leukopenia | 1 (4) | 2 (5) | 0 (0) | 0 (0) |
| Respiratory | | | | |
| Epistaxis | 0 (0) | 1 (3) | 0 (0) | 0 (0) |
| Skin and skin structures | | | | |
| Rash | 2 (8) | 2 (5) | 0 (0) | 1 (1) |

[1] "NRTI" indicates the subjects were also treated with a nucleoside reverse transcriptase inhibitor.

Although no drug-related events were reported in Study PACTG 377, treatment emergent adverse events included neutropenia and gastrointestinal events in 33% (7/21 each) of children less than 2 years of age treated with VIRACEPT (27 - 33 mg/kg TID) in the presence of NRTIs +/- NNRTIs. Neutropenia occurred in all treatment groups including the arm that did not include VIRACEPT (three grade 2, three grade 3, and one grade 4). In the majority of cases, the neutropenia was reported as mild in nature and often resolved without discontinuation from study.

In neonates, Study PENTA 7 (20 subjects, VIRACEPT at 75 mg/kg BID) reported one treatment-emergent, drug-related adverse event of Grade 2 rash/erythema in the ddI + d4T + VIRACEPT arm; this event resolved without discontinuation of treatment.

**Adverse Events from Pre/Postnatal Exposure**
In neonates, Study PACTG 353 (31 subjects, VIRACEPT at 40 mg/kg BID) indicates that the drug-related adverse events include neutropenia (two Grade 3 and one Grade 4) and decreased hemoglobin (seven Grade 3).

**Post-Marketing Adverse Drug Reaction**
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:* QT prolongation, torsades de pointes.

*Digestive System:* jaundice.

*Metabolic/Nutritional System:* bilirubinemia, metabolic acidosis.

## DRUG INTERACTIONS

**Serious Drug Interactions**

- alfuzosin
- amiodarone, quinidine
- rifampin
- dihydroergotamine, ergonovine, ergotamine, methylergonovine
- lovastatin, simvastatin
- pimozide, lurasidone, Quetiapine
- sildenafil for the treatment of pulmonary arterial hypertension
- omeprazole
- midazolam, triazolam
- salmeterol

(See Table 7)

**Overview**
Nelfinavir is an inhibitor of CYP3A (cytochrome P450 3A). 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 drugs that could increase or prolong both its therapeutic and adverse effects see Table 7 and 8. Nelfinavir is metabolized via 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. Caution should therefore be exercised when coadministering drugs that induce CYP3A or CYP2C19 or potentially toxic drugs which are themselves metabolized by CYP3A or CYP2C19. Based on *in vitro* data, nelfinavir is unlikely to inhibit other cytochrome P450 isoforms at concentrations in the therapeutic range.

**Drug-Drug Interactions**

Specific drug interaction studies were performed with nelfinavir and a number of drugs. Table 5 summarizes the effect of nelfinavir on the geometric mean AUC and $C_{max}$ of coadministered drugs. Table 6 shows the effects of coadministered drugs on the geometric mean AUC and $C_{max}$ of nelfinavir.

| **Table 5: Drug Interactions**<br>**Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Nelfinavir** | | | | |
|---|---|---|---|---|
| **Coadministered Drug** | **Nelfinavir Dose** | **N** | **Coadministered Drug** | |
| | | | **AUC (95% CI)** | **$C_{max}$ (95% CI)** |
| **HIV-Protease Inhibitors** | | | | |
| indinavir 800 mg Single Dose | 750 mg q8h x 7 days | 6 | ↑ 51% (25-83%) | ↔ |
| ritonavir 500 mg Single Dose | 750 mg q8h x 5 doses | 10 | ↔ | ↔ |
| saquinavir 1200 mg Single Dose[1] | 750 mg tid x 4 days | 14 | ↑392% (271-553%) | ↑179% (105-280%) |
| amprenavir 800 mg tid x 14 days | 750 mg tid x 14 days | 6 | ↔ | ↔ |
| **Nucleoside Reverse Transcriptase Inhibitors** | | | | |
| lamivudine 150 mg Single Dose | 750 mg q8h x 7-10 days | 11 | ↑10% (1-20%) | ↑31% (5-62%) |
| zidovudine 200 mg Single Dose | 750 mg q8h x 7-10 days | 11 | ↓35% (28-41%) | ↓31% (8-49%) |
| stavudine 30-40 mg bid x 56 days | 750 mg tid x 56 days | 8 | ↔ | ↔ |
| **Non-Nucleoside Reverse Transcriptase Inhibitors** | | | | |
| efavirenz 600 mg once daily x 7 days | 750 mg q8h x 7days | 10 | ↔ | ↔ |
| delavirdine 400 mg q8h x 14 days | 750 mg q8h x 7 days | 7 | ↓31% (62- 25%) | ↓27% (53- 14%) |
| **Anti-infective Agents** | | | | |
| rifabutin 150 mg once daily x 8 days[2] | 750 mg q8h x 7-8 days[3] | 12 | ↑83% (69-99%) | ↑19% (9-30%) |
| rifabutin 300 mg once daily x 8 days | 750 mg q8h x 7-8 days | 10 | ↑207% (151-276%) | ↑146% (112-186%) |
| azithromycin 1200 mg single dose | 750 mg tid x 11 days | 12 | ↑ 112% (73-160%) | ↑136% (66-237%) |
| **HMG-CoA Reductase Inhibitors** | | | | |
| atorvastatin 10 mg once daily x 28 days | 1250 mg bid x 14 days | 15 | ↑74% (34-126%) | ↑122% (58-211%) |
| simvastatin 20 mg once daily x 28 days | 1250 mg bid x 14 days | 16 | ↑505% (372-675%) | ↑517% (340-764%) |
| **Other Agents** | | | | |

| **Table 5: Drug Interactions<br>Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Nelfinavir** | | | | |
|---|---|---|---|---|
| **Coadministered Drug** | **Nelfinavir Dose** | **N** | **Coadministered Drug** | |
| | | | **AUC (95% CI)** | **$C_{max}$ (95% CI)** |
| ethinyl estradiol 35µg once daily x 15 days | 750 mg q8h x 7days | 12 | ↓47% (41-63%) | ↓28% (14-39%) |
| norethindrone 0.4 mg once daily x 15 days | 750 mg q8h x 7 days | 12 | ↓18% (12-27%) | ↔ |
| methadone 80 mg + / - 21 mg once daily[4] > 1 month | 1250 mg bid x 8 days | 13 | ↓47% (41-52%) | ↓46% (42-49%) |
| phenytoin 300 mg once daily x 14 days | 1250 mg bid x 7 days | 12 | ↓29% (15-35%) | ↓21% (12-29%) |

↑ Indicates increase ↓Indicates decrease ↔Indicates no change- (p value>0.05)

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

[2] Rifabutin 150 mg once daily (od) changes are relative to Rifabutin 300 mg od x 8 days without coadministration with nelfinavir

[3] Comparable changes in Rifabutin concentrations were observed with VIRACEPT 1250 mg q12h x 7 days.

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

| **Table 6: Drug Interactions**<br>**Changes in Pharmacokinetic Parameters for Nelfinavir in the Presence of the Coadministered Drug** | | | | |
|---|---|---|---|---|
| | | | **Nelfinavir** | |
| **Coadministered Drug** | **Nelfinavir Dose** | **N** | **AUC (95% CI)** | **Cmax (95% CI)** |
| **HIV-Protease Inhibitors** | | | | |
| indinavir 800 mg q8h x 7 days | 750 mg Single Dose | 6 | ↑83% (34-150%) | ↑31% (13-52%) |
| ritonavir 500 mg q12h x 3 doses | 750 mg Single Dose | 10 | ↑152% (86-242%) | ↑44% (25-67%) |
| saquinavir 1200 mg tid x 4 days[1] | 750 mg Single Dose | 14 | ↑18% (5-33%) | ↔ |
| **Nucleoside Reverse Transcriptase Inhibitors** | | | | |
| zidovudine 200 mg + lamivudine 150 mg Single Dose | 750 mg q8h x 7-10 days | 11 | ↔ | ↔ |
| didanosine 200 mg Single Dose | 750 mg Single Dose | 9 | ↔ | ↔ |
| **Non-Nucleoside Reverse Transcriptase Inhibitors** | | | | |
| efavirenz 600 mg once daily x 7 days | 750 mg q8h x 7 days | 10 | ↑20% (5-38%) | ↑21% (8-36%) |
| nevirapine 200 mg once daily x 14 days followed by 200 mg bid x 14 days | 750 ↑↑mg tid x 36 days | 23 | ↔[2] | ↔[2] |
| delavirdine 400 mg q8h x 7 days | 750 mg q8h x 14 days | 12 | ↑107% (78-142%) | ↑88% (61-119%) |
| **Anti-infective Agents** | | | | |
| ketoconazole 400 mg once daily x 7 days | 500 mg q8h x 5-6 days | 12 | ↑35% (21-49%) | ↑25% (8-44%) |
| rifampin 600 mg once daily x 7 days | 750 mg q8h x 5-6 days | 12 | ↓82% (77-86%) | ↓76% (67-83%) |
| rifabutin 150 mg once daily x 8 days | 750 mg q8h x 7-8 days<br><br>1250 mg q12h x 7-8 days | 11<br><br>11 | ↓23% (12-33%)<br>↔ | ↓18% (6-29%)<br>↔ |

| **Table 6: Drug Interactions**<br>**Changes in Pharmacokinetic Parameters for Nelfinavir in the Presence of the Coadministered Drug** | | | | |
|---|---|---|---|---|
| | | | **Nelfinavir** | |
| **Coadministered Drug** | **Nelfinavir Dose** | **N** | **AUC (95% CI)** | **Cmax (95% CI)** |
| rifabutin 300 mg once daily x 8 days | 750 mg q8h x 7-8 days | 10 | ↓32% (10-48%) | ↓25% (6-38%) |
| azithromycin 1200 mg single dose | 750 mg tid x 9 days | 12 | ↓15% (6-24%) | ↔ |
| **Other Agents** | | | | |
| phenytoin 300 mg once daily x 7 days | 1250 mg bid x 14 days | 15 | ↔ | ↔ |
| omeprazole 40 mg qd x 4 days | 1250 mg bid x 4 days | 19 | ↓36% (15-52%) | ↓37% (20-51%) |

↑Indicates increase ↓Indicates decrease ↔Indicates no change (p value>0.05)

[1]Using the soft gelatin capsule formulation of saquinavir 1200 mg
[2]The overall effect of nevirapine on [NFV+M8 metabolite] was an 11 ± 35% (median -15%) reduction in the [NFV+M8 metabolite] area under the plasma concentration-time curve.

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 a meal 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, itraconazole, trimethoprim/sulfamethoxazole.

| Table 7: Drugs That Should Not be Coadministered With VIRACEPT | |
|---|---|
| Drug Class : Drug Name | Clinical Comment |
| Alpha 1-adrenoceptor antagonist:<br>Alfuzosin | CONTRAINDICATED due to potential for serious and/or life threatening adverse events such as hypotension. |
| Antiarrhythmics:<br>amiodarone, quinidine | CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias. |
| Antimycobacterial:<br>Rifampin | CONTRAINDICATED due to possible loss of virologic response and possible resistance to VIRACEPT or other co-administered antiretroviral agents. |
| Antipsychotics:<br>Quetiapine<br><br>Lurasidone<br><br>Pimozide | <br>Coadministration of quetiapine and VIRACEPT is not recommended.<br><br>CONTRAINDICATED due to potential for serious and/or life-threatening reactions<br>CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias. |
| Ergot Derivatives:<br>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. |
| HMG-CoA Reductase Inhibitors (statins):<br>lovastatin, simvastatin | CONTRAINDICATED due to potential for serious reactions such as risk of myopathy including rhabdomyolysis. |
| Inhaled Beta Agonist:<br>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. |

| | |
|---|---|
| PDE-5 Inhibitor:<br>sildenafil for the treatment of pulmonary arterial hypertension | Sildenafil is contraindicated when coadministered with VIRACEPT. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, prolonged erection, and syncope). |
| Proton Pump Inhibitors:<br>omeprazole | Can result in a decrease in nelfinavir concentrations that may lead to a loss of virologic response and possible resistance to VIRACEPT |
| Sedative/Hypnotics:<br>midazolam, triazolam | CONTRAINDICATED due to potential for serious and/or life threatening reactions such as prolonged or increased sedation or respiratory depression. |

| Table 8: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May be Recommended Based on Drug Interaction Studies (See Table 5 & 6 for Magnitude of Interaction) | | |
|---|---|---|
| **Concomitant Drug Class: Drug Name** | **Effect on Concentration** | **Clinical Comment** |
| **HIV-Antiviral Agents** | | |
| Protease Inhibitors:<br><br>indinavir<br><br><br>ritonavir<br><br>saquinavir (sgc)[1] | <br><br>↑nelfinavir<br>↑ indinavir<br><br>↑nelfinavir<br><br>↑saquinavir | Appropriate doses for this combination, with respect to safety and efficacy, have not been established. |
| Non-nucleoside Reverse Transcriptase Inhibitor:<br>delavirdine | <br><br>↑ nelfinavir<br>↓delavirdine | Appropriate doses for this combination with respect to safety and efficacy have not been established. |
| Nucleoside Reverse Transcriptase Inhibitor:<br>didanosine | NA[2] | 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 a meal). |

| Table 8: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May be Recommended Based on Drug Interaction Studies (See Table 5 & 6 for Magnitude of Interaction) | | |
|---|---|---|
| **Concomitant Drug Class: Drug Name** | **Effect on Concentration** | **Clinical Comment** |
| **Other Agents** | | |
| Anti-gout: Colchicine | ↑ colchicine | The following dose modifications for colchicine are recommended:<br><br>For treatment of gout-flares: 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.<br><br>Prophylaxis of gout-flares: 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.<br><br>For treatment of familial Mediterranean fever (FMF): Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).<br><br>**Patients with renal or hepatic impairment should not be given colchicine with VIRACEPT** (see **WARNINGS AND PRECAUTIONS**). |
| Anti-Coagulant: Warfarin | Coadministration of wafarin and VIRACEPT may affect concentrations of warfarin. | It is recommended that the international normalized ratio (INR) be monitored carefully during treatment with VIRACEPT, especially when commencing therapy. |
| Anti-Convulsants: carbamazepine, phenobarbital | NA[3] | May decrease nelfinavir plasma concentrations: VIRACEPT may not be effective due to decreased nelfinavir plasma concentrations in patients taking these agents concomitantly. |

| Table 8: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May be Recommended Based on Drug Interaction Studies (See Table 5 & 6 for Magnitude of Interaction) | | |
|---|---|---|
| **Concomitant Drug Class: Drug Name** | **Effect on Concentration** | **Clinical Comment** |
| Anti-Convulsant: Phenytoin | ↓phenytoin | 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 CYP3A4 inhibitor such as VIRACEPT, the combination should be used with caution and a lower dose of trazodone should be considered. |
| Anti-Mycobacterial: rifabutin | ↑rifabutin<br>↑nelfinavir (750 mg TID)<br>↔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. |
| Antipsychotics: Quetiapine | ↑quetiapine | VIRACEPT should not be used in combination with quetiapine. Due to CYP3A4 inhibition by VIRACEPT, concentrations of quetiapine are expected to increase, which can result in serious and/or life-threatening adverse reactions. If coadministration is necessary, monitoring and quetiapine dose reduction may be required (see WARNINGS AND PRECAUTIONS, General. |
| Endothelin Receptor Antagonist: Bosentan | ↑ bosentan | Start at or adjust bosentan to 62.5 mg once daily or every other day based upon individual tolerability when used with VIRACEPT. |

| | | |
|---|---|---|
| PDE-5 Inhibitor: Sildenafil, Vardenafil and Tadalafil | ↑ sildenafil<br>↑ vardenafil<br>↑ tadalafil | Concomitant use of PDE-5 inhibitors with protease inhibitors, such as nelfinavir, should be done with caution.<br><br>Co-administration of nelfinavir with a PDE-5 inhibitor is expected to substantially increase the PDE-5 concentration and may result in an increase in PDE-5 inhibitor-associated adverse events including hypotension, syncope, visual changes and priapism.<br><br><u>Use of PDE-5 inhibitors for pulmonary arterial hypertension:</u><br><br>• Use of sildenafil is contraindicated when used for the treatment of pulmonary arterial hypertension (see **CONTRAINDICATIONS**).<br><br>• Coadministration of tadalafil with VIRACEPT for the treatment of pulmonary arterial hypertension is not recommended. |
| | | <u>Use of PDE-5 inhibitors for erectile dysfunction:</u><br><br>Vardenafil should not be coadministered with VIRACEPT.<br><br>If concomitant use of VIRACEPT with PDE-5 Inhibitor is required, sildenafil at a single dose not exceeding 25 mg in 48 hours or tadalafil at a single dose not exceeding 10 mg dose in 72 hours, is recommended.<br><br>Use with increased monitoring for adverse events.<br><br>Drug interaction studies have not been conducted between nelfinavir and other PDE-5 inhibitors. |

| | | |
|---|---|---|
| HMG-CoA Reductase Inhibitor: atorvastatin | ↑atorvastatin | Use lowest possible dose of atorvastatin with careful monitoring. Do not exceed a total atorvastatin dose of 40 mg/day during coadministration with VIRACEPT. |
| Immuno-suppressants: cyclosporine, tacrolimus | ↑immunosuppressants | Plasma concentrations may be increased by VIRACEPT. |
| Inhaled/Nasal Steroid: Fluticasone | ↑fluticasone | Concomitant use of fluticasone proprionate and VIRACEPT may increase plasma concentrations of fluticasone proprionate. Caution should be undertaken for usage. Consider alternatives to fluticasone proprionate, particularly for long-term use. |
| Narcotic Analgesic: Methadone | ↓methadone | Dosage of methadone may need to be increased when co-administered 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. |

[1] Using the soft gelatin capsule (sgc) formulation of saquinavir
[2] Not applicable.
[3] Not available.

**Drug-Food Interactions**

Food increases nelfinavir exposure and decreases nelfinavir pharmacokinetic variability relative to the fasted state. VIRACEPT should be taken with a meal (see **DETAILED PHARMACOLOGY**).

**Drug-Herb Interactions**

**St. John's Wort:** St. John's Wort (*Hypericum perforatum*) or St. John's Wort-containing products should not be used while taking VIRACEPT. Coadministration of St. John's Wort with protease inhibitors, including nelfinavir, is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of nelfinavir and lead to loss of virologic response and possible resistance to nelfinavir or the class of protease inhibitors (see **CONTRAINDICATIONS**).

**Drug-Laboratory Test Interactions**
Interactions with laboratory tests have not been established.

## DOSAGE AND ADMINISTRATION

**Recommended Dose and Dosage Adjustment**

**Adults and Adolescents (13 years of age and older):** The recommended dose of VIRACEPT (nelfinavir mesylate) tablets is 1250 mg (as free base; five 250 mg tablets or two 625 mg tablets) twice daily or 750 mg (three 250 mg tablets) three times daily orally. VIRACEPT should be taken with a meal. It is recommended that VIRACEPT be used in combination with other antiretroviral agents.

**Geriatrics (>65 years of age)**
Clinical studies of nelfinavir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects (see **WARNINGS and PRECAUTIONS**, Geriatric Use.

**Children (2 -13 years):** The recommended oral dose of VIRACEPT for pediatric patients 2 to 13 years of age is 25 - 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 sufficiently established to recommend a BID dosing regimen.

Overall, use of VIRACEPT in the pediatric population is associated with highly variable drug exposure. The high variability may be due to increased clearance compared to adults and difficulties with compliance and adequate food intake with dosing (see **WARNINGS AND PRECAUTIONS-Pediatrics; and PHARMACOLOGY- Special Populations**)

For children unable to take tablets, VIRACEPT Oral Powder may be administered (see **Administration**). The maximum recommended dose is 2500 mg per day. The healthcare provider should assess appropriate formulation and dosage for each patient. Crushed tablets can be used in lieu of powder.

The recommended pediatric dose of VIRACEPT to be administered three times daily is described in Table 9.

**Table 9: Pediatric Dose to be Administered Three Times Daily**

| Body Weight | | Number of Level 1 gm Scoops | Number of Level Teaspoons | Number of 250 mg Tablets |
|---|---|---|---|---|
| Kg | Lbs | | | |
| 7 to < 8.5 | 15.5 to 18.5 | 4 | 1 | --- |
| 8.5 to < 10.5 | 18.5 to < 23 | 5 | 1 1/4 | 1 |
| 10.5 to < 12 | 23 to < 26.5 | 6 | 1 1/2 | --- |
| 12 to < 14 | 26.5 to < 31 | 7 | 1 3/4 | --- |
| 14 to < 16 | 31 to < 35 | 8 | 2 | --- |
| 16 to < 18 | 35 to < 39.5 | 9 | 2 1/4 | --- |
| 18 to < 23 | 39.5 to < 50.5 | 10 | 2 ½ | 2 |
| ≥ 23 | ≥ 50.5 | 15 | 3 3/4 | 3 |

**Missed Dose**

If a dose is missed, patients should take the next dose as soon as possible. A dose should not be doubled.

**Administration**

***Tablets:*** Patients unable to swallow tablets may place whole tablets or crushed tablets in a small amount of water to disperse before ingestion or they may mix crushed tablets in a small amount of food. Once mixed with food or dispersed in water, the entire contents must be consumed in order to obtain the full dose. It is recommended that the entire contents be consumed immediately after mixing with food or dispersing in water. The drinking glass should be rinsed and the rinse swallowed to insure the entire dose is consumed. Acidic food or juice (i.e., orange juice, apple juice or apple sauce) are not recommended to be used in combination with VIRACEPT because the combination may result in a bitter taste.

***Reconstitution of Oral Powder:*** The oral powder may be mixed with a small amount of water, milk, formula, soy formula, soy milk or nutritional preparations; once mixed, the entire contents must be consumed in order to obtain the full dose. The recommended use period for storage of the product in these media is 6 hours under refrigeration (2-8°C). Dosing media not recommended include any acidic food or juice (e.g., orange juice, apple juice or apple sauce) because the combination may result in a bitter taste. VIRACEPT Oral Powder should not be reconstituted with water in its original container.

## OVERDOSAGE

For the management of a suspected drug overdose, contact your regional Poison Control Centre.

Human experience of acute overdose with VIRACEPT (nelfinavir mesylate) is limited. There is no specific antidote for overdose with VIRACEPT. Administration of activated charcoal should be

used to aid removal of unabsorbed drug. Since nelfinavir mesylate is highly protein bound, dialysis is unlikely to significantly remove drug from blood.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Nelfinavir is an inhibitor of the human immunodeficiency virus (HIV) protease. The HIV protease is an enzyme required for the proteolytic cleavage of the viral polyprotein precursors to the individual proteins found in infectious HIV. Nelfinavir reversibly binds to the active site of the HIV protease and prevents it from cleaving the *gag-pol* polyprotein resulting in the formation of immature non-infectious viral particles.

### Pharmacodynamics

#### Antiretroviral Activity In vitro

The antiretroviral 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 $EC_{95}$ (95% effective concentration) of nelfinavir ranged from 7 to 111 nM. Drug combination studies with protease inhibitors showed nelfinavir has 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. When nelfinavir was combined with reverse transcriptase inhibitors *in vitro*, nelfinavir demonstrated additive (didanosine or stavudine) to synergistic (zidovudine, lamivudine, zalcitabine, abacavir, tenofovir, delavirdine, efavirenz or nevirapine) antiviral activity without enhanced cytotoxicity.

HIV isolates with reduced susceptibility to nelfinavir have been selected *in vitro*. Genotypic analysis of a variant which exhibited a nine-fold decrease in sensitivity showed a unique substitution of an aspartic acid (D) to an asparagine (N) in HIV protease at amino acid residue 30 (D30N). Consistent with the *in vitro* results, the predominant genotypic change in clinical HIV isolates with reduced susceptibility to nelfinavir is the D30N substitution (See **VIROLOGY**).

#### Effect 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 dose of VIRACEPT 3125 mg was administered following an administration of VIRACEPT 1250 mg twice daily. The exposure at 3125 mg was 1.4-fold that at 1250 mg.

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.

## Pharmacokinetics

Absorption: Administration of a single 1250 mg dose of VIRACEPT (nelfinavir mesylate) 250 mg tablets (total of 5 tablets) to normal, healthy volunteers with a meal containing 125 to 1000 kilocalories and 20% to 50% calories from fat was associated with a 2.2 to 5.2 and 2.0 to 3.3 fold increase in nelfinavir AUC and $C_{max}$, respectively, relative to fasting. 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 **DETAILED PHARMACOLOGY - Absorption, ADVERSE REACTIONS**). To enhance bioavailability and minimize pharmacokinetic variability, nelfinavir should be taken with a meal.

**Distribution:** The apparent volume of distribution ($VD_{area}/F$) for nelfinavir to adult humans was approximately 150L, i.e. 2L/kg. Nelfinavir in serum is extensively protein-bound (>98%). In both humans and animals, the estimated distribution volumes exceed total body water, suggesting extensive penetration of nelfinavir into tissues (see **DETAILED PHARMACOLOGY - Distribution**).

**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 isoforms 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 equal to the parent drug.

**Elimination:** Oral clearance estimates after single doses (24-33 L/h) and multiple doses (26-61 L/h) indicate that nelfinavir is a drug with medium to high hepatic bioavailability. The terminal half-life in plasma was typically 2.5 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 nelfinavir (22%) and numerous oxidative metabolites. Only 1-2% of the dose was recovered in urine, of which unchanged nelfinavir was the major component.

**Special Populations and Conditions**

**Pharmacokinetics in Children:** 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 pharmacokinetics results are reported in Table 13 (see **DETAILED PHARMACOLOGY – Special Populations, *Pharmacokinetics in Children***).

**Hepatic Insufficiency**: Pharmacokinetics of nelfinavir after a single dose of 750 mg VIRACEPT was studied in patients with liver impairment and healthy volunteers. A 49%-69% increase was observed in AUC of nelfinavir in the hepatically impaired groups (Child-Turcotte-Pugh Classes A to C) compared to the healthy group. The single, oral 750 mg dose of VIRACEPT was safe and

well tolerated by the healthy and hepatically impaired subjects participating in this study. Specific dosage recommendations for VIRACEPT cannot be made based on the results of this study; it is recommended to monitor liver function tests in patients who are hepatically impaired.

## STORAGE AND STABILITY

VIRACEPT Tablets and Oral Powder should be stored at 15° to 30°C in a USP tight container. Exposure to temperature as low as -20°C for periods of up to 24 hours will not adversely affect VIRACEPT Tablets stability.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

VIRACEPT Tablets, 625 mg nelfinavir (from nelfinavir mesylate) are white, oval-shaped, clear film-coated tablets engraved with "V" on one side and "625" on the other. Available in plastic bottles containing 120 tablets.

VIRACEPT Tablets, 250 mg nelfinavir (from nelfinavir mesylate) are light blue, capsule-shaped, clear film-coated tablets engraved with “VIRACEPT” on one side and “250 mg” on the other. Available in plastic bottles containing 270 or 300 tablets.

VIRACEPT Oral Powder is an off-white, sweetened powder containing 50 mg nelfinavir (from nelfinavir mesylate) in each level scoopful (1 gram). Available in a multiple use bottle containing 144 grams of powder with scoop.

**Composition**

Each tablet also contains the following common inactive ingredients: calcium silicate, crospovidone, hypromellose, magnesium stearate 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. In addition to nelfinavir mesylate, the oral powder contains inactive ingredients: aspartame, crospovidone, dibasic potassium phosphate, hypromellose, maltodextrin, microcrystalline cellulose, natural and artificial flavors, and sucrose palmitate.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION
### Drug Substance

**Proper name:** nelfinavir mesylate (USAN)
nelfinavir (INN)

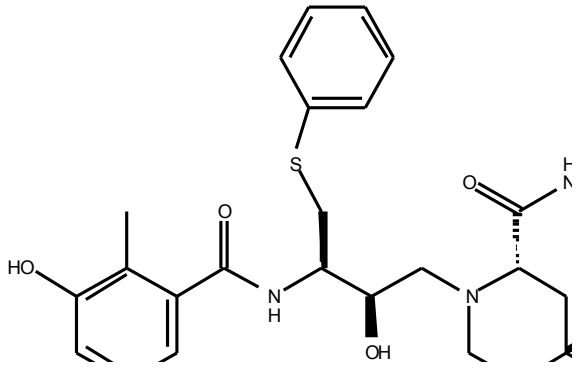
**Chemical name:** [3S-[2(2S*,3S*),3α,4aβ,8aβ]]-N-(1,1-dimethylethyl)decahydro-2-[2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylthio)butyl]-3-isoquinolinecarboxamide mono-methanesulfonate (salt).

(3S,4aS,8aS)-N-*tert*-Butyl-2-[(2R,3R)-3-(3,2-cresotamido)-2-hydroxy-4-(phenylthio)butyl]decahydro-3-isoquinolinecarboxamide monomethanesulfonate (salt)

**Molecular formula:** $C_{32}H_{45}N_3O_4S.CH_4O_3S$

**Molecular weight:** 663.90 (567.79 as the free base)

**Structural formula:**




**Description:** Nelfinavir mesylate is a white to off-white amorphous powder, slightly soluble in water at pH $\leq$ 4 and freely soluble in methanol, ethanol, 2-propanol and propylene glycol.

**Melting Point:**

No melting point is observed, the compound slowly becomes glassy, evolves gas, melts and decomposes over the range of 100° - 200°C.

**$pK_a$ and pH values:**

A pH of 4 was measured for a 0.45 mg/mL solution of nelfinavir mesylate in water. The $pK_a$ was determined by potentiometric titration:
$pK_{a,1} = 6.00 \pm 0.10$
$pK_{a,2} = 11.06 \pm 0.10$

**Partition Coefficient:**

The log P of AG1346 nelfinavir free base was determined by potentiometric titration. Log $P_{octanol/water}$ was determined by comparing the aqueous $pK_a$ to the $pK_a$ obtained with octanol:
log $P_{octanol/water}$ = 4.07 ± 0.2
log D @ pH 7.4 = 4.02

## CLINICAL TRIALS

### Clinical Studies

In the clinical study 542 described below, the primary efficacy measure was the percent of patients with plasma HIV RNA levels below the lower limit of assay quantification. This has been performed using both the Roche RT-PCR (Amplicor) HIV-1 Monitor assay (LOQ 400 copies/mL) and the Ultrasensative PCR assay (LOQ 50 copies/mL). In the analysis presented in each figure, patients who terminated the study early for any reason, 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 the LOQ at the missing time points.

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

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 (150 mg BID). The median age of these patients was 36, with 84% male and 91% Caucasian. Patients had received less than 6 months of therapy with nucleoside transcriptase inhibitors and were naive to protease inhibitors. Overall mean baseline $CD_4$ cell count was 296 cells/$mL^3$ 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 $CD_4$ 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/mm3 at 48 weeks.

**Table 10: Outcomes of Randomized Treatment Through 48 Weeks (Study 542)**

| 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 ARV 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 on 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

In the clinical study 511 described below, the primary efficacy measure was the percent of patients with plasma HIV RNA < 400 copies/mL, using the Roche RT-PCR (Amplicor) HIV-1 Monitor assay. In the analysis presented in each figure, patients who terminated the study early for any reason, 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 at the missing time points.

Study 511: VIRACEPT + zidovudine (ZDV) + lamivudine versus zidovudine + lamivudine

Study 511 was a double-blind, randomized, placebo controlled trial in HIV-1 infected patients with no prior antiretroviral therapy. At baseline patients were randomized to one of three treatment groups: VIRACEPT 500 mg TID plus zidovudine (ZDV; 200 mg TID) plus lamivudine (150 mg BID), VIRACEPT 750 mg TID plus zidovudine (ZDV; 200 mg TID) plus lamivudine (150 mg BID) or zidovudine (200 mg TID) plus lamivudine (150 mg TID) alone. The median age of these patients was 35, with 89% male and 78% Caucasian. The mean baseline serum viral RNA was 5.21 $\log_{10}$ copies/mL (160,394 copies/mL) and the mean baseline $CD_4$ cell count for all patients was 288 cells/$mm^3$. After 24 weeks of treatment, patients initially randomized to zidovudine plus lamivudine plus placebo were randomized to receive either VIRACEPT 750 mg or 500 mg in place of placebo.

At 48 weeks, approximately 75% of the patients treated with VIRACEPT 750 mg TID plus zidovudine and lamivudine remained below the level of detection of the assay (<400 copies/mL) (on treatment analysis); a mean increase of 198 cells/μL was observed in CD4 cell count for the VIRACEPT 750 mg treatment group.

## VIROLOGY

***Mechanism of Action:*** HIV protease is an enzyme required for the proteolytic cleavage of the viral polyprotein precursors to the individual proteins found in infectious HIV. The cleavage of these viral polyproteins is essential for the maturation of infectious virus. Nelfinavir binds to the active site of HIV protease and prevents cleavage of the polyproteins resulting in the formation of immature non-infectious viral particles.

***Antiretroviral Activity in vitro:*** The antiretroviral 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 the HIV-2 strain ROD. The $EC_{95}$ (95% effective concentration) of nelfinavir ranged from 7 to 111 nM. Drug combination studies with protease inhibitors showed nelfinavir has 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. When nelfinavir was combined with reverse transcriptase inhibitors *in vitro*, nelfinavir demonstrated additive (didanosine or stavudine) to synergistic (zidovudine, lamivudine, zalcitabine, abacavir, tenofovir, delavirdine, efavirenz or nevirapine) antiviral activity without enhanced cytotoxicity.

***Drug Resistance:*** HIV isolates with reduced susceptibility to nelfinavir have been selected *in vitro*. Genotypic analysis of a variant which exhibited a nine-fold decrease in sensitivity showed a unique substitution of an aspartic acid (D) to an asparagine (N) in HIV protease at amino acid residue 30 (D30N). Genotypic changes in HIV protease genes obtained from 58 patients enrolled in phase I/II trials were also evaluated. Consistent with the *in vitro* results, the predominant change observed was the D30N substitution. In a subset (16 of 55) of these patients followed for up to 44 weeks, this substitution was maintained. In an *in vitro* study of 55 resistant isolates, some of the mutations described for other protease inhibitors were either not observed (G48V, V82F/T, I84V) or only occasionally observed (L90M, 3 of 55 isolates). The overall incidence of the D30N mutation in the viral protease of evaluable patients (n=157) 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. The L90M substitution has been observed less frequently and its emergence forms a second pathway to reduced nelfinavir susceptibility that is potentially mutually exclusive with that of the D30N pathway.

***Cross-Resistance to Other Antiretroviral Agents:*** *Non-clinical Studies* - Cross-resistance between nelfinavir and reverse transcriptase inhibitors is unlikely because of the different enzyme targets involved. Isolates with high level resistance to zidovudine, lamivudine or nevirapine remain fully susceptible to nelfinavir *in vitro*. Patient derived recombinant HIV isolates containing the D30N mutation (n=4) and demonstrating high-level (>10-fold) nelfinavir resistance remain 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 nelfinavir and had varying levels of susceptibility to saquinavir, indinavir, lopinavir

and amprenavir *in vitro*. Six clinical isolates containing the D30N substitution showed no change in sensitivity to saquinavir, ritonavir, indinavir or amprenavir *in vitro*. In addition, an HIV recombinant virus containing the D30N substitution exhibited a reduced sensitivity to nelfinavir, yet retained full sensitivity to the other protease inhibitors. 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 protease inhibitors (e.g. G48V, V82A/F/T, 184V, L90M) appeared to confer high-level cross-resistance to nelfinavir.

*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). 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.

## DETAILED PHARMACOLOGY

### Pharmacokinetics

***Absorption:***

Pharmacokinetics 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, 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 11.

**Table 11: Summary of a Pharmacokinetic Study in HIV-positive Patients with Multiple Dosing of 1250 mg BID for 28 days and 750 mg TID for 28 days**

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

Data are mean ± SD

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

In healthy volunteers receiving a single 1250 mg dose, the 625 mg tablet was not bioequivalent to the 250 mg tablet formulation. Under fasted conditions (n=27), the AUC and $C_{max}$ were 34% and 24% higher, respectively, for the 625 mg tablets. In a relative bioavailability assessment under fed conditions (n=28), the AUC was 24% higher for the 625 mg tablet; the $C_{max}$ was comparable for both formulations (15% higher for the 625 mg tablet). (See **ADVERSE REACTIONS**).

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

***Effect of Food on Oral Absorption:***

Food increases nelfinavir exposure and decreases nelfinavir pharmacokinetic variability relative to the fasted state. Healthy volunteers received a single dose of 1250 mg of VIRACEPT 250 mg tablets (5 tablets) under fasted or fed conditions (three different meals). Results from the study are summarized in Table 12.

**Table 12: Changes 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 | 21 | 2.2 | 2 | 1 |
| 500 | 20 | 22 | 3.1 | 2.3 | 2 |
| 1000 | 50 | 23 | 5.2 | 3.3 | 2 |

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:** In both animals and humans, the estimated volumes of distribution (2-7 L/kg) exceeded total body water, suggesting extensive penetration of nelfinavir into tissues. Although no studies have been conducted in humans, studies with a single 50 mg/kg dose of $^{14}$C-nelfinavir in rats showed that concentrations in the brain greatly exceeded the *in vitro* $EC_{95}$ for antiviral activity. Nelfinavir in serum is extensively protein-bound ($\geq$ 98%). High plasma concentrations of saquinavir increase the percent of free nelfinavir *in vitro*.

**Special Populations:**

***Pharmacokinetics in Children:*** The pharmacokinetics of nelfinavir have been investigated in 5 studies in pediatric patients from birth to 13 years of age either receiving nelfinavir three times or

twice daily. The dosing regimens and associated $AUC_{24}$ values are summarized in Table 13. (see **WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION**).

Table 13: Summary of Steady-state $AUC_{24}$ of Nelfinavir in Pediatric Studies

| Protocol No. | Dosing Regimen | N[1] | Age (years) | $AUC_{24}$ (mg·hr/L)[2] (95% CI) |
|---|---|---|---|---|
| AG1343-524 | 20 mg/kg TID | 14 | >2 | 48.3 (34.0-68.4) |
| AG1343-556 | 25-35 mg/kg TID | 86 | ≥2 | 33 (9.0-121) |
| PACTG-725 | 55 mg/kg BID | 6 | >2 | 89.9 (50.4-160) |
| PENTA 7 | 40 mg/kg TID | 4 | <2 | 33.0 (22.5-48.4) |
| PENTA 7 | 75 mg/kg BID | 12 | <2 | 33.8 (26.6-42.9) |
| PACTG-353 | 40 mg/kg BID | 10 | 1-6 weeks | 36.5 (26.4-50.5) |

[1]N: number of subjects with evaluable pharmacokinetics results
[2]The $AUC_{24}$ presented is the geometric mean

In children between the ages of 2 and 13 years, the oral clearance of nelfinavir is approximately 2 to 3 times higher than in adults. Administration of VIRACEPT (nelfinavir mesylate) oral powder or tablets with food at a dose of approximately 25-30 mg/kg three times daily achieves steady-state plasma concentrations similar to adult patients receiving 500 to 750 mg TID

**Drug Interactions** (also see **DRUG INTERACTIONS**)
CYP3A and CYP2C19 appear to be the predominant enzymes for nelfinavir metabolism in humans. The potential ability of nelfinavir to inhibit the major human cytochrome P450 isoforms (CYP3A, CYP2C19, CYP2D6, CYP2C9, CYP1A2 and CYP2E1) has been investigated *in vitro*. Only CYP3A was inhibited at concentrations in the therapeutic range; however, nelfinavir was a less potent inhibitor of CYP3A (i.e., larger Ki) compared to other known inhibitors (Table 14).

**Table 14**
**Comparison of CYP3A* inhibition in Human Liver Microsomes**

| Inhibitor | Ki (μM) |
|---|---|
| Ritonavir | 0.1 |
| Ketoconazole | 0.1 |
| Indinavir | 0.7 |
| Saquinavir | 4.0 |
| Nelfinavir | 4.8 |

*All experiments were conducted using pooled human male and female microsomes by evaluation of testosterone 6β-hydroxylase activity

## TOXICOLOGY

### Acute Toxicity
The no observed adverse effect level (NOAEL) was > 500 mg/kg in both the mouse and rat and the LD50 exceeded 5000 mg/kg when nelfinavir was evaluated in rats as the free base.

### Repeat Dose Toxicity Studies
In rats treated with up to 1000 mg/kg/day of nelfinavir mesylate for a maximum of 26 weeks, there were no treatment-related deaths and no macroscopic or microscopic findings indicative of systemic toxicity. Increased in liver weights and dose-dependent thyroid follicular cell hypertrophy were considered related to compound-related with metabolic induction in the liver. These findings were partially reversible in animals following a four-week treatment-free recovery period. Plasma concentrations of nelfinavir in the 15 - 17 µg/mL range were recorded at the high dose level, although repeat dosing in this species consistently led to reduced blood levels.

Four repeat dose GLP toxicity studies of 1, 2, 4 and 26 weeks duration were conducted with nelfinavir in cynomolgus monkeys using treatment levels of up to 800 mg/kg/day, considered the maximum daily deliverable dose. Twice-daily administration was employed for the majority of studies to maximize systemic exposure. In the 28-day study which involved dose levels up to 150 mg/kg/day, no adverse clinical signs and no evidence of systemic toxicity were noted. Plasma levels in the human therapeutic range were sustained throughout the treatment period. In a 26-week study conducted at dose levels 100, 250 and 800 mg/kg/day nelfinavir, long-term treatment (predominantly after 18 weeks) with 250 or 800 mg/kg/day was associated with an increased frequency of soft feces. Three high dose animals (800 mg/kg/day) and one mid-dose animal (250 mg/kg/day) were sacrificed prior to scheduled termination after exhibiting weight loss, reduced food consumption and general physical decline. These animals showed histopathological findings consistent with stress coupled with enteritis and/or minor inflammation in the gastrointestinal tract. An additional animal which exhibited similar symptoms was successfully treated with a 10-day course of oral neomycin sulfate, a non systemically absorbed antibiotic. This result suggests that the observed adverse effects were local in origin, possibly resulting from perturbation of gut microflora. Gastrointestinal exposure (mg/kg) at the high dose level was approximately 20-fold greater than in man at the recommended dose.

Other findings in the monkey were minor or of uncertain toxicological significance such as reduced bilirubin and alkaline phosphatase activities. There were no histopathological findings except for two high dose animals which showed gastrointestinal effects similar to those seen in the animals which did not complete the full course of treatment as described above. There was no evidence of renal or hepatic injury associated with nelfinavir treatment.

### Fertility and Reproduction
No compound-related effects were noted on either male or female mating and fertility indices or intrauterine survival of F1 embryos in a fertility and early embryonic development study conducted in the rat at nelfinavir doses up to 1000 mg/kg/day. Likewise, no maternal or developmental effects were demonstrated in an embryo-fetal development study conducted in rats at doses up to 1000 mg/kg/day. In another embryo-fetal study conducted in the rabbit, no fetal development effects

were demonstrated at nelfinavir doses up to 1000 mg/kg/day (maternally-toxic). However, even at the highest dose evaluated, systemic nelfinavir exposure in rabbits was appreciably lower than that achieved in humans administered therapeutic doses of VIRACEPT. In a peri-/post-natal development study conducted in the rat at nelfinavir doses up to 1000 mg/kg/day, no compound-related effects were demonstrated on pregnancy, parturition and lactation of the $F_0$ generation, or growth, viability, development and reproductive performance of the $F_1$ generation. Toxicokinetic analyses showed that nelfinavir mesylate absorption in pregnant rats was comparable to that recorded for non-gravid females, and preliminary data from a lacteal secretion study has established that nelfinavir mesylate is excreted in milk at levels similar to those recorded in plasma.

**Carcinogenesis and Mutagenesis**

In a 2-year carcinogenicity study, rats were administered nelfinavir at concentration of 0, 100, 300, and 1000 mg/kg/day via oral gavage. Nelfinavir exposures (AUC) achieved in high-dose animals represent 3- to 4-fold increases over human exposure at the recommended therapeutic dose (750 mg TID or 1250 mg BID). Treatment-related histopathological findings were limited to thyroid follicular cell hyperplasia, adenomas, and carcinomas in male rats at 300 and 1000 mg/kg/day and in female rats at 1000 mg/kg/day. The mechanism of follicular cell proliferation that resulted in neoplasms in this study was not apparent from the various evaluations conducted. Moreover, chronic nelfinavir treatment in rats has been demonstrated to produce effects consistent with microsomal enzyme induction. Microsomal enzyme induction by a variety of compounds has been identified as a mechanism which predisposes rats, but not humans, to thyroid neolasms. The weight of evidence indicates that nelfinavir is unlikely to be a carcinogen in humans and nelfinavir was not mutagenic or clastogenic in a battery of *in vitro* and *in vivo* tests including microbial mutagenesis (Ames), mouse lymphoma, chromosome aberrations in human lymphocytes, and an *in vivo* rat micronucleus assay.

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# PART III: CONSUMER INFORMATION

**PRVIRACEPT®**
**Nelfinavir tablets,**
**250 mg, 625 mg**
**(as nelfinavir mesylate)**

**Nelfinavir powder, 50 mg/g**
**(as nelfinavir mesylate)**

**This leaflet is part III of a three-part "Product Monograph" published when VIRACEPT was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VIRACEPT.** Your doctor and pharmacist are your primary sources of information about your health and the medicine you take. Consult with your doctor or pharmacist if you have questions about your health, any medication you take, or the information given here.

## ABOUT THIS MEDICATION

**What the medication is used for:**
VIRACEPT is the brand name of the antiviral agent, nelfinavir mesylate. It is a member of a class of drugs called protease inhibitors. VIRACEPT is an important part of your anti-HIV therapy. It is active against the Human Immunodeficiency Virus (HIV), helping to reduce the number of HIV particles in blood.

Your doctor has prescribed VIRACEPT for you because you have HIV infection. HIV infection is a disease spread by contact with blood or sexual contact with an infected person.

VIRACEPT should be taken in combination with other antiretroviral agents. This combination has been shown to reduce significantly the number of HIV particles in the blood and to increase significantly circulating $CD_4$ cells.

This product has been prescribed for you personally, and you should not pass it on to others.

VIRACEPT is not a cure for HIV infection or AIDS. People taking VIRACEPT may still develop opportunistic infections or other illnesses associated with HIV disease. Some of these conditions are pneumonia, herpes virus infections, *Mycobacterium avium* complex (MAC) infections, and Kaposi's sarcoma. You should, therefore, remain under the care of your doctor while taking VIRACEPT.

Treatment with VIRACEPT has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Continue to practice safer sex and do not reuse or share needles. Even when you are on the anti-HIV medications and your HIV viral load is "undetectable", you still have HIV in your body and you can still pass HIV to others. It is very important to take precautions to avoid passing HIV to others.

**What it does:**
VIRACEPT is a medicine which interferes with the action of an HIV protease enzyme, to prevent normal viral protein formation. This interference creates immature, non-infectious viral particles which helps reduce the infection.

**When it should not be used:**
- If you are allergic or hypersensitive to nelfinavir or any of the components in the product (see **What the important nonmedicinal ingredients are**)

- If you are taking one or more of the following drugs:

| Drug class | Drugs |
|---|---|
| - gastrointestinal prokinetic | cisapride* |
| - antiarrythmics | amiodarone, quinidine |
| - ergot derivatives | dihydroergotamine, ergonovine, ergotamine, methylergonovine |
| - ~~neuroleptic~~ | ~~pimozide~~ |
| - sedative/hypnotics | midazolam, triazolam |
| - HMG-CoA reductase inhibitors | lovastatin, simvastatin |
| - herbal products | St. John's Wort (*hypericum perforatum*) |
| - alpha 1-adrenoceptor antagonist | alfuzosin |
| - PDE-5 inhibitors | sildenafil when used to treat pulmonary arterial hypertension (PAH) |
| - antimycobacterial agents | rifampin |
| - Antipsychotics | lurasidone; pimozide, |

* is no longer marketed in Canada

**What is the medicinal ingredient:**
Nelfinavir mesylate

**What the important nonmedicinal ingredients are:**
Crospovidone. Other non-medicinal ingredients present in VIRACEPT film-coated tablets include calcium silicate, magnesium stearate, hypromellose and triacetin. In addition the 625 mg tablet contains colloidal silicon dioxide and the 250 mg tablet contains FD&C blue #2 powder.
Other non-medicinal ingredients present in VIRACEPT oral powder include microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, hydroxypropyl methycellulose, aspartame, sucrose palmitate, and natural and artificial flavour.

**What dosage forms it comes in:**
Film-coated Tablets - 250 mg and 625 mg nelfinavir (from nelfinavir mesylate);
Oral Powder - 50 mg/g nelfinavir (from nelfinavir mesylate)

## WARNINGS AND PRECAUTIONS

Tell your health care provider before taking VIRACEPT if:

- you have any medical problems, including liver disease, bleeding problems (hemophilia), or diabetes
- You are taking any medications including nonprescription, herbal or street drugs, natural health products as many drugs may interfere with the action of VIRACEPT, or VIRACEPT may interfere with these other drugs. (See **Interactions with this medication** section)
- You are pregnant or planning to become pregnant. VIRACEPT is not recommended for use in pregnant women. If you take VIRACEPT while pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.
- You are breastfeeding or planning to breastfeed. There is a possibility that VIRACEPT may be excreted in breast milk. It is recommended that HIV-infected women not breastfeed their infants under any circumstances to avoid transmission of HIV. You should discuss with your doctor the best way to feed your baby.

Other warnings:

- VIRACEPT may reduce the effectiveness of birth control pills, so an alternative or additional contraceptive measure should be used.
- If you take sildenafil or other PDE-5 inhibitors and VIRACEPT together, you may be at increased risk of side effects such as low blood pressure, visual changes, and penile erection lasting more than 4 hours. If you suffer these side effects, seek immediate medical assistance.
- Do not take St. John's Wort (*Hypericum perforatum*) (see **Interactions with this medication** section)
- VIRACEPT should not be used in combination with quetiapine, due to serious and possibly life-threatening reactions, including sedation and coma. If coadministration is necessary, your doctor may need to monitor and adjust the dose of quetiapine.
- VIRACEPT should generally **not** be used with salmeterol. This may cause serious and life-threatening reactions in the heart such as:
    - Change in heart rhythm (QT prolongation)
    - Irregular or hard heartbeats, pause in heartbeats (palpitations)
    - Fast heartbeats ( sinus tachycardia)

    If your doctor decides you need Viracept, your doctor may change the dose or follow your condition.
- VIRACEPT powder (50 mg/g) contains aspartame, a source of phenylalanine and therefore may not be suitable for persons with phenylketonuria.
- The activity of VIRACEPT in children below the age of 2 is not yet known and should not be used in this group unless the doctor decides it is needed.

As VIRACEPT has not been shown to reduce the risk of transmission of HIV to others through sexual contact, practicing safer sex, such as using condoms is very important.

Talk to your doctor before you start taking any new prescription or non-prescription medicines or herbal supplements with VIRACEPT.

## INTERACTIONS WITH THIS MEDICATION

The following medications may interfere with the action of VIRACEPT, or VIRACEPT may interfere with the actions of these other medications. Your doctor will advise you whether these should be used or whether dosage adjustments may be necessary for VIRACEPT or these other drugs:

- Cholesterol lowering medicines - atorvastatin and fluvastatin
- carbamazepine, phenobarbital, phenytoin, dexamethasone, calcium channel blockers, quetiapine
- indinavir, ritonavir, saquinavir, rifabutin, delavirdine, omeprazole, fluticasone proprionate, trazodone
- sildenafil or other PDE-5 inhibitors. Your doctor will discuss with you the possible side effects of using both VIRACEPT and PDE-5 inhibitors together (see **Other warnings**)
- bosentan, salmeterol, warfarin
- colchicine if you have liver or kidney problems

## PROPER USE OF THIS MEDICATION

**Usual Dose:**

Take VIRACEPT exactly as prescribed by your doctor. Do not increase or decrease the number of pills or doses per day or stop taking your anti-HIV medicines before speaking with your doctor, even if you are feeling better.

The following statements apply to VIRACEPT unless otherwise prescribed by your physician. Please observe these instructions for use, otherwise you will not fully benefit from VIRACEPT.

The recommended adult dose (adults and adolescents 13 years and older) of VIRACEPT is 1250 mg given as five 250 mg tablets or two 625 mg tablets taken two times a day or 750 mg given as three 250 mg tablets to be taken three times a day, as prescribed by your physician. VIRACEPT tablets should be taken by mouth with a meal to help achieve higher VIRACEPT levels.

The usual dose of VIRACEPT oral powder or tablets for children 2 to 13 years of age is 25-30 mg per kg three times daily as shown below. VIRACEPT oral powder and tablets should be taken by mouth, with a meal. The maximum recommended dose is 2500 mg per day. For children able to take tablets, VIRACEPT tablets may be administered instead of the oral powder.

**Children Dose to be Administered Three Times Daily**

| Body Weight | | Number of Level 1 gm Scoops[1] | Number of Level Teaspoons[2] | Number of 250 mg Tablets |
|---|---|---|---|---|
| Kg | Lbs | | | |
| 7 to < 8.5 | 15.5 to 18.5 | 4 | 1 | --- |
| 8.5 to < 10.5 | 18.5 to < 23 | 5 | 1 1/4 | 1 |
| 10.5 to < 12 | 23 to < 26.5 | 6 | 1 1/2 | --- |
| 12 to < 14 | 26.5 to < 31 | 7 | 1 3/4 | --- |
| 14 to < 16 | 31 to < 35 | 8 | 2 | --- |
| 16 to < 18 | 35 to < 39.5 | 9 | 2 1/4 | --- |
| 18 to < 23 | 39.5 to < 50.5 | 10 | 2 ½ | 2 |
| ≥ 23 | ≥ 50.5 | 15 | 3 3/4 | 3 |

**[1] 1 level scoop contains 50 mg of VIRACEPT**
**[2] 1 level teaspoon contains 200 mg of VIRACEPT**

***Special considerations when taking VIRACEPT:***
***Tablets:*** VIRACEPT Tablets are film-coated to help make them easier to swallow. If you are unable to swallow the tablets, they may be placed whole or crushed in a small amount of water to disperse before swallowing. They may also be crushed and mixed with a small amount of food. Once dispersed in water or mixed with food, the entire contents must be consumed. You should rinse your glass or dish with water and consume the rinse to ensure you have consumed your entire dose. Acidic food or juice (i.e., orange juice, apple juice or apple sauce) should not be used because it may result in a bitter taste.

***Oral Powder:*** VIRACEPT oral powder may be mixed with a small amount of water, milk, formula, soy formula, soy milk, or nutritional preparations; once mixed, the entire contents must be consumed in order to obtain the full dose. It is recommended that VIRACEPT oral powder mixed in these media be consumed immediately. If it is not consumed immediately, the mixture must be stored under refrigeration (2-8ºC) for up to 6 hours. VIRACEPT oral powder should not be mixed with orange juice, apple juice, apple sauce or other liquids or foods that are acidic because the combination may result in a bitter taste. VIRACEPT Oral Powder should not be reconstituted with water in its original container.

**How to optimize your use of VIRACEPT**
VIRACEPT should be taken in combination with other antiretroviral agents. Clinical trials have found that combination antiviral therapy is more effective than one drug alone at reducing the amount of HIV in the blood and at reducing the development of resistance.
If you are taking both didanosine and VIRACEPT you should take VIRACEPT with a meal one hour after or more than two hours before you take didanosine.

**Overdose:**

In case of drug overdose, contact your health care practitioner, hospital emergency department or regional Poison Control Centre, even if there are no symptoms.

**Missed Dose:**
It is very important that you take your VIRACEPT and other antiretroviral therapy every dose as prescribed by your doctor. If you miss a dose you should take the next dose as soon as possible. However, if you skip a dose, do not double the next dose. You should contact your doctor or pharmacist if you are unsure what to do.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

If you notice any unwanted effects not mentioned in this leaflet or if you are unsure about the effect of this product, please consult your doctor or pharmacist.

Any drug may have unintended or undesirable effects, so-called side effects. VIRACEPT has been shown to be generally well tolerated. Side effects include diarrhea, flatulence, nausea, rash, weakness, decreased white blood cell counts and increased values for liver enzyme and kidney function tests. The side effects observed in children and adults receiving VIRACEPT are similar. Some children experienced low white blood cells (leukopenia/neutropenia), which resolved without treatment interruption in most cases.

Diarrhea is the most common side effect in people taking VIRACEPT. In clinical studies, about 15-20% of patients receiving VIRACEPT 750 mg (three 250 mg tablets) three times daily or 1250 mg (five 250 mg tablets or two 625 mg tablets) two times daily had four or more loose stools a day. Diarrhea may be more common in patients receiving the 625 mg formulation. In most cases your doctor may advise you on the appropriate treatment for diarrhea caused by the medication and may include antidiarrheal medications such as loperamide or other approved agents.

Other side effects may occur with VIRACEPT. Ask your doctor or pharmacist for more information about side effects. Your doctor and pharmacist will have a more complete list of

side effects. Inform your doctor promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention. Your doctor or pharmacist may be able to help you manage these side effects.

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| **Symptom / effect** | | **Talk with your doctor or pharmacist** | | **Stop taking drug and call your doctor or pharmacist** |
| | | **Only if severe** | **In all cases** | |
| **Uncommon** | **Allergic reaction** with symptoms such as swollen mouth, throat, skin, difficulty in breathing or rash.<br>**Low white blood cell count** (leukopenia, neutropenia) with symptoms such as severe fatigue, infection or fever. | | √<br>√ | |
| **Rare** | **New or worsening diabetes** with high blood sugar that is sometimes severe, with symptoms such as frequent urination or increased thirst may occur.<br>**Specifically for hemophiliacs (type A and type B).** If nosebleed, bleeding gums, unexplained bruising, or dark urine and stools. | | √<br>√ | |

New onset diabetes mellitus, high blood sugar or an increase in severity of existing diabetes mellitus has been reported in patients receiving some protease inhibitors. In some of the cases high blood sugar was severe and some of the cases also associated with ketoacidosis.

In patients with hemophilia type A and B, there have been reports of increased bleeding while taking this treatment or another protease inhibitor. Should this happen to you, seek immediate advice from your doctor.

Changes in body fat have been seen in some patients taking antiretroviral agents. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

Changes in your 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, or you could develop an autoimmune disease in which your immune system reacts against your own body (e.g. Grave's disease (which affects the thyroid gland), Guillain-Barre syndrome (which affects the nervous system) or polymyositis (which affects the muscles) and it may develop at any time, sometimes months later after the start of HIV therapy). Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling, or fatigue or any new symptoms contact your doctor immediately.

VIRACEPT is mainly metabolized by the liver. The effects of VIRACEPT in patients with liver disease is unknown, therefore if you have liver disease it is very important that you alert your physician to any side-effects you have while taking VIRACEPT.

Make sure you tell your doctor or pharmacist of any medical problems that you may have, related or unrelated to HIV, before you start taking or while taking VIRACEPT. If, in any emergency situation, you are seeing a doctor other than your regular physician, make sure you tell them all the drugs that you are taking, including VIRACEPT.

## HOW TO STORE IT

Store VIRACEPT in its original container between 15°C and 30ºC.

**Keep out of the reach and sight of children.**
**Use before the expiry date on the label.**
**This medicine has been prescribed for your medical problem. Do not give it to anyone else.**
**Discuss all your questions about your health with your doctor. If you have questions about VIRACEPT, ask your doctor, nurse or pharmacist.**

**REPORTING SUSPECTED SIDE EFFECTS**

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    **Health Canada**
    **Postal Locator 1908C**
    **Ottawa, ON K1A 0K9**

**Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.**

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.pfizer.ca or by contacting the sponsor, Pfizer Canada Inc. at 1-800-463-6001.

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