**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

VIRACEPT 50 mg/g oral powder.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VIRACEPT 50 mg/g oral powder contains 58.45 mg of nelfinavir mesilate corresponding to 50 mg of nelfinavir (as free base) per gram of powder. For excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Oral powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

VIRACEPT is indicated in antiretroviral combination treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children of 3 years of age and older.

In protease inhibitor (PI) experienced patients the choice of nelfinavir should be based on individual viral resistance testing and treatment history.

See section 5.1.

### 4.2 Posology and method of administration

Therapy with VIRACEPT should be initiated by a physician experienced in the management of HIV infection.

VIRACEPT 50 mg/g oral powder should always be ingested with food (see section 5.2).

Patients older than 13 years: VIRACEPT 250 mg tablets are recommended for adults and older children (see Summary of Product Characteristics for VIRACEPT 250 mg tablets). The recommended dose of VIRACEPT 50 mg/g oral powder is **1250 mg twice a day** (BID) **or 750 mg three times a day** (TID), for patients unable to take tablets. All patients older than 13 years should take **either** 5 level scoops of the blue 5 gram spoon twice daily **or** 3 level scoops of the blue 5 gram spoon three times daily.
The efficacy of the BID regimen has been evaluated versus the TID regimen primarily in patients naïve to PIs (see section 5.1, pharmacodynamic properties).

Patients aged 3 to 13 years: for children, the recommended starting dose is **50-55 mg/kg BID** or if using a **TID regimen, 25 – 30 mg/kg body weight** per dose. For children able to take tablets, VIRACEPT tablets may be administered instead of the oral powder (see Summary of Product Characteristics for VIRACEPT tablets).

The recommended dose of VIRACEPT oral powder to be administered **BID to children aged 3 to 13 years, using a combination of both the white 1 gram and the blue 5 gram scoop** is shown in the following table. The prescriber should advise the patient to use the handle of the second scoop to scrape off extra powder and obtain a level scoop.

| Dose to be administered two times a day to children aged 3 to 13 | | | | |
|---|---|---|---|---|
| **Body Weight of the patient** | **Blue Scoop** 5 gram | | **White Scoop** 1 gram | **Total grams of Powder per dose** |
| 7.5 to 8.5 kg | 1 | plus | 3 | 8 g |
| 8.5 to 10.5 kg | 2 | | - | 10 g |
| 10.5 to 12 kg | 2 | plus | 2 | 12 g |
| 12 to 14 kg | 2 | plus | 4 | 14 g |
| 14 to 16 kg | 3 | plus | 1 | 16 g |
| 16 to 18 kg | 3 | plus | 3 | 18 g |
| 18 to 22 kg | 4 | plus | 1 | 21 g |
| over 22 kg | 5 | | - | 25 g |

The recommended dose of VIRACEPT oral powder to be administered **TID to children aged 3 to 13 years, using a combination of both the white 1 gram and the blue 5 gram scoop** is shown in the following table. The prescriber should advise the patient to use the handle of the second scoop to scrape off extra powder and obtain a level scoop.

| Dose to be administered three times a day to children aged 3 to 13 | | | | |
|---|---|---|---|---|
| **Body Weight of the patient** | **Blue Scoop** 5 gram | | **White Scoop** 1 gram | **Total grams of Powder per dose** |
| 7.5 to 8.5 kg | - | | 4 | 4 g |
| 8.5 to 10.5 kg | 1 | | - | 5 g |
| 10.5 to 12 kg | 1 | plus | 1 | 6 g |
| 12 to 14 kg | 1 | plus | 2 | 7 g |
| 14 to 16 kg | 1 | plus | 3 | 8 g |
| 16 to 18 kg | 1 | plus | 4 | 9 g |
| 18 to 23 kg | 2 | plus | - | 10 g |
| over 23 kg | 3 | | - | 15 g |

The oral powder may be mixed with water, milk, formula, soy formula, soy milk, dietary supplements, or pudding. It is recommended that VIRACEPT 50 mg/g oral powder mixed in these media be used within 6 hours. Dosing media not recommended, due to taste, includes any acidic food or juice (e.g., orange juice, apple juice or apple sauce). Do not add water to bottles of VIRACEPT 50 mg/g oral powder.

Renal and hepatic impairment: there are no data specific for patients with renal impairment and therefore specific dosage recommendations cannot be made. Nelfinavir is principally metabolised and eliminated by the liver. There are not sufficient data from patients with liver impairment and therefore specific dose recommendations cannot be made (see section 5.2). Caution should be used when administering VIRACEPT to patients with impaired renal or hepatic function.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Co-administration with medicinal products with narrow therapeutic windows and which are substrates of CYP3A4 (e.g., terfenadine, astemizole, cisapride, amiodarone, quinidine, pimozide, triazolam, midazolam, ergot derivatives; see section 4.5).

Co-administration with rifampicin (see section 4.5).

Herbal preparations containing St. John's wort *(Hypericum perforatum)* must not be used while taking nelfinavir due to the risk of decreased plasma concentrations and reduced clinical effects of nelfinavir (see section 4.5).

## 4.4 Special warnings and special precautions for use

Patients should be instructed that VIRACEPT is not a cure for HIV infection, that they may continue to develop infections or other illnesses associated with HIV disease, and that VIRACEPT has not been shown to reduce the risk of transmission of HIV disease through sexual contact or blood contamination.

For use during pregnancy and lactation, see section 4.6.

**Immune Reactivation Syndrome:**
In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

**Liver Disease:**
The safety and efficacy of nelfinavir has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

**Renal Impairment:**
Caution should be used when administering VIRACEPT to patients with impaired renal function (see section 4.2).

The safety and activity of nelfinavir in children below the age of 3 years have not been established.

Caution is advised whenever VIRACEPT is co-administered with medicinal products which are inducers or inhibitors and/or substrates of CYP3A4; such combinations may require dose adjustment (see also sections 4.3, 4.5 and 4.8).

The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A4 for metabolism, thus concomitant use of VIRACEPT with simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. Caution must also be exercised if VIRACEPT is used concurrently with atorvastatin, which is metabolised to a lesser extent by CYP3A4. In this situation a reduced dose of atorvastatin should be considered. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5).

Particular caution should be used when prescribing sildenafil in patients receiving PIs, including nelfinavir. Co-administration of a PI with sildenafil is expected to substantially increase sildenafil concentration and may result in an increase in sildenafil associated adverse events, including hypotension, visual changes, and priapism (see section 4.5).

Potent inducers of CYP3A (e.g., phenobarbital and carbamazepine) may reduce nelfinavir plasma concentrations. Physicians should consider using alternatives when a patient is taking VIRACEPT (see sections 4.3 and 4.5).

VIRACEPT may lead to a decreased AUC of phenytoin; therefore phenytoin concentrations should be monitored during concomitant use with VIRACEPT (see section 4.5).

Methadone AUC may be decreased when co-administered with VIRACEPT; therefore upward adjustment of methadone dose may be required during concomitant use with VIRACEPT (see section 4.5).

Co-administration of the combination oral contraceptive containing norethindrone and 17 α-ethinylestradiol with VIRACEPT resulted in a decrease in AUC of the contraceptive drug; therefore alternative contraceptive measure should also be considered (see section 4.5).

VIRACEPT 50 mg/g oral powder contains aspartame as a sweetening agent. Aspartame provides a source of phenylalanine and, therefore, may not be suitable for persons with phenylketonuria.

New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving PIs. In some of these the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes or hyperglycaemia.

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with PIs. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with PIs was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and nucleoside analogue reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

## 4.5 Interaction with other medicinal products and other forms of interaction

Nelfinavir is primarily metabolised via the cytochrome P450 isoenzymes CYP3A and CYP2C19 (see section 5.2). Co-administration with medicinal products that are substrates for CYP3A4 and which have narrow therapeutic windows (e.g., terfenadine, astemizole, cisapride, amiodarone, quinidine, pimozide, triazolam, midazolam, ergot derivatives) is contraindicated (see section 4.3 and below). Caution should be used when co-administering medicinal products that induce CYP3A or potentially toxic medicinal products which are themselves metabolised by CYP3A (see section 4.3 and below). Based on *in vitro* data, nelfinavir is unlikely to inhibit other cytochrome P450 isoforms at concentrations in the therapeutic range.

Other antiretrovirals:

*Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs):*

Clinically significant interactions have not been observed between nelfinavir and nucleoside analogues (specifically zidovudine plus lamivudine, stavudine, and stavudine plus didanosine). At present, there is no evidence of inadequate efficacy of zidovudine in the CNS that could be associated with the modest reduction in plasma levels of zidovudine when co-administered with nelfinavir. Since it is recommended that didanosine be administered on an empty stomach, VIRACEPT should be administered (with food) one hour after or more than 2 hours before didanosine.

*Other Protease Inhibitors (PIs):*

Ritonavir: administration of a single 750 mg dose of nelfinavir following 3 doses of ritonavir 500 mg BID resulted in a 152 % increase in AUC and a 156 % increase in the elimination half-life of nelfinavir. Administration of a single 500 mg dose of ritonavir following six doses of nelfinavir 750 mg TID resulted in minimal increase (8 %) in ritonavir plasma AUC.
Addition of low dose ritonavir (either 100 or 200 mg BID) to nelfinavir 1250 mg BID resulted in a 20 % increase in nelfinavir plasma AUC after morning administration and a 39 % increase after evening administration at steady state. The AUC of the nelfinavir metabolite M8 increased by 74 % and 86 % after morning and evening administrations, respectively (see section 5.2 regarding the formation and further metabolism of M8). There were no significant differences between low doses of ritonavir (either 100 or 200 mg BID) for effects on AUCs of nelfinavir and M8. The clinical relevance of these findings has not been established.

Indinavir: administration of a single 750 mg dose of nelfinavir following indinavir 800 mg every 8 hours for 7 days resulted in an 83 % increase in nelfinavir plasma AUC and a 22 % increase in the elimination half-life of nelfinavir. Administration of a single 800 mg dose of indinavir following nelfinavir 750 mg TID for 7 days resulted in a 51 % increase in indinavir plasma AUC concentrations, with a 5-fold increase in trough concentrations measured at 8 hours, but no increase in peak concentrations. The safety of this combination has not been established.

Saquinavir soft gelatin capsule: administration of a single 750 mg dose of nelfinavir following 4 days of saquinavir soft gelatin capsule 1200 mg TID resulted in a 30 % increase in nelfinavir plasma AUC. Administration of a single 1200 mg dose of saquinavir soft gelatin capsule following 4 days of nelfinavir 750 mg TID resulted in a 392 % increase in saquinavir plasma AUC.

Amprenavir: Co-administration of amprenavir 800 mg TID with nelfinavir 750 mg TID resulted in a small increase in nelfinavir and amprenavir plasma AUC and a 189 % increase in amprenavir $C_{min.}$ No dose adjustment is necessary for either medicinal product when nelfinavir is administered in combination with amprenavir.

*Non-nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs):*

Efavirenz: Co-administration of efavirenz 600 mg once daily (qd) with nelfinavir 750 mg TID increased nelfinavir AUC by 20 % with no change in efavirenz AUC. A dose adjustment is not needed when efavirenz is administered with VIRACEPT.

Delavirdine: Co-administration of nelfinavir 750 mg TID with delavirdine 400 mg TID resulted in a 107 % increase in nelfinavir AUC and a 31 % decrease in delavirdine AUC. The safety of this drug combination has not been established and this combination is not recommended.

Nevirapine: Current evidence suggests that there is unlikely to be a clinically relevant interaction when nelfinavir 750 mg TID and nevirapine 200 mg BID are co-administered. A dose adjustment is not needed when nevirapine is administered with VIRACEPT.

**Metabolic enzyme inducers:** rifampicin decreases nelfinavir plasma AUC by 82 % and its concomitant use with nelfinavir is contraindicated (see section 4.3). Other potent inducers of CYP3A (e.g., phenobarbital, carbamazepine) may also reduce nelfinavir plasma concentrations. If therapy with such medicinal products is warranted, physicians should consider using alternatives when a patient is taking VIRACEPT.

Rifabutin: Co-administration of nelfinavir 750 mg TID and rifabutin 300 mg once a day results in a 32 % decrease in nelfinavir plasma AUC and a 207 % increase in rifabutin plasma AUC (see also section 4.4). Co-administration of nelfinavir 750 mg TID with half the standard dose of rifabutin 150 mg once a day resulted in a 23 % decrease in nelfinavir plasma AUC and an 83 % increase in rifabutin plasma AUC. In contrast co-administration of VIRACEPT 1250 mg BID with half the standard dose of rifabutin 150 mg qd resulted in no change in nelfinavir plasma AUC. Dosage reduction of rifabutin to 150 mg once a day is necessary when nelfinavir 750 mg TID or 1250 mg BID and rifabutin are co-administered.

Phenytoin: Co-administration of nelfinavir 1250 mg BID with phenytoin 300 mg once a day did not change the concentration of nelfinavir. However, AUC values of phenytoin and free phenytoin were reduced by 29 % and 28 % by co-administration of nelfinavir, respectively. No dose adjustment for nelfinavir is recommended. Phenytoin concentrations should be monitored during co-administration with nelfinavir.

**St. John's wort *(Hypericum perforatum):*** Plasma levels of nelfinavir can be reduced by concomitant use of the herbal preparation St. John's wort *(Hypericum perforatum)*. This is due to induction of drug metabolising enzymes and/or transport proteins by St. John's wort. Herbal preparations containing St. John's wort must not be used concomitantly with VIRACEPT. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible nelfinavir levels. Nelfinavir levels may increase on stopping St. John's wort, and the dose of VIRACEPT may need adjusting. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment (see section 4.3).

**Metabolic enzyme inhibitors:** co-administration of nelfinavir and a strong inhibitor of CYP3A, ketoconazole, resulted in a 35 % increase in nelfinavir plasma AUC. This change is not considered clinically significant and no dose adjustment is needed when ketoconazole and VIRACEPT are co-administered. Based on the metabolic profiles, a clinically relevant drug interaction would not be expected with other specific inhibitors of CYP3A (e.g., fluconazole, itraconazole, clarithromycin, erythromycin); however, the possibility cannot be excluded.

Co-administration of nelfinavir with inhibitors of CYP2C19 (e.g., fluconazole, fluoxetine, paroxetine, omeprazole, lansoprazole, imipramine, amitriptyline and diazepam) may be expected to reduce the conversion of nelfinavir to its major active metabolite M8 (*tert-butyl* hydroxy nelfinavir) with a concomitant increase in plasma nelfinavir levels (see section 5.2). Limited clinical trial data from patients receiving one or more of these medicinal products with nelfinavir indicated that a clinically significant effect on safety and efficacy is not expected. However, such an effect cannot be ruled out.

**HMG-CoA reductase inhibitors** which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with VIRACEPT. Co-administration of nelfinavir 1250 mg BID and simvastatin 20 mg once a day increased the plasma AUC of simvastatin by 506 %. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicinal products with VIRACEPT is not recommended. Atorvastatin is less dependent on CYP3A4 for metabolism. Co-administration of nelfinavir 1250 mg BID and atorvastatin 10 mg once a day increased the AUC of atorvastatin by 74 %. When used with VIRACEPT, the lowest possible dose of atorvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4, and interactions are not expected with PIs. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

**Methadone**: Co-administration of nelfinavir 1250 mg BID with methadone 80 +/- 21 mg once a day in HIV negative methadone maintenance patients resulted in a 47 % decrease in methadone AUC. None of the subjects experienced withdrawal symptoms in this study; however, due to the pharmacokinetic changes, it should be expected that some patients who received this drug combination may experience withdrawal symptoms and require an upward adjustment of the methadone dose.

**Other potential interactions (see also section 4.3):** Nelfinavir increases terfenadine plasma concentrations; therefore, VIRACEPT must not be administered concurrently with terfenadine because of the potential for serious and/or life-threatening cardiac arrhythmias. Because similar interactions are likely with astemizole and cisapride, VIRACEPT must not be administered concurrently with these drugs. Although specific studies have not been done, potent sedatives metabolised by CYP3A, such as triazolam or midazolam, must not be co-administered with VIRACEPT due to the potential for prolonged sedation or respiratory depression resulting from competitive inhibition of the metabolism of these medicinal products when they are co-administered.

Similarly, concomitant administration of nelfinavir with any of amiodarone, quinidine, pimozide and ergot derivatives is contraindicated. For other compounds that are substrates for CYP3A (e.g., calcium channel blockers including bepridil, immunosuppressants including tacrolimus and ciclosporin, and sildenafil) plasma concentrations may be elevated when co-administered with VIRACEPT; therefore, patients should be monitored for toxicities associated with such medicinal products.

**Oral contraceptives:** administration of nelfinavir 750 mg TID and a combination oral contraceptive which included 0.4 mg of norethindrone and 35 μg of 17 α-ethinylestradiol for 7 days resulted in a 47 % decrease in ethinylestradiol and an 18 % decrease in norethindrone plasma AUC. Alternative contraceptive measures should be considered.

## 4.6 Pregnancy and lactation

No treatment-related adverse effects were seen in animal reproductive toxicity studies in rats at doses providing systemic exposure comparable to that observed with the clinical dose. Clinical experience in pregnant women is limited. VIRACEPT should be given during pregnancy only if the expected benefit justifies the possible risk to the foetus.

It is recommended that HIV-infected women must not breast-feed their infants under any circumstances in order to avoid transmission of HIV. Studies in lactating rats showed that nelfinavir is excreted in breast milk. There is no data available on nelfinavir excretion into human breast milk. Mothers must be instructed to discontinue breast-feeding if they are receiving VIRACEPT.

## 4.7 Effects on ability to drive and use machines

VIRACEPT has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

**Experience from clinical trials with the VIRACEPT 250 mg tablet**
The safety of the VIRACEPT 250 mg tablet was studied in controlled clinical trials with over 1300 patients.
The majority of patients in these studies received either 750 mg TID either alone or in combination with nucleoside analogues or 1250 mg BID in combination with nucleoside analogues.

The most frequently reported adverse drug reaction among patients (n=514) receiving VIRACEPT in two phase III, double-blind studies was diarrhoea (70.6 %, n=350). Diarrhoea was of mild or moderate intensity in 97.7 % of these 350 patients. Although formal analyses of the time to onset of diarrhoea were not performed, onset of diarrhoea generally occurs shortly after beginning treatment with VIRACEPT; onset of diarrhoea is less likely to occur in patients who have been receiving VIRACEPT for longer periods of time. In addition, over 4000 patients ≥ 13 years in the expanded access programmes received VIRACEPT at a dose of 750 mg TID. The majority of adverse events were of mild intensity.

Across the two phase III, double-blind studies adverse reactions of moderate to severe intensity reported by investigators as at least possibly related to VIRACEPT or of unknown relationship in ≥ 2 % of patients treated with the 750 mg TID dose of VIRACEPT (n = 200) in combination with nucleoside analogues (for 24 weeks) included the following undesirable effects:

Gastrointestinal disorders: diarrhoea (25.9 %), flatulence (2.5 %), nausea (4.5 %),

Skin and subcutaneous tissue disorders: rash (3.0 %).

Safety data up to 48 weeks is available from 554 patients in the study comparing 1250 mg VIRACEPT BID (n=344) versus 750 mg VIRACEPT TID (n=210), each in combination with lamivudine and stavudine. The incidence of adverse reactions of moderate to severe intensity reported by investigators as at least possibly related to VIRACEPT or of unknown relationship in ≥ 2 % of patients treated was similar for the BID and TID arms: diarrhoea (21.2 % versus 18.2 %), nausea (2.9 % versus 3.3 %) and rash (1.7 % versus 1.4 %).

Marked clinical laboratory abnormalities (change from grade 0 to grade 3 or 4, or change from grade 1 to grade 4) reported in ≥ 2 % of patients treated with 750 mg TID of VIRACEPT (for 24 weeks) across the same studies included increased creatine kinase (3.9 %), and decreased neutrophils (4.5 %). Marked increases in transaminases occurred in less than 2 % of patients receiving VIRACEPT 750 mg TID and were sometimes accompanied by clinical signs and symptoms of acute hepatitis. Some of these patients were known to be chronic carriers of hepatitis B and/or C viruses. With the exception of diarrhoea, there were no significant differences in the adverse experiences reported by patients treated with VIRACEPT versus the control arms containing zidovudine plus lamivudine or stavudine alone.

In the study comparing VIRACEPT 1250 mg BID with VIRACEPT 750 mg TID each in combination with lamivudine and stavudine, the incidence of marked clinical laboratory abnormalities (change from grade 0 to grade 3 or 4, or change from grade 1 to grade 4) reported in ≥ 2 % of patients was: AST (2 % versus 1 %), ALT (3 % versus 0 %), neutropenia (2 % versus 1 %).

**Post marketing experience**
The following additional adverse reactions have been reported in the post-marketing experience:

Infections and infestations:
*Rare (≥ 0.01 % - ≤ 0.1 %)*: hepatitis, abnormal liver enzymes and jaundice when nelfinavir is used in combination with other antiretroviral agents.

Immune system disorders:
*Uncommon (≥ 0.1 % - ≤ 1 %)*: hypersensitivity reactions including bronchospasm, fever, pruritus, facial oedema and rash (maculopapular or bullous).

Metabolism and nutrition disorders:
*Rare (≥ 0.01 % - ≤ 0.1 %)*: new onset diabetes mellitus, or exacerbation of existing diabetes mellitus.

Vascular disorders:
*Rare (≥ 0.01 % - ≤ 0.1 %)*: increased spontaneous bleeding in patients with haemophilia.

Gastrointestinal disorders:
*Rare (≥ 0.01 % - ≤ 0.1 %)*: abdominal distension,
*Uncommon (≥ 0.1 % - ≤ 1 %):* vomiting, pancreatitis/increased amylase.

Skin and subcutaneous tissue disorders:
*Uncommon - rare (≥ 0.01 % - ≤ 1 %)*: Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).
*Very rare (≤ 0.01 %), including isolated reports*: Erythema multiforme.

Musculoskeletal and connective tissue disorders:
*Rare (≥ 0.01 % - ≤ 0.1 %)*: Increased CPK, myalgia, myositis and rhabdomyolysis have been reported with PIs, particularly in combination with nucleoside analogues.

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactaemia (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

### 4.9 Overdose

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

Overdoses of nelfinavir could theoretically be associated with prolongation of the QT-interval of the ECG (see also section 5.3). Monitoring of overdosed patients is warranted.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiviral agent, ATC code: J05A E04.

**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 reversibly binds to the active site of HIV protease and prevents cleavage of the polyproteins resulting in the formation of immature non-infectious viral particles.

**Antiviral activity *in vitro***: the antiviral activity of nelfinavir *in vitro* has been demonstrated in both HIV acute and chronic infections in lymphoblastoid cell lines, peripheral blood lymphocytes and monocytes/macrophages. Nelfinavir was found to be active against a broad range of 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 (mean of 58 nM). Nelfinavir demonstrated additive to synergistic effects against HIV in combination with reverse transcriptase inhibitors zidovudine (ZDV), lamivudine (3TC), didanosine (ddI), zalcitabine (ddC) and stavudine (d4T) without enhanced cytotoxicity.

**Drug Resistance***:* HIV isolates with reduced susceptibility to nelfinavir have been selected *in vitro*. HIV isolates from selected patients treated with nelfinavir alone or in combination with reverse transcriptase inhibitors were monitored for phenotypic (n=19) and genotypic (n=195, 157 of which were assessable) changes in clinical trials over a period of 2 to 82 weeks. One or more viral protease mutations at amino acid positions 30, 35, 36, 46, 71, 77 and 88 were detected in > 10 % of patients with assessable isolates. Of 19 patients for whom both phenotypic and genotypic analyses were performed on clinical isolates, 9 patients isolates showed reduced susceptibility (5- to 93-fold) to nelfinavir *in vitro*. Isolates from all 9 patients possessed one or more mutations in the viral protease gene. Amino acid position 30 appeared to be the most frequent mutation site.

The overall incidence of the D30N mutation in the viral protease of assessable isolates (n=157) from patients receiving nelfinavir monotherapy or nelfinavir in combination with zidovudine and lamivudine or stavudine was 54.8 %. The overall incidence of other mutations associated with primary PI resistance was 9.6 % for the L90M substitution where as substitutions at 48, 82 and 84 were not observed.

**Cross resistance**: HIV isolates obtained from 5 patients during nelfinavir therapy showed a 5- to 93-fold decrease in nelfinavir susceptibility *in vitro* when compared to matched baseline isolates but did not demonstrate a concordant decrease in susceptibility to indinavir, ritonavir, saquinavir or amprenavir *in vitro*. Conversely, following ritonavir therapy, 6 of 7 clinical isolates with decreased ritonavir susceptibility (8- to 113-fold) *in vitro* compared to baseline also exhibited decreased susceptibility to nelfinavir *in vitro* (5- to 40 fold). An HIV isolate obtained from a patient receiving saquinavir therapy showed decreased susceptibility to saquinavir (7- fold) but did not demonstrate a concordant decrease in susceptibility to nelfinavir. Cross-resistance between nelfinavir and reverse transcriptase inhibitors is unlikely because different enzyme targets are involved. Clinical isolates (n=5) with decreased susceptibility to zidovudine, lamivudine, or nevirapine remain fully susceptible to nelfinavir *in vitro*.

**Clinical pharmacodynamic data:** treatment with nelfinavir alone or in combination with other antiretroviral agents has been documented to reduce viral load and increase CD4 cell counts in HIV-1 seropositive patients. Decreases in HIV RNA observed with nelfinavir monotherapy were less pronounced and of shorter duration. The effects of nelfinavir (alone or combined with other antiretroviral agents) on biological markers of disease activity, CD4 cell count and viral RNA, were evaluated in several studies involving HIV-1 infected patients.

The efficacy of the BID regimen has been evaluated versus the TID regimen with VIRACEPT 250 mg tablets primarily in patients naïve to PIs. A randomised open-label study compared the HIV RNA suppression of nelfinavir 1250 mg BID versus nelfinavir 750 mg TID in PI naïve patients also receiving stavudine (30-40 mg BID) and lamivudine (150 mg BID).

| **Proportion of patients with HIV RNA below LOQ (sensitive and ultrasensitive assays) at Week 48** | | | | |
|---|---|---|---|---|
| **Assay** | **Analysis** | **Viracept BID (%)** | **Viracept TID (%)** | **95% CI** |
| Sensitive | Observed data | 135/164 (82%) | 146/169 (86%) | (-12, +4) |
| | LOCF | 145/200 (73%) | 161/206 (78%) | (-14, +3) |
| | ITT (NC = F) | 135/200 (68%) | 146/206 (71%) | (-12, +6) |
| Ultrasensitive | Observed data | 114/164 (70%) | 125/169 (74%) | (-14, +5) |
| | LOCF | 121/200 (61%) | 136/206 (66%) | (-15, +4) |
| | ITT (NC = F) | 114/200 (57%) | 125/206 (61%) | (-13, +6) |

*LOCF= Last observation carried forward*
*ITT = Intention to Treat*
*NC = F: non-completers = failures*

The BID regimen produced statistically significantly higher peak nelfinavir plasma levels versus the TID regimen. Small, non-statistically significant differences were observed in other pharmacokinetic parameters with no trend favouring one regimen over the other. Although study 542 showed no statistically significant differences between the two regimens in efficacy in a predominantly antiretroviral naïve patient population, the significance of these findings for antiretroviral experienced patients is unknown.

In a study of 297 HIV-1 seropositive patients receiving zidovudine and lamivudine plus nelfinavir (2 different doses) or zidovudine and lamivudine alone, the mean baseline CD4 cell count was 288 cells/mm$^3$ and the mean baseline plasma HIV RNA was 5.21 $\log_{10}$ copies/ml (160,394 copies/ml). The mean decrease in plasma HIV RNA using a PCR assay (< 400 copies/ml) at 24 weeks was 2.33 $\log_{10}$ in patients receiving combination therapy with nelfinavir 750 mg TID, compared to 1.34 $\log_{10}$ in patients receiving zidovudine and lamivudine alone. At 24 weeks, the percentage of patients whose plasma HIV RNA levels had decreased to below the limit of detection of the assay (< 400 copies/ml) were 81 % and 8 % for the groups treated with nelfinavir 750 mg TID plus zidovudine and lamivudine or zidovudine and lamivudine, respectively. Mean CD4 cell counts at 24 weeks were increased by 150 and 95 cells/mm$^3$ for the groups treated with nelfinavir 750 mg TID plus zidovudine and lamivudine or zidovudine and lamivudine, respectively. At 48 weeks, approximately 75 % of the patients treated with nelfinavir 750 mg TID plus zidovudine and lamivudine remained below the level of detection of the assay (< 400 copies/ml); mean increase in CD4 cell counts was 198 cells/mm$^3$ at 48 weeks in this group.

No important differences in safety or tolerability were observed between the BID and TID dosing groups, with the same proportion of patients in each arm experiencing adverse events of any intensity, irrespective of relationship to trial medication.

Plasma levels of certain HIV-1 protease inhibitors, which are metabolized predominantly by CYP3A4, can be increased by the co-administration of low-dose ritonavir, which is an inhibitor of this metabolism. Treatment paradigms for several protease inhibitors, which are subject to this interaction, require the co-administration of low-dose ritonavir ('boosting') in order to enhance plasma levels and optimize antiviral efficacy. Plasma levels of nelfinavir, which is metabolized predominantly by CYP2C19 and only partially by CYP3A4, are not greatly increased by coadministration with ritonavir, and therefore co-administration of nelfinavir with low-dose ritonavir does not appear to be beneficial. Two studies have compared the safety and efficacy of nelfinavir (unboosted) with ritonavir- boosted protease inhibitors, each in combination with other antiretroviral agents.

Study M98-863 is a randomised, double blind trial of 653 antiretroviral-naïve patients investigating lopinavir/ritonavir (400/100 mg BID n=326) compared to nelfinavir (750mg TID n=327), each in combination with lamivudine (150 mg twice daily) and stavudine (40 mg twice daily). Median baseline HIV-1 RNA was 4.98 log10 copies/ml and 5.01 log10 copies/ml in the nelfinavir and lopinavir/ritonavir treatment groups respectively. Median baseline CD4+ cell count was 232 cells/mm3 in both groups. At week 48, 63% nelfinavir and 75% lopinavir/ritonavir patients had HIV-1 RNA < 400 copies/ml, whereas 52% nelfinavir and 67% lopinavir/ritonavir patients had HIV-1 RNA <50 copies/ml (intent-to-treat, missing = failure). The mean increase from baseline in CD4+ cell count at week 48 was 195 cells/mm3 and 207 cells/mm3 in the nelfinavir and lopinavir/ritonavir groups respectively. Through 48 weeks of therapy, a statistically significantly higher proportion of patients in the lopinavir/ritonavir arm had HIV-1 RNA < 50 copies/ml compared to the nelfinavir arm.

Study APV30002 is a randomised, open-label trial of 649 antiretroviral treatment naïve patients with advanced HIV-disease, investigating fosamprenavir/ritonavir (1400mg/200mg QD n=322) compared to nelfinavir (1250mg BID n=327), each in combination with lamivudine (150 mg twice daily) and abacavir (300 mg twice daily). Median baseline HIV-1 RNA was 4.8 log10 copies/ml in both treatment groups. Median baseline CD4+ cell counts were 177 and 166 x106 cells/l for the nelfinavir and fosamprenavir/ritonavir groups respectively. At week 48, non-inferiority was shown with 68% of patients in the group treated with nelfinavir and 69% patients treated with fosamprenavir/ritonavir having plasma HIV-1 RNA <400 copies/ml whereas 53% in the nelfinavir and 55% in the fosamprenavir/ritonavir patients had HIV-1 RNA <50 copies/ml (intent-to-treat, rebound/discontinuation = failure). The median increase from baseline in CD4+ cell count over 48 weeks was 207 cells/mm3 and 203 cells/mm3 in the nelfinavir and fosamprenavir/ritonavir groups respectively. The virological failure was greater in the nelfinavir group (17%) than in the fosamprenavir/ritonavir group (7%). Treatment emergent NRTI resistance was significantly less frequent with fosamprenavir/ritonavir compared to nelfinavir (13% versus 57%; p<0.001).

## 5.2 Pharmacokinetic properties

The pharmacokinetic properties of nelfinavir have been evaluated in healthy volunteers and HIV-infected patients. No substantial differences have been observed between healthy volunteers and HIV-infected patients.

**Absorption**: after single or multiple oral doses of 500 to 750 mg (two to three 250 mg tablets) with food, peak nelfinavir plasma concentrations were typically achieved in 2 to 4 hours.

After multiple dosing with 750 mg every 8 hours for 28 days (steady-state), peak plasma concentrations ($C_{max}$) averaged 3-4 µg/ml and plasma concentrations prior to the next dose (trough) were 1-3 µg/ml. A greater than dose-proportional increase in nelfinavir plasma concentrations was observed after single doses; however, this was not observed after multiple dosing.

A pharmacokinetic study in HIV-positive patients compared multiple doses of 1250 mg twice daily (BID) with multiple doses of 750 mg three times daily (TID) for 28 days. Patients receiving VIRACEPT BID (n=10) achieved nelfinavir $C_{max}$ of 4.0 ± 0.8 µg/ml and morning and evening trough concentrations of 2.2 ± 1.3 µg/ml and 0.7 ± 0.4 µg/ml, respectively. Patients receiving VIRACEPT TID (n=11) achieved nelfinavir peak plasma concentrations ($C_{max}$) of 3.0 ± 1.6 µg/ml and morning and evening trough concentrations of 1.4 ± 0.6 µg/ml and 1.0 ± 0.5 µg/ml, respectively. 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 precise 8- or 12-hour intervals.

The pharmacokinetics of nelfinavir are similar during BID and TID administration. In patients, the nelfinavir $AUC_{0-24}$ with 1250 mg BID administration was 52.8 ± 15.7 µg·h/ml (n=10) and with 750 mg TID administration was 43.6 ± 17.8 µg·h/ml (n=11). Trough drug exposures remain at least twenty fold greater than the mean IC95 throughout the dosing interval for both regimens. The clinical relevance of relating *in vitro* measures to drug potency and clinical outcome has not been established. A greater than dose-proportional increase in nelfinavir plasma concentrations was observed after single doses; however, this was not observed after multiple dosing.

The absolute bioavailability of VIRACEPT has not been determined.

**Effect of food on gastrointestinal absorption**: maximum plasma concentrations and area under the plasma concentration-time curve were consistently 2 to 3-fold higher under fed conditions compared to fasting. The increased plasma concentrations with food were independent of fat content of the meals. The effect of meal content on nelfinavir exposure was investigated in a study using the 250 mg film-coated tablets formulation. Steady state nelfinavir AUC and $C_{max}$ were respectively 15 % and 20 % higher when doses followed a 800 kcal/50 % fat meal compared to those following a light meal (350 kcal/33 % fat), suggesting that meal content has less effect on nelfinavir exposures during multiple dosing than would be anticipated based on data from single dose studies.

**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 were lower than in other tissues, but exceeded the *in vitro* $EC_{95}$ for antiviral activity. Nelfinavir in serum is extensively protein-bound (≥ 98 %).

**Metabolism:** unchanged nelfinavir comprised 82-86 % of the total plasma radioactivity after a single oral 750 mg dose of $^{14}$C-nelfinavir. *In vitro*, multiple cytochrome P-450 isoforms including CYP3A, CYP2C19/C9 and CYP2D6 are responsible for metabolism of nelfinavir. One major and several minor oxidative metabolites were found in plasma.

The major oxidative metabolite, M8 (*tert-butyl* hydroxy nelfinavir), has *in vitro* antiviral activity equal to the parent drug and its formation is catalysed by the polymorphic cytochrome CYP2C19. The further degradation of M8 appears to be catalysed by CYP3A4. In subjects with normal CYP2C19 activity, plasma levels of this metabolite are approximately 25 % of the total plasma nelfinavir-related concentration. It is expected that in CYP2C19 poor metabolisers or in patients receiving concomitantly strong CYP2C19 inhibitors (see section 4.5), nelfinavir plasma levels would be elevated whereas levels of *tert-butyl* hydroxy nelfinavir would be negligible or non-measurable. Limited clinical data suggest that patients with very low or non-measurable plasma concentrations of the metabolite and elevated concentrations of nelfinavir do not show a reduced virological response or a different safety profile when compared with the whole study population.

**Elimination:** oral clearance estimates after single doses (24-33 l/h) and multiple doses (26-61 l/h) indicate that nelfinavir exhibits medium to high hepatic bioavailability. The terminal half-life in plasma was typically 3.5 to 5 hours. The majority (87 %) of an oral 750 mg dose containing $^{14}$C-nelfinavir was recovered in the faeces; total faecal radioactivity consisted of nelfinavir (22 %) and numerous oxidative metabolites (78 %). Only 1-2 % of the dose was recovered in urine, of which unchanged nelfinavir was the major component.

**Pharmacokinetics in special clinical situations:**

***Pharmacokinetics in children and the elderly:*** in children between the ages of 2 and 13 years, the clearance of orally administered nelfinavir is approximately 2 to 3 times higher than in adults, with large intersubject variability. Administration of VIRACEPT oral powder or tablets with food at a dose of approximately 25-30 mg/kg TID achieves steady-state plasma concentrations similar to adult patients receiving 750 mg TID.

In an open prospective study, the pharmacokinetics of BID and TID VIRACEPT regimens in 18 HIV infected children aged 2-14 years were investigated. Children weighing less than 25 kg received 30-37 mg/kg nelfinavir TID or 45-55 mg/kg nelfinavir BID. Children over 25 kg received 750 mg TID or 1250 mg BID. The $C_{min}$, $C_{max}$ and $AUC_{0-24}$ were all significantly higher with the BID regimen compared with the TID regimen. In addition, in twice daily application, 14 out of 18 (78 %) and 11 out of 18 (61 %) reached $C_{min}$ values of 1-3 µg/ml and $C_{max}$ values of 3-4 µg/ml, whereas in TID application only 4 out of 18 (22 %) and 7 out of 18 (39 %) reached these values.

There are no data available in the elderly.

***Pharmacokinetics in patients with liver impairment:***

Pharmacokinetics of nelfinavir after a single dose of 750 mg 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 with impairment (Child-Turcotte Classes A to C) compared to the healthy group. Specific dose recommendations for nelfinavir cannot be made based on the results of this study.

## 5.3 Preclinical safety data

During *in vitro* studies, cloned human cardiac potassium channels (hERG) were inhibited by high concentrations of nelfinavir and its active metabolite M8. hERG potassium channels were inhibited by 20 % at nelfinavir and M8 concentrations that are about four- to five-fold and seventy-fold, respectively, above the average free therapeutic levels in humans. By contrast, no effects suggesting prolongation of the QT-interval of the ECG were observed at similar doses in dogs or in isolated cardiac tissue. The clinical relevance of these *in vitro* data is unknown. However, based on data from products known to prolong the QT-interval, a block of hERG potassium channels of > 20 % may be clinically relevant. Therefore the potential for QT prolongation should be considered in cases of overdose (see section 4.9).

**Acute and chronic toxicity:** oral acute and chronic toxicity studies were conducted in the mouse (500 mg/kg/day), rat (up to 1,000 mg/kg/day) and monkey (up to 800 mg/kg/day). There were increased liver weights and dose-related thyroid follicular cell hypertrophy in rats. Weight loss and general physical decline was observed in monkeys together with general evidence of gastrointestinal toxicity.

**Mutagenicity**: *in vitro* and *in vivo* studies with and without metabolic activation have shown that nelfinavir has no mutagenic or genotoxic activity.

**Carcinogenicity:** Two year oral carcinogenicity studies with nelfinavir mesilate were conducted in mice and rats. In mice, administration of up to 1000 mg/kg/day did not result in any evidence for an oncogenic effect. In rats administration of 1000 mg/kg/day resulted in increased incidences of thyroid follicular cell adenoma and carcinoma, relative to those for controls. Systemic exposures were 3 to 4 times those for humans given therapeutic doses. Administration of 300 mg/kg/day resulted in an increased incidence of thyroid follicular cell adenoma. Chronic nelfinavir treatment of rats has been demonstrated to produce effects consistent with enzyme induction, which predisposed rats, but not humans, to thyroid neoplasms. The weight of evidence indicates that nelfinavir is unlikely to be a carcinogen in humans.

# 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

The oral powder contains microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hydroxypropyl methylcellulose, aspartame (E951), sucrose palmitate, and natural and artificial flavour.

### 6.2 Incompatibilities

VIRACEPT oral powder should not be mixed with acidic substances due to taste (see section 4.2).

### 6.3 Shelf-life

2 years.

### 6.4 Special precautions for storage

Store in the original container. Do not store above 30°C.

### 6.5 Nature and contents of container

VIRACEPT 50 mg/g oral powder is provided in HDPE plastic bottles fitted with polypropylene child resistant closures with a polyethylene liner. Each bottle contains 144 grams of oral powder and is supplied with a 1 gram (white) and a 5 gram (blue) polypropylene scoop.

### 6.6 Instructions for use, handling and disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/054/001

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22.1.1998 / 3.2.2003

## 10. DATE OF REVISION OF THE TEXT

## 1. NAME OF THE MEDICINAL PRODUCT

VIRACEPT 250 mg tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VIRACEPT 250 mg tablets contain 292.25 mg of nelfinavir mesilate corresponding to 250 mg of nelfinavir (as free base). For excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablets.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

VIRACEPT is indicated in antiretroviral combination treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children of 3 years of age and older.

In protease inhibitor (PI) experienced patients the choice of nelfinavir should be based on individual viral resistance testing and treatment history.

See section 5.1.

### 4.2 Posology and method of administration

Therapy with VIRACEPT should be initiated by a physician experienced in the management of HIV infection.

VIRACEPT tablets are administered orally and should always be ingested with food (see section 5.2).

Patients older than 13 years: the recommended dosage of VIRACEPT tablets is 1250 mg (five 250 mg tablets) twice a day (BID) or 750 mg (three 250 mg tablets) three times a day (TID) by mouth.
The efficacy of the BID regimen has been evaluated versus the TID regimen primarily in patients naïve to PIs (see section 5.1, pharmacodynamic properties).

Patients aged 3 to 13 years: for children, the recommended starting dose is 50-55 mg/kg BID or, if using a TID regimen, 25 – 30 mg/kg body weight per dose. For children unable to take tablets, VIRACEPT oral powder may be administered (see Summary of Product Characteristics for VIRACEPT oral powder).

The recommended dose of VIRACEPT tablets to be administered **BID to children aged 3 to 13 years** is as follows:

| Body Weight kg | Number of VIRACEPT 250 mg tablets per dose* |
|---|---|
| 18 to < 22 | 4 |
| ≥ 22 | 5 |

The recommended dose of VIRACEPT tablets to be administered **TID to children aged 3 to 13 years** is as follows:

| Body Weight kg | Number of VIRACEPT 250 mg tablets per dose* |
|---|---|
| 18 to < 23 | 2 |
| ≥ 23 | 3 |

*see Summary of Product Characteristics for VIRACEPT oral powder for patients with less than 18 kg body weight.

Renal and hepatic impairment: there are no data specific for patients with renal impairment and therefore specific dosage recommendations cannot be made. Nelfinavir is principally metabolised and eliminated by the liver. There are not sufficient data from patients with liver impairment and therefore specific dose recommendations cannot be made (see section 5.2). Caution should be used when administering VIRACEPT to patients with impaired renal or hepatic function.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Co-administration with medicinal products with narrow therapeutic windows and which are substrates of CYP3A4 (e.g., terfenadine, astemizole, cisapride, amiodarone, quinidine, pimozide, triazolam, midazolam, ergot derivatives; see section 4.5).

Co-administration with rifampicin (see section 4.5).

Herbal preparations containing St. John's wort *(Hypericum perforatum)* must not be used while taking nelfinavir due to the risk of decreased plasma concentrations and reduced clinical effects of nelfinavir (see section 4.5).

## 4.4 Special warnings and special precautions for use

Patients should be instructed that VIRACEPT is not a cure for HIV infection, that they may continue to develop infections or other illnesses associated with HIV disease, and that VIRACEPT has not been shown to reduce the risk of transmission of HIV disease through sexual contact or blood contamination.

For use during pregnancy and lactation, see section 4.6.

**Immune Reactivation Syndrome:**
In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

**Liver Disease:**
The safety and efficacy of nelfinavir has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

**Renal Impairment:**
Caution should be used when administering VIRACEPT to patients with impaired renal function (see section 4.2).

The safety and activity of nelfinavir in children below the age of 3 years have not been established.

Caution is advised whenever VIRACEPT is co-administered with medicinal products which are inducers or inhibitors and/or substrates of CYP3A4; such combinations may require dose adjustment (see also sections 4.3, 4.5 and 4.8).

The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A4 for metabolism, thus concomitant use of VIRACEPT with simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. Caution must also be exercised if VIRACEPT is used concurrently with atorvastatin, which is metabolised to a lesser extent by CYP3A4. In this situation a reduced dose of atorvastatin should be considered. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5).

Particular caution should be used when prescribing sildenafil in patients receiving PIs, including nelfinavir. Co-administration of a PI with sildenafil is expected to substantially increase sildenafil concentration and may result in an increase in sildenafil associated adverse events, including hypotension, visual changes, and priapism (see section 4.5).

Potent inducers of CYP3A (e.g., phenobarbital and carbamazepine) may reduce nelfinavir plasma concentrations. Physicians should consider using alternatives when a patient is taking VIRACEPT (see sections 4.3 and 4.5).

VIRACEPT may lead to a decreased AUC of phenytoin; therefore phenytoin concentrations should be monitored during concomitant use with VIRACEPT (see section 4.5).

Methadone AUC may be decreased when co-administered with VIRACEPT; therefore upward adjustment of methadone dose may be required during concomitant use with VIRACEPT (see section 4.5).

Co-administration of the combination oral contraceptive containing norethindrone and 17 -ethinylestradiol with VIRACEPT resulted in a decrease in AUC of the contraceptive drug; therefore alternative contraceptive measure should also be considered (see section 4.5).

New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving PIs. In some of these the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes or hyperglycaemia.

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with PIs. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with PIs was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and nucleoside analogue reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

## 4.5 Interaction with other medicinal products and other forms of interaction

Nelfinavir is primarily metabolised via the cytochrome P450 isoenzymes CYP3A and CYP2C19 (see section 5.2). Co-administration with medicinal products that are substrates for CYP3A4 and which have narrow therapeutic windows (e.g., terfenadine, astemizole, cisapride, amiodarone, quinidine, pimozide, triazolam, midazolam, ergot derivatives) is contraindicated (see section 4.3 and below). Caution should be used when co-administering medicinal products that induce CYP3A or potentially toxic medicinal products which are themselves metabolised by CYP3A (see section 4.3 and below). Based on *in vitro* data, nelfinavir is unlikely to inhibit other cytochrome P450 isoforms at concentrations in the therapeutic range.

**Other antiretrovirals**:

*Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs):*

Clinically significant interactions have not been observed between nelfinavir and nucleoside analogues (specifically zidovudine plus lamivudine, stavudine, and stavudine plus didanosine). At present, there is no evidence of inadequate efficacy of zidovudine in the CNS that could be associated with the modest reduction in plasma levels of zidovudine when coadministered with nelfinavir. Since it is recommended that didanosine be administered on an empty stomach, VIRACEPT should be administered (with food) one hour after or more than 2 hours before didanosine.

*Other Protease Inhibitors (PIs)*

Ritonavir: administration of a single 750 mg dose of nelfinavir following 3 doses of ritonavir 500 mg BID resulted in a 152 % increase in AUC and a 156 % increase in the elimination half-life of nelfinavir. Administration of a single 500 mg dose of ritonavir following six doses of nelfinavir 750 mg TID resulted in minimal increase (8 %) in ritonavir plasma AUC.
Addition of low dose ritonavir (either 100 or 200 mg BID) to nelfinavir 1250 mg BID resulted in a 20 % increase in nelfinavir plasma AUC after morning administration and a 39 % increase after evening administration at steady state. The AUC of the nelfinavir metabolite M8 increased by 74 % and 86 % after morning and evening administrations, respectively (see section 5.2 regarding the formation and further metabolism of M8). There were no significant differences between low doses of ritonavir (either 100 or 200 mg BID) for effects on AUCs of nelfinavir and M8. The clinical relevance of these findings has not been established.

Indinavir: administration of a single 750 mg dose of nelfinavir following indinavir 800 mg every 8 hours for 7 days resulted in an 83 % increase in nelfinavir plasma AUC and a 22 % increase in the elimination half-life of nelfinavir. Administration of a single 800 mg dose of indinavir following nelfinavir 750 mg TID for 7 days resulted in a 51 % increase in indinavir plasma AUC concentrations, with a 5-fold increase in trough concentrations measured at 8 hours, but no increase in peak concentrations. The safety of this combination has not been established.

Saquinavir soft gelatin capsule: administration of a single 750 mg dose of nelfinavir following 4 days of saquinavir soft gelatin capsule 1200 mg TID resulted in a 30 % increase in nelfinavir plasma AUC. Administration of a single 1200 mg dose of saquinavir soft gelatin capsule following 4 days of nelfinavir 750 mg TID resulted in a 392 % increase in saquinavir plasma AUC.

Amprenavir: Co-administration of amprenavir 800 mg TID with nelfinavir 750 mg TID resulted in a small increase in nelfinavir and amprenavir plasma AUC and a 189 % increase in amprenavir $C_{min.}$ No dose adjustment is necessary for either medicinal product when nelfinavir is administered in combination with amprenavir.

*Non-nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs):*

Efavirenz: Co-administration of efavirenz 600 mg once daily (qd) with nelfinavir 750 mg TID increased nelfinavir AUC by 20 % with no change in efavirenz AUC. A dose adjustment is not needed when efavirenz is administered with VIRACEPT.

Delavirdine: Co-administration of nelfinavir 750 mg TID with delavirdine 400 mg TID resulted in a 107 % increase in nelfinavir AUC and a 31 % decrease in delavirdine AUC. The safety of this drug combination has not been established and this combination is not recommended.

Nevirapine: Current evidence suggests that there is unlikely to be a clinically relevant interaction when nelfinavir 750 mg TID and nevirapine 200 mg BID are co-administered. A dose adjustment is not needed when nevirapine is administered with VIRACEPT.

**Metabolic enzyme inducers:** rifampicin decreases nelfinavir plasma AUC by 82 % and its concomitant use with nelfinavir is contraindicated (see section 4.3). Other potent inducers of CYP3A (e.g., phenobarbital, carbamazepine) may also reduce nelfinavir plasma concentrations. If therapy with such medicinal products is warranted, physicians should consider using alternatives when a patient is taking VIRACEPT.

Rifabutin: Co-administration of nelfinavir 750 mg TID and rifabutin 300 mg once a day results in a 32 % decrease in nelfinavir plasma AUC and a 207 % increase in rifabutin plasma AUC (see also section 4.4). Co-administration of nelfinavir 750 mg TID with half the standard dose of rifabutin 150 mg once a day resulted in a 23 % decrease in nelfinavir plasma AUC and an 83 % increase in rifabutin plasma AUC. In contrast co-administration of VIRACEPT 1250 mg BID with half the standard dose of rifabutin 150 mg qd resulted in no change in nelfinavir plasma AUC. Dosage reduction of rifabutin to 150 mg once a day is necessary when nelfinavir 750 mg TID or 1250 mg BID and rifabutin are co-administered.

Phenytoin: Co-administration of nelfinavir 1250 mg BID with phenytoin 300 mg once a day did not change the concentration of nelfinavir. However, AUC values of phenytoin and free phenytoin were reduced by 29 % and 28 % by co-administration of nelfinavir, respectively. No dose adjustment for nelfinavir is recommended. Phenytoin concentrations should be monitored during co-administration with nelfinavir.

**St. John's wort *(Hypericum perforatum):*** Plasma levels of nelfinavir can be reduced by concomitant use of the herbal preparation St. John's wort *(Hypericum perforatum)*. This is due to induction of drug metabolising enzymes and/or transport proteins by St. John's wort. Herbal preparations containing St. John's wort must not be used concomitantly with VIRACEPT. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible nelfinavir levels. Nelfinavir levels may increase on stopping St. John's wort, and the dose of VIRACEPT may need adjusting. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment (see section 4.3).

**Metabolic enzyme inhibitors:** co-administration of nelfinavir and a strong inhibitor of CYP3A, ketoconazole, resulted in a 35 % increase in nelfinavir plasma AUC. This change is not considered clinically significant and no dose adjustment is needed when ketoconazole and VIRACEPT are co-administered. Based on the metabolic profiles, a clinically relevant drug interaction would not be expected with other specific inhibitors of CYP3A (e.g., fluconazole, itraconazole, clarithromycin, erythromycin); however, the possibility cannot be excluded.

Co-administration of nelfinavir with inhibitors of CYP2C19 (e.g., fluconazole, fluoxetine, paroxetine, omeprazole, lansoprazole, imipramine, amitriptyline and diazepam) may be expected to reduce the conversion of nelfinavir to its major active metabolite M8 (*tert-butyl* hydroxy nelfinavir) with a concomitant increase in plasma nelfinavir levels (see section 5.2). Limited clinical trial data from patients receiving one or more of these medicinal products with nelfinavir indicated that a clinically significant effect on safety and efficacy is not expected. However, such an effect cannot be ruled out.

**HMG-CoA reductase inhibitors** which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with VIRACEPT. Co-administration of nelfinavir 1250 mg BID and simvastatin 20 mg once a day increased the plasma AUC of simvastatin by 506 %. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicinal products with VIRACEPT is not recommended. Atorvastatin is less dependent on CYP3A4 for metabolism. Co-administration of nelfinavir 1250 mg BID and atorvastatin 10 mg once a day increased the AUC of atorvastatin by 74 %. When used with VIRACEPT, the lowest possible dose of atorvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4, and interactions are not expected with PIs. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

**Methadone**: Co-administration of nelfinavir 1250 mg BID with methadone 80 +/- 21 mg once a day in HIV negative methadone maintenance patients resulted in a 47 % decrease in methadone AUC. None of the subjects experienced withdrawal symptoms in this study; however, due to the pharmacokinetic changes, it should be expected that some patients who received this drug combination may experience withdrawal symptoms and require an upward adjustment of the methadone dose.

**Other potential interactions (see also section 4.3):** Nelfinavir increases terfenadine plasma concentrations; therefore, VIRACEPT must not be administered concurrently with terfenadine because of the potential for serious and/or life-threatening cardiac arrhythmias. Because similar interactions are likely with astemizole and cisapride, VIRACEPT must not be administered concurrently with these drugs. Although specific studies have not been done, potent sedatives metabolised by CYP3A, such as triazolam or midazolam, must not be co-administered with VIRACEPT due to the potential for prolonged sedation or respiratory depression resulting from competitive inhibition of the metabolism of these medicinal products when they are co-administered.

Similarly, concomitant administration of nelfinavir with any of amiodarone, quinidine, pimozide and ergot derivatives is contraindicated. For other compounds that are substrates for CYP3A (e.g., calcium channel blockers including bepridil, immunosuppressants including tacrolimus and ciclosporin, and sildenafil) plasma concentrations may be elevated when co-administered with VIRACEPT; therefore, patients should be monitored for toxicities associated with such medicinal products.

**Oral contraceptives:** administration of nelfinavir 750 mg TID and a combination oral contraceptive which included 0.4 mg of norethindrone and 35 μg of 17 α-ethinylestradiol for 7 days resulted in a 47 % decrease in ethinylestradiol and an 18 % decrease in norethindrone plasma AUC. Alternative contraceptive measures should be considered.

## 4.6 Pregnancy and lactation

No treatment-related adverse effects were seen in animal reproductive toxicity studies in rats at doses providing systemic exposure comparable to that observed with the clinical dose. Clinical experience in pregnant women is limited. VIRACEPT should be given during pregnancy only if the expected benefit justifies the possible risk to the foetus.

It is recommended that HIV-infected women must not breast-feed their infants under any circumstances in order to avoid transmission of HIV. Studies in lactating rats showed that nelfinavir is excreted in breast milk. There is no data available on nelfinavir excretion into human breast milk. Mothers must be instructed to discontinue breast-feeding if they are receiving VIRACEPT.

## 4.7 Effects on ability to drive and use machines

VIRACEPT has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

**Experience from clinical trials with the VIRACEPT 250 mg tablet**
The safety of the VIRACEPT 250 mg tablet was studied in controlled clinical trials with over 1300 patients.
The majority of patients in these studies received either 750 mg TID either alone or in combination with nucleoside analogues or 1250 mg BID in combination with nucleoside analogues.

The most frequently reported adverse drug reaction among patients (n=514) receiving VIRACEPT in two phase III, double-blind studies was diarrhoea (70.6 %, n=350). Diarrhoea was of mild or moderate intensity in 97.7 % of these 350 patients. Although formal analyses of the time to onset of diarrhoea were not performed, onset of diarrhoea generally occurs shortly after beginning treatment with VIRACEPT; onset of diarrhoea is less likely to occur in patients who have been receiving VIRACEPT for longer periods of time. In addition, over 4000 patients ≥ 13 years in the expanded access programmes received VIRACEPT at a dose of 750 mg TID. The majority of adverse events were of mild intensity.

Across the two phase III, double-blind studies adverse reactions of moderate to severe intensity reported by investigators as at least possibly related to VIRACEPT or of unknown relationship in > 2 % of patients treated with the 750 mg TID dose of VIRACEPT (n = 200) in combination with nucleoside analogues (for 24 weeks) included the following undesirable effects:

Gastrointestinal disorders: diarrhoea (25.9 %), flatulence (2.5 %), nausea (4.5 %),

Skin and subcutaneous tissue disorders: rash (3.0 %).

Safety data up to 48 weeks is available from 554 patients in the study comparing 1250 mg VIRACEPT BID (n=344) versus 750 mg VIRACEPT TID (n=210), each in combination with lamivudine and stavudine. The incidence of adverse reactions of moderate to severe intensity reported by investigators as at least possibly related to VIRACEPT or of unknown relationship in ≥ 2 % of patients treated was similar for the BID and TID arms: diarrhoea (21.2 % versus 18.2 %), nausea (2.9 % versus 3.3 %) and rash (1.7 % versus 1.4 %).

Marked clinical laboratory abnormalities (change from grade 0 to grade 3 or 4, or change from grade 1 to grade 4) reported in ≥ 2 % of patients treated with 750 mg TID of VIRACEPT (for 24 weeks) across the same studies included increased creatine kinase (3.9 %), and decreased neutrophils (4.5 %). Marked increases in transaminases occurred in less than 2 % of patients receiving VIRACEPT 750 mg TID and were sometimes accompanied by clinical signs and symptoms of acute hepatitis. Some of these patients were known to be chronic carriers of hepatitis B and/or C viruses. With the exception of diarrhoea, there were no significant differences in the adverse experiences reported by patients treated with VIRACEPT versus the control arms containing zidovudine plus lamivudine or stavudine alone.

In the study comparing VIRACEPT 1250 mg BID with VIRACEPT 750 mg TID each in combination with lamivudine and stavudine, the incidence of marked clinical laboratory abnormalities (change from grade 0 to grade 3 or 4, or change from grade 1 to grade 4) reported in ≥ 2 % of patients was: AST (2 % versus 1 %), ALT (3 % versus 0 %), neutropenia (2 % versus 1 %).

**Post marketing experience**
The following additional adverse reactions have been reported in the post-marketing experience:

Infections and infestations:
*Rare (≥ 0.01 % - ≤ 0.1 %)*: hepatitis, abnormal liver enzymes and jaundice when nelfinavir is used in combination with other antiretroviral agents.

Immune system disorders:
*Uncommon (≥ 0.1 % - ≤ 1 %)*: hypersensitivity reactions including bronchospasm, fever, pruritus, facial oedema and rash (maculopapular or bullous).

Metabolism and nutrition disorders:
*Rare (≥ 0.01 % - ≤ 0.1 %)*: new onset diabetes mellitus, or exacerbation of existing diabetes mellitus.

Vascular disorders:
*Rare (≥ 0.01 % - ≤ 0.1 %)*: increased spontaneous bleeding in patients with haemophilia.

Gastrointestinal disorders:
*Rare (≥ 0.01 % - ≤ 0.1 %)*: abdominal distension,
*Uncommon (≥ 0.1 % - ≤ 1 %):* vomiting, pancreatitis/increased amylase.

Skin and subcutaneous tissue disorders:
*Uncommon - rare (≥ 0.01 % - ≤ 1 %)*: Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).
*Very rare (≤ 0.01 %), including isolated reports*: Erythema multiforme.

Musculoskeletal and connective tissue disorders:
*Rare (≥ 0.01 % - ≤ 0.1 %)*: Increased CPK, myalgia, myositis and rhabdomyolysis have been reported with PIs, particularly in combination with nucleoside analogues.

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactaemia (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

### 4.9 Overdose

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

Overdoses of nelfinavir could theoretically be associated with prolongation of the QT-interval of the ECG (see also section 5.3). Monitoring of overdosed patients is warranted.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiviral agent, ATC code: J05A E04.

**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 reversibly binds to the active site of HIV protease and prevents cleavage of the polyproteins resulting in the formation of immature non-infectious viral particles.

**Antiviral activity *in vitro***: the antiviral activity of nelfinavir *in vitro* has been demonstrated in both HIV acute and chronic infections in lymphoblastoid cell lines, peripheral blood lymphocytes and monocytes/macrophages. Nelfinavir was found to be active against a broad range of 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 (mean of 58 nM). Nelfinavir demonstrated additive to synergistic effects against HIV in combination with reverse transcriptase inhibitors zidovudine (ZDV), lamivudine (3TC), didanosine (ddI), zalcitabine (ddC) and stavudine (d4T) without enhanced cytotoxicity.

**Drug Resistance***:* HIV isolates with reduced susceptibility to nelfinavir have been selected *in vitro*. HIV isolates from selected patients treated with nelfinavir alone or in combination with reverse transcriptase inhibitors were monitored for phenotypic (n=19) and genotypic (n=195, 157 of which were assessable) changes in clinical trials over a period of 2 to 82 weeks. One or more viral protease mutations at amino acid positions 30, 35, 36, 46, 71, 77 and 88 were detected in > 10 % of patients with assessable isolates. Of 19 patients for whom both phenotypic and genotypic analyses were performed on clinical isolates, 9 patients isolates showed reduced susceptibility (5- to 93-fold) to nelfinavir *in vitro*. Isolates from all 9 patients possessed one or more mutations in the viral protease gene. Amino acid position 30 appeared to be the most frequent mutation site.

The overall incidence of the D30N mutation in the viral protease of assessable isolates (n=157) from patients receiving nelfinavir monotherapy or nelfinavir in combination with zidovudine and lamivudine or stavudine was 54.8 %. The overall incidence of other mutations associated with primary PI resistance was 9.6 % for the L90M substitution where as substitutions at 48, 82 and 84 were not observed.

**Cross resistance**: HIV isolates obtained from 5 patients during nelfinavir therapy showed a 5- to 93-fold decrease in nelfinavir susceptibility *in vitro* when compared to matched baseline isolates but did not demonstrate a concordant decrease in susceptibility to indinavir, ritonavir, saquinavir or amprenavir *in vitro*. Conversely, following ritonavir therapy, 6 of 7 clinical isolates with decreased ritonavir susceptibility (8- to 113-fold) *in vitro* compared to baseline also exhibited decreased susceptibility to nelfinavir *in vitro* (5- to 40 fold). An HIV isolate obtained from a patient receiving saquinavir therapy showed decreased susceptibility to saquinavir (7- fold) but did not demonstrate a concordant decrease in susceptibility to nelfinavir. Cross-resistance between nelfinavir and reverse transcriptase inhibitors is unlikely because different enzyme targets are involved. Clinical isolates (n=5) with decreased susceptibility to zidovudine, lamivudine, or nevirapine remain fully susceptible to nelfinavir *in vitro*.

**Clinical pharmacodynamic data:** treatment with nelfinavir alone or in combination with other antiretroviral agents has been documented to reduce viral load and increase CD4 cell counts in HIV-1 seropositive patients. Decreases in HIV RNA observed with nelfinavir monotherapy were less pronounced and of shorter duration. The effects of nelfinavir (alone or combined with other antiretroviral agents) on biological markers of disease activity, CD4 cell count and viral RNA, were evaluated in several studies involving HIV-1 infected patients.

The efficacy of the BID regimen has been evaluated versus the TID regimen with VIRACEPT 250 mg tablets primarily in patients naïve to PIs. A randomised open-label study compared the HIV RNA suppression of nelfinavir 1250 mg BID versus nelfinavir 750 mg TID in PI naïve patients also receiving stavudine (30-40 mg BID) and lamivudine (150 mg BID).

| **Proportion of patients with HIV RNA below LOQ (sensitive and ultrasensitive assays) at Week 48** | | | | |
|---|---|---|---|---|
| **Assay** | **Analysis** | **Viracept BID (%)** | **Viracept TID (%)** | **95% CI** |
| Sensitive | Observed data | 135/164 (82%) | 146/169 (86%) | (-12, +4) |
| | LOCF | 145/200 (73%) | 161/206 (78%) | (-14, +3) |
| | ITT (NC = F) | 135/200 (68%) | 146/206 (71%) | (-12, +6) |
| Ultrasensitive | Observed data | 114/164 (70%) | 125/169 (74%) | (-14, +5) |
| | LOCF | 121/200 (61%) | 136/206 (66%) | (-15, +4) |

| | | | | |
|---|---|---|---|---|
| | ITT (NC = F) | 114/200 (57%) | 125/206 (61%) | (-13, +6) |

*LOCF= Last observation carried forward*
*ITT = Intention to Treat*
*NC = F: non-completers = failures*

The BID regimen produced statistically significantly higher peak nelfinavir plasma levels versus the TID regimen. Small, non-statistically significant differences were observed in other pharmacokinetic parameters with no trend favouring one regimen over the other. Although study 542 showed no statistically significant differences between the two regimens in efficacy in a predominantly antiretroviral naïve patient population, the significance of these findings for antiretroviral experienced patients is unknown.

In a study of 297 HIV-1 seropositive patients receiving zidovudine and lamivudine plus nelfinavir (2 different doses) or zidovudine and lamivudine alone, the mean baseline CD4 cell count was 288 cells/$mm^3$ and the mean baseline plasma HIV RNA was 5.21 $log_{10}$ copies/ml (160,394 copies/ml). The mean decrease in plasma HIV RNA using a PCR assay (< 400 copies/ml) at 24 weeks was 2.33 $log_{10}$ in patients receiving combination therapy with nelfinavir 750 mg TID, compared to 1.34 $log_{10}$ in patients receiving zidovudine and lamivudine alone. At 24 weeks, the percentage of patients whose plasma HIV RNA levels had decreased to below the limit of detection of the assay (< 400 copies/ml) were 81 % and 8 % for the groups treated with nelfinavir 750 mg TID plus zidovudine and lamivudine or zidovudine and lamivudine, respectively. Mean CD4 cell counts at 24 weeks were increased by 150 and 95 cells/$mm^3$ for the groups treated with nelfinavir 750 mg TID plus zidovudine and lamivudine or zidovudine and lamivudine, respectively. At 48 weeks, approximately 75 % of the patients treated with nelfinavir 750 mg TID plus zidovudine and lamivudine remained below the level of detection of the assay (< 400 copies/ml); mean increase in CD4 cell counts was 198 cells/$mm^3$ at 48 weeks in this group.

No important differences in safety or tolerability were observed between the BID and TID dosing groups, with the same proportion of patients in each arm experiencing adverse events of any intensity, irrespective of relationship to trial medication.

Plasma levels of certain HIV-1 protease inhibitors, which are metabolized predominantly by CYP3A4, can be increased by the co-administration of low-dose ritonavir, which is an inhibitor of this metabolism. Treatment paradigms for several protease inhibitors, which are subject to this interaction, require the co-administration of low-dose ritonavir ('boosting') in order to enhance plasma levels and optimize antiviral efficacy. Plasma levels of nelfinavir, which is metabolized predominantly by CYP2C19 and only partially by CYP3A4, are not greatly increased by coadministration with ritonavir, and therefore co-administration of nelfinavir with low-dose ritonavir does not appear to be beneficial. Two studies have compared the safety and efficacy of nelfinavir (unboosted) with ritonavir- boosted protease inhibitors, each in combination with other antiretroviral agents.

Study M98-863 is a randomised, double blind trial of 653 antiretroviral-naïve patients investigating lopinavir/ritonavir (400/100 mg BID n=326) compared to nelfinavir (750mg TID n=327), each in combination with lamivudine (150 mg twice daily) and stavudine (40 mg twice daily). Median baseline HIV-1 RNA was 4.98 log10 copies/ml and 5.01 log10 copies/ml in the nelfinavir and lopinavir/ritonavir treatment groups respectively. Median baseline CD4+ cell count was 232 cells/mm3 in both groups. At week 48, 63% nelfinavir and 75% lopinavir/ritonavir patients had HIV-1 RNA < 400 copies/ml, whereas 52% nelfinavir and 67% lopinavir/ritonavir patients had HIV-1 RNA <50 copies/ml (intent-to-treat, missing = failure). The mean increase from baseline in CD4+ cell count at week 48 was 195 cells/mm3 and 207 cells/mm3 in the nelfinavir and lopinavir/ritonavir groups respectively. Through 48 weeks of therapy, a statistically significantly higher proportion of patients in the lopinavir/ritonavir arm had HIV-1 RNA < 50 copies/ml compared to the nelfinavir arm.

Study APV30002 is a randomised, open-label trial of 649 antiretroviral treatment naïve patients with advanced HIV-disease, investigating fosamprenavir/ritonavir (1400mg/200mg QD n=322) compared to nelfinavir (1250mg BID n=327), each in combination with lamivudine (150 mg twice daily) and abacavir (300 mg twice daily). Median baseline HIV-1 RNA was 4.8 log10 copies/ml in both treatment groups. Median baseline CD4+ cell counts were 177 and 166 x106 cells/l for the nelfinavir

and fosamprenavir/ritonavir groups respectively. At week 48, non-inferiority was shown with 68% of patients in the group treated with nelfinavir and 69% patients treated with fosamprenavir/ritonavir having plasma HIV-1 RNA <400 copies/ml whereas 53% in the nelfinavir and 55% in the fosamprenavir/ritonavir patients had HIV-1 RNA <50 copies/ml (intent-to-treat, rebound/discontinuation = failure). The median increase from baseline in CD4+ cell count over 48 weeks was 207 cells/mm3 and 203 cells/mm3 in the nelfinavir and fosamprenavir/ritonavir groups respectively. The virological failure was greater in the nelfinavir group (17%) than in the fosamprenavir/ritonavir group (7%). Treatment emergent NRTI resistance was significantly less frequent with fosamprenavir/ritonavir compared to nelfinavir (13% versus 57%; $p<0.001$).

## 5.2 Pharmacokinetic properties

The pharmacokinetic properties of nelfinavir have been evaluated in healthy volunteers and HIV-infected patients. No substantial differences have been observed between healthy volunteers and HIV-infected patients.

**Absorption**: after single or multiple oral doses of 500 to 750 mg (two to three 250 mg tablets) with food, peak nelfinavir plasma concentrations were typically achieved in 2 to 4 hours. After multiple dosing with 750 mg every 8 hours for 28 days (steady-state), peak plasma concentrations ($C_{max}$) averaged 3-4 µg/ml and plasma concentrations prior to the next dose (trough) were 1-3 µg/ml. A greater than dose-proportional increase in nelfinavir plasma concentrations was observed after single doses; however, this was not observed after multiple dosing.

A pharmacokinetic study in HIV-positive patients compared multiple doses of 1250 mg twice daily (BID) with multiple doses of 750 mg three times daily (TID) for 28 days. Patients receiving VIRACEPT BID (n=10) achieved nelfinavir $C_{max}$ of 4.0 ± 0.8 µg/ml and morning and evening trough concentrations of 2.2 ± 1.3 µg/ml and 0.7 ± 0.4 µg/ml, respectively. Patients receiving VIRACEPT TID (n=11) achieved nelfinavir peak plasma concentrations ($C_{max}$) of 3.0 ± 1.6 µg/ml and morning and evening trough concentrations of 1.4 ± 0.6 µg/ml and 1.0 ± 0.5 µg/ml, respectively. 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 precise 8- or 12-hour intervals.

The pharmacokinetics of nelfinavir are similar during BID and TID administration. In patients, the nelfinavir $AUC_{0-24}$ with 1250 mg BID administration was 52.8 ± 15.7 µg·h/ml (n=10) and with 750 mg TID administration was 43.6 ± 17.8 µg·h/ml (n=11). Trough drug exposures remain at least twenty fold greater than the mean IC95 throughout the dosing interval for both regimens. The clinical relevance of relating *in vitro* measures to drug potency and clinical outcome has not been established. A greater than dose-proportional increase in nelfinavir plasma concentrations was observed after single doses; however, this was not observed after multiple dosing.

The absolute bioavailability of VIRACEPT has not been determined.

**Effect of food on gastrointestinal absorption**: maximum plasma concentrations and area under the plasma concentration-time curve were consistently 2 to 3-fold higher under fed conditions compared to fasting. The increased plasma concentrations with food were independent of fat content of the meals. The effect of meal content on nelfinavir exposure was investigated in a study using the 250 mg film-coated tablets formulation. Steady state nelfinavir AUC and $C_{max}$ were respectively 15 % and 20 % higher when doses followed a 800 kcal/50 % fat meal compared to those following a light meal (350 kcal/33 % fat), suggesting that meal content has less effect on nelfinavir exposures during multiple dosing than would be anticipated based on data from single dose studies.

**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 were lower than in other tissues, but exceeded the *in vitro* $EC_{95}$ for antiviral activity. Nelfinavir in serum is extensively protein-bound (≥ 98 %).

**Metabolism:** unchanged nelfinavir comprised 82-86 % of the total plasma radioactivity after a single oral 750 mg dose of $^{14}$C-nelfinavir. *In vitro*, multiple cytochrome P-450 isoforms including CYP3A, CYP2C19/C9 and CYP2D6 are responsible for metabolism of nelfinavir. One major and several minor oxidative metabolites were found in plasma.

The major oxidative metabolite, M8 (*tert-butyl* hydroxy nelfinavir), has *in vitro* antiviral activity equal to the parent drug and its formation is catalysed by the polymorphic cytochrome CYP2C19. The further degradation of M8 appears to be catalysed by CYP3A4. In subjects with normal CYP2C19 activity plasma levels of this metabolite are approximately 25 % of the total plasma nelfinavir-related concentration. It is expected that in CYP2C19 poor metabolisers or in patients receiving concomitantly strong CYP2C19 inhibitors (see section 4.5), nelfinavir plasma levels would be elevated whereas levels of *tert-butyl* hydroxy nelfinavir would be negligible or non-measurable. Limited clinical data suggest that patients with very low or non-measurable plasma concentrations of the metabolite and elevated concentrations of nelfinavir do not show a reduced virological response or a different safety profile when compared with the whole study population.

**Elimination:** oral clearance estimates after single doses (24-33 l/h) and multiple doses (26-61 l/h) indicate that nelfinavir exhibits medium to high hepatic bioavailability. The terminal half-life in plasma was typically 3.5 to 5 hours. The majority (87 %) of an oral 750 mg dose containing $^{14}$C-nelfinavir was recovered in the faeces; total faecal radioactivity consisted of nelfinavir (22 %) and numerous oxidative metabolites (78 %). Only 1-2 % of the dose was recovered in urine, of which unchanged nelfinavir was the major component.

**Pharmacokinetics in special clinical situations:**

***Pharmacokinetics in children and the elderly:*** in children between the ages of 2 and 13 years, the clearance of orally administered nelfinavir is approximately 2 to 3 times higher than in adults, with large intersubject variability. Administration of VIRACEPT oral powder or tablets with food at a dose of approximately 25-30 mg/kg TID achieves steady-state plasma concentrations similar to adult patients receiving 750 mg TID.

In an open prospective study, the pharmacokinetics of BID and TID VIRACEPT regimens in 18 HIV infected children aged 2-14 years were investigated. Children weighing less than 25 kg received 30-37 mg/kg nelfinavir TID or 45-55 mg/kg nelfinavir BID. Children over 25 kg received 750 mg TID or 1250 mg BID.

The $C_{min}$, $C_{max}$ and $AUC_{0-24}$ were all significantly higher with the BID regimen compared with the TID regimen. In addition, in twice daily application, 14 out of 18 (78 %) and 11 out of 18 (61 %) reached $C_{min}$ values of 1-3 µg/ml and $C_{max}$ values of 3-4 µg/ml, whereas in TID application only 4 out of 18 (22 %) and 7 out of 18 (39 %) reached these values.

There are no data available in the elderly.

***Pharmacokinetics in patients with liver impairment:***

Pharmacokinetics of nelfinavir after a single dose of 750 mg 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 with impairment (Child-Turcotte Classes A to C) compared to the healthy group. Specific dose recommendations for nelfinavir cannot be made based on the results of this study.

## 5.3 Preclinical safety data

During *in vitro* studies, cloned human cardiac potassium channels (hERG) were inhibited by high concentrations of nelfinavir and its active metabolite M8. hERG potassium channels were inhibited by 20 % at nelfinavir and M8 concentrations that are about four- to five-fold and seventy-fold, respectively, above the average free therapeutic levels in humans. By contrast, no effects suggesting prolongation of the QT-interval of the ECG were observed at similar doses in dogs or in isolated cardiac tissue. The clinical relevance of these *in vitro* data is unknown. However, based on data from

products known to prolong the QT-interval, a block of hERG potassium channels of > 20 % may be clinically relevant. Therefore the potential for QT prolongation should be considered in cases of overdose (see section 4.9).

**Acute and chronic toxicity:** oral acute and chronic toxicity studies were conducted in the mouse (500 mg/kg/day), rat (up to 1,000 mg/kg/day) and monkey (up to 800 mg/kg/day). There were increased liver weights and dose-related thyroid follicular cell hypertrophy in rats. Weight loss and general physical decline was observed in monkeys together with general evidence of gastrointestinal toxicity.

**Mutagenicity**: *in vitro* and *in vivo* studies with and without metabolic activation have shown that nelfinavir has no mutagenic or genotoxic activity.

**Carcinogenicity:** Two year oral carcinogenicity studies with nelfinavir mesilate were conducted in mice and rats. In mice, administration of up to 1000 mg/kg/day did not result in any evidence for an oncogenic effect. In rats administration of 1000 mg/kg/day resulted in increased incidences of thyroid follicular cell adenoma and carcinoma, relative to those for controls. Systemic exposures were 3 to 4 times those for humans given therapeutic doses. Administration of 300 mg/kg/day resulted in an increased incidence of thyroid follicular cell adenoma. Chronic nelfinavir treatment of rats has been demonstrated to produce effects consistent with enzyme induction, which predisposed rats, but not humans, to thyroid neoplasms. The weight of evidence indicates that nelfinavir is unlikely to be a carcinogen in humans.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Each tablet contains calcium silicate, crospovidone, magnesium stearate, indigo carmine (E132) as powder.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf-life

3 years.

### 6.4 Special precautions for storage

Store in the original container. Do not store above 30°C.

### 6.5 Nature and contents of container

VIRACEPT tablets are provided in HDPE plastic bottles fitted with HDPE child resistant closures with polyethylene liners.

### 6.6 Instructions for use, handling and disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way

Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/054/003

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22.1.1998 / 3.2.2003

## 10. DATE OF REVISION OF THE TEXT

## 1. NAME OF THE MEDICINAL PRODUCT

VIRACEPT 250 mg film-coated tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VIRACEPT 250 mg film-coated tablets contain 292.25 mg of nelfinavir mesilate corresponding to 250 mg of nelfinavir (as free base). For excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablets.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

VIRACEPT is indicated in antiretroviral combination treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children of 3 years of age and older.

In protease inhibitor (PI) experienced patients the choice of nelfinavir should be based on individual viral resistance testing and treatment history.

See section 5.1.

### 4.2 Posology and method of administration

Therapy with VIRACEPT should be initiated by a physician experienced in the management of HIV infection.

VIRACEPT film-coated tablets are administered orally and should always be ingested with food (see section 5.2).

Patients older than 13 years: the recommended dosage of VIRACEPT film-coated tablets is 1250 mg (five 250 mg tablets) twice a day (BID) or 750 mg (three 250 mg tablets) three times a day (TID) by mouth.
The efficacy of the BID regimen has been evaluated versus the TID regimen primarily in patients naïve to PIs (see section 5.1, pharmacodynamic properties).

Patients aged 3 to 13 years: for children, the recommended starting dose is 50-55 mg/kg BID or, if using a TID regimen, 25 – 30 mg/kg body weight per dose. For children unable to take tablets, VIRACEPT oral powder may be administered (see Summary of Product Characteristics for VIRACEPT oral powder).

The recommended dose of VIRACEPT film-coated tablets to be administered **BID to children aged 3 to 13 years** is as follows:

| Body Weight kg | Number of VIRACEPT 250 mg film-coated tablets per dose* |
|---|---|
| 18 to < 22 | 4 |
| ≥ 22 | 5 |

The recommended dose of VIRACEPT film-coated tablets to be administered **TID to children aged 3 to 13 years** is as follows:

| Body Weight kg | Number of VIRACEPT 250 mg film-coated tablets per dose* |
|---|---|
| 18 to < 23 | 2 |
| ≥ 23 | 3 |

*see Summary of Product Characteristics for VIRACEPT oral powder for patients with less than 18 kg body weight.

Renal and hepatic impairment: there are no data specific for patients with renal impairment and therefore specific dosage recommendations cannot be made. Nelfinavir is principally metabolised and eliminated by the liver. There are not sufficient data from patients with liver impairment and therefore specific dose recommendations cannot be made (see section 5.2). Caution should be used when administering VIRACEPT to patients with impaired renal or hepatic function.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Co-administration with medicinal products with narrow therapeutic windows and which are substrates of CYP3A4 (e.g., terfenadine, astemizole, cisapride, amiodarone, quinidine, pimozide, triazolam, midazolam, ergot derivatives; see section 4.5).

Co-administration with rifampicin (see section 4.5).

Herbal preparations containing St. John's wort *(Hypericum perforatum)* must not be used while taking nelfinavir due to the risk of decreased plasma concentrations and reduced clinical effects of nelfinavir (see section 4.5).

## 4.4 Special warnings and special precautions for use

Patients should be instructed that VIRACEPT is not a cure for HIV infection, that they may continue to develop infections or other illnesses associated with HIV disease, and that VIRACEPT has not been shown to reduce the risk of transmission of HIV disease through sexual contact or blood contamination.

For use during pregnancy and lactation, see section 4.6.

**Immune Reactivation Syndrome:**
In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

**Liver Disease:**
The safety and efficacy of nelfinavir has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

**Renal Impairment:**
Caution should be used when administering VIRACEPT to patients with impaired renal function (see section 4.2).

The safety and activity of nelfinavir in children below the age of 3 years have not been established.

Caution is advised whenever VIRACEPT is co-administered with medicinal products which are inducers or inhibitors and/or substrates of CYP3A4; such combinations may require dose adjustment (see also sections 4.3, 4.5 and 4.8).

The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A4 for metabolism, thus concomitant use of VIRACEPT with simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. Caution must also be exercised if VIRACEPT is used concurrently with atorvastatin, which is metabolised to a lesser extent by CYP3A4. In this situation a reduced dose of atorvastatin should be considered. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5).

Particular caution should be used when prescribing sildenafil in patients receiving PIs, including nelfinavir. Co-administration of a PI with sildenafil is expected to substantially increase sildenafil concentration and may result in an increase in sildenafil associated adverse events, including hypotension, visual changes, and priapism (see section 4.5).

Potent inducers of CYP3A (e.g., phenobarbital and carbamazepine) may reduce nelfinavir plasma concentrations. Physicians should consider using alternatives when a patient is taking VIRACEPT (see sections 4.3 and 4.5).

VIRACEPT may lead to a decreased AUC of phenytoin; therefore phenytoin concentrations should be monitored during concomitant use with VIRACEPT (see section 4.5).

Methadone AUC may be decreased when co-administered with VIRACEPT; therefore upward adjustment of methadone dose may be required during concomitant use with VIRACEPT (see section 4.5).

Co-administration of the combination oral contraceptive containing norethindrone and 17 α-ethinylestradiol with VIRACEPT resulted in a decrease in AUC of the contraceptive drug; therefore alternative contraceptive measure should also be considered (see section 4.5).

New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving PIs. In some of these the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes or hyperglycaemia.

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with PIs. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with PIs was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and nucleoside analogue reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

## 4.5 Interaction with other medicinal products and other forms of interaction

Nelfinavir is primarily metabolised via the cytochrome P450 isoenzymes CYP3A and CYP2C19 (see section 5.2). Co-administration with medicinal products that are substrates for CYP3A4 and which have narrow therapeutic windows (e.g., terfenadine, astemizole, cisapride, amiodarone, quinidine, pimozide, triazolam, midazolam, ergot derivatives) is contraindicated (see section 4.3 and below). Caution should be used when co-administering medicinal products that induce CYP3A or potentially toxic medicinal products which are themselves metabolised by CYP3A (see section 4.3 and below). Based on *in vitro* data, nelfinavir is unlikely to inhibit other cytochrome P450 isoforms at concentrations in the therapeutic range.

Other antiretrovirals:

*Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs):*

Clinically significant interactions have not been observed between nelfinavir and nucleoside analogues (specifically zidovudine plus lamivudine, stavudine, and stavudine plus didanosine). At present, there is no evidence of inadequate efficacy of zidovudine in the CNS that could be associated with the modest reduction in plasma levels of zidovudine when coadministered with nelfinavir. Since it is recommended that didanosine be administered on an empty stomach, VIRACEPT should be administered (with food) one hour after or more than 2 hours before didanosine.

*Other Protease Inhibitors (PIs)*

Ritonavir: administration of a single 750 mg dose of nelfinavir following 3 doses of ritonavir 500 mg BID resulted in a 152 % increase in AUC and a 156 % increase in the elimination half-life of nelfinavir. Administration of a single 500 mg dose of ritonavir following six doses of nelfinavir 750 mg TID resulted in minimal increase (8 %) in ritonavir plasma AUC.
Addition of low dose ritonavir (either 100 or 200 mg BID) to nelfinavir 1250 mg BID resulted in a 20 % increase in nelfinavir plasma AUC after morning administration and a 39 % increase after evening administration at steady state. The AUC of the nelfinavir metabolite M8 increased by 74 % and 86 % after morning and evening administrations, respectively (see section 5.2 regarding the formation and further metabolism of M8). There were no significant differences between low doses of ritonavir (either 100 or 200 mg BID) for effects on AUCs of nelfinavir and M8. The clinical relevance of these findings has not been established.

Indinavir: administration of a single 750 mg dose of nelfinavir following indinavir 800 mg every 8 hours for 7 days resulted in an 83 % increase in nelfinavir plasma AUC and a 22 % increase in the elimination half-life of nelfinavir. Administration of a single 800 mg dose of indinavir following nelfinavir 750 mg TID for 7 days resulted in a 51 % increase in indinavir plasma AUC concentrations, with a 5-fold increase in trough concentrations measured at 8 hours, but no increase in peak concentrations. The safety of this combination has not been established.

Saquinavir soft gelatin capsule: administration of a single 750 mg dose of nelfinavir following 4 days of saquinavir soft gelatin capsule 1200 mg TID resulted in a 30 % increase in nelfinavir plasma AUC. Administration of a single 1200 mg dose of saquinavir soft gelatin capsule following 4 days of nelfinavir 750 mg TID resulted in a 392 % increase in saquinavir plasma AUC.

Amprenavir: Co-administration of amprenavir 800 mg TID with nelfinavir 750 mg TID resulted in a small increase in nelfinavir and amprenavir plasma AUC and a 189 % increase in amprenavir $C_{min.}$ No dose adjustment is necessary for either medicinal product when nelfinavir is administered in combination with amprenavir.

*Non-nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs):*

Efavirenz: Co-administration of efavirenz 600 mg once daily (qd) with nelfinavir 750 mg TID increased nelfinavir AUC by 20 % with no change in efavirenz AUC. A dose adjustment is not needed when efavirenz is administered with VIRACEPT.

Delavirdine: Co-administration of nelfinavir 750 mg TID with delavirdine 400 mg TID resulted in a 107 % increase in nelfinavir AUC and a 31 % decrease in delavirdine AUC. The safety of this drug combination has not been established and this combination is not recommended.

Nevirapine: Current evidence suggests that there is unlikely to be a clinically relevant interaction when nelfinavir 750 mg TID and nevirapine 200 mg BID are co-administered. A dose adjustment is not needed when nevirapine is administered with VIRACEPT.

**Metabolic enzyme inducers:** rifampicin decreases nelfinavir plasma AUC by 82 % and its concomitant use with nelfinavir is contraindicated (see section 4.3). Other potent inducers of CYP3A (e.g., phenobarbital, carbamazepine) may also reduce nelfinavir plasma concentrations. If therapy with such medicinal products is warranted, physicians should consider using alternatives when a patient is taking VIRACEPT.

Rifabutin: Co-administration of nelfinavir 750 mg TID and rifabutin 300 mg once a day results in a 32 % decrease in nelfinavir plasma AUC and a 207 % increase in rifabutin plasma AUC (see also section 4.4). Co-administration of nelfinavir 750 mg TID with half the standard dose of rifabutin 150 mg once a day resulted in a 23 % decrease in nelfinavir plasma AUC and an 83 % increase in rifabutin plasma AUC. In contrast co-administration of VIRACEPT 1250 mg BID with half the standard dose of rifabutin 150 mg qd resulted in no change in nelfinavir plasma AUC. Dosage reduction of rifabutin to 150 mg once a day is necessary when nelfinavir 750 mg TID or 1250 mg BID and rifabutin are co-administered.

Phenytoin: Co-administration of nelfinavir 1250 mg BID with phenytoin 300 mg once a day did not change the concentration of nelfinavir. However, AUC values of phenytoin and free phenytoin were reduced by 29 % and 28 % by co-administration of nelfinavir, respectively. No dose adjustment for nelfinavir is recommended. Phenytoin concentrations should be monitored during co-administration with nelfinavir.

**St. John's wort *(Hypericum perforatum):*** Plasma levels of nelfinavir can be reduced by concomitant use of the herbal preparation St. John's wort *(Hypericum perforatum)*. This is due to induction of drug metabolising enzymes and/or transport proteins by St. John's wort. Herbal preparations containing St. John's wort must not be used concomitantly with VIRACEPT. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible nelfinavir levels. Nelfinavir levels may increase on stopping St. John's wort, and the dose of VIRACEPT may need adjusting. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment (see section 4.3).

**Metabolic enzyme inhibitors:** co-administration of nelfinavir and a strong inhibitor of CYP3A, ketoconazole, resulted in a 35 % increase in nelfinavir plasma AUC. This change is not considered clinically significant and no dose adjustment is needed when ketoconazole and VIRACEPT are co-administered. Based on the metabolic profiles, a clinically relevant drug interaction would not be expected with other specific inhibitors of CYP3A (e.g., fluconazole, itraconazole, clarithromycin, erythromycin); however, the possibility cannot be excluded.

Co-administration of nelfinavir with inhibitors of CYP2C19 (e.g., fluconazole, fluoxetine, paroxetine, omeprazole, lansoprazole, imipramine, amitriptyline and diazepam) may be expected to reduce the conversion of nelfinavir to its major active metabolite M8 (*tert-butyl* hydroxy nelfinavir) with a concomitant increase in plasma nelfinavir levels (see section 5.2). Limited clinical trial data from patients receiving one or more of these medicinal products with nelfinavir indicated that a clinically significant effect on safety and efficacy is not expected. However, such an effect cannot be ruled out.

**HMG-CoA reductase inhibitors** which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with VIRACEPT. Co-administration of nelfinavir 1250 mg BID and simvastatin 20 mg once a day increased the plasma AUC of simvastatin by 506 %. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicinal products with VIRACEPT is not recommended. Atorvastatin is less dependent on CYP3A4 for metabolism. Co-administration of nelfinavir 1250 mg BID and atorvastatin 10 mg once a day increased the AUC of atorvastatin by 74 %. When used with VIRACEPT, the lowest possible dose of atorvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4, and interactions are not expected with PIs. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

**Methadone**: Co-administration of nelfinavir 1250 mg BID with methadone 80 +/- 21 mg once a day in HIV negative methadone maintenance patients resulted in a 47 % decrease in methadone AUC. None of the subjects experienced withdrawal symptoms in this study; however, due to the pharmacokinetic changes, it should be expected that some patients who received this drug combination may experience withdrawal symptoms and require an upward adjustment of the methadone dose.

**Other potential interactions (see also section 4.3):** Nelfinavir increases terfenadine plasma concentrations; therefore, VIRACEPT must not be administered concurrently with terfenadine because of the potential for serious and/or life-threatening cardiac arrhythmias. Because similar interactions are likely with astemizole and cisapride, VIRACEPT must not be administered concurrently with these drugs. Although specific studies have not been done, potent sedatives metabolised by CYP3A, such as triazolam or midazolam, must not be co-administered with VIRACEPT due to the potential for prolonged sedation or respiratory depression resulting from competitive inhibition of the metabolism of these medicinal products when they are co-administered.

Similarly, concomitant administration of nelfinavir with any of amiodarone, quinidine, pimozide and ergot derivatives is contraindicated. For other compounds that are substrates for CYP3A (e.g. calcium channel blockers including bepridil, immunosuppressants including tacrolimus and ciclosporin and sildenafil) plasma concentrations may be elevated when co-administered with VIRACEPT; therefore, patients should be monitored for toxicities associated with such medicinal products.

**Oral contraceptives:** administration of nelfinavir 750 mg TID and a combination oral contraceptive which included 0.4 mg of norethindrone and 35 μg of 17 α-ethinylestradiol for 7 days resulted in a 47 % decrease in ethinylestradiol and an 18 % decrease in norethindrone plasma AUC. Alternative contraceptive measures should be considered.

## 4.6 Pregnancy and lactation

No treatment-related adverse effects were seen in animal reproductive toxicity studies in rats at doses providing systemic exposure comparable to that observed with the clinical dose. Clinical experience in pregnant women is limited. VIRACEPT should be given during pregnancy only if the expected benefit justifies the possible risk to the foetus.

It is recommended that HIV-infected women must not breast-feed their infants under any circumstances in order to avoid transmission of HIV. Studies in lactating rats showed that nelfinavir is excreted in breast milk. There is no data available on nelfinavir excretion into human breast milk. Mothers must be instructed to discontinue breast-feeding if they are receiving VIRACEPT.

## 4.7 Effects on ability to drive and use machines

VIRACEPT has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

**Experience from clinical trials with the VIRACEPT 250 mg tablet**
The safety of the VIRACEPT 250 mg tablet was studied in controlled clinical trials with over 1300 patients.
The majority of patients in these studies received either 750 mg TID either alone or in combination with nucleoside analogues or 1250 mg BID in combination with nucleoside analogues.

The most frequently reported adverse drug reaction among patients (n=514) receiving VIRACEPT in two phase III, double-blind studies was diarrhoea (70.6 %, n=350). Diarrhoea was of mild or moderate intensity in 97.7 % of these 350 patients. Although formal analyses of the time to onset of diarrhoea were not performed, onset of diarrhoea generally occurs shortly after beginning treatment with VIRACEPT; onset of diarrhoea is less likely to occur in patients who have been receiving VIRACEPT for longer periods of time. In addition, over 4000 patients ≥ 13 years in the expanded access programmes received VIRACEPT at a dose of 750 mg TID. The majority of adverse events were of mild intensity.

Across the two phase III, double-blind studies adverse reactions of moderate to severe intensity reported by investigators as at least possibly related to VIRACEPT or of unknown relationship in ≥ 2 % of patients treated with the 750 mg TID dose of VIRACEPT (n = 200) in combination with nucleoside analogues (for 24 weeks) included the following undesirable effects:

Gastrointestinal disorders: diarrhoea (25.9 %), flatulence (2.5 %), nausea (4.5 %),

Skin and subcutaneous tissue disorders: rash (3.0 %).

Safety data up to 48 weeks is available from 554 patients in the study comparing 1250 mg VIRACEPT BID (n=344) versus 750 mg VIRACEPT TID (n=210), each in combination with lamivudine and stavudine. The incidence of adverse reactions of moderate to severe intensity reported by investigators as at least possibly related to VIRACEPT or of unknown relationship in ≥ 2 % of patients treated was similar for the BID and TID arms: diarrhoea (21.2 % versus 18.2 %), nausea (2.9 % versus 3.3 %) and rash (1.7 % versus 1.4 %).

Marked clinical laboratory abnormalities (change from grade 0 to grade 3 or 4, or change from grade 1 to grade 4) reported in ≥ 2 % of patients treated with 750 mg TID of VIRACEPT (for 24 weeks) across the same studies included increased creatine kinase (3.9 %), and decreased neutrophils (4.5 %). Marked increases in transaminases occurred in less than 2 % of patients receiving VIRACEPT 750 mg TID and were sometimes accompanied by clinical signs and symptoms of acute hepatitis. Some of these patients were known to be chronic carriers of hepatitis B and/or C viruses. With the exception of diarrhoea, there were no significant differences in the adverse experiences reported by patients treated with VIRACEPT versus the control arms containing zidovudine plus lamivudine or stavudine alone.

In the study comparing VIRACEPT 1250 mg BID with VIRACEPT 750 mg TID each in combination with lamivudine and stavudine, the incidence of marked clinical laboratory abnormalities (change from grade 0 to grade 3 or 4, or change from grade 1 to grade 4) reported in ≥ 2 % of patients was: AST (2 % versus 1 %), ALT (3 % versus 0 %), neutropenia (2 % versus 1 %).

**Post marketing experience**
The following additional adverse reactions have been reported in the post-marketing experience:

Infections and infestations:
*Rare (≥ 0.01 % - ≤ 0.1 %)*: hepatitis, abnormal liver enzymes and jaundice when nelfinavir is used in combination with other antiretroviral agents.

Immune system disorders:
*Uncommon (≥ 0.1 % - ≤ 1 %)*: hypersensitivity reactions including bronchospasm, fever, pruritus, facial oedema and rash (maculopapular or bullous).

Metabolism and nutrition disorders:
*Rare (≥ 0.01 % - ≤ 0.1 %)*: new onset diabetes mellitus, or exacerbation of existing diabetes mellitus.

Vascular disorders:
*Rare (≥ 0.01 % - ≤ 0.1 %)*: increased spontaneous bleeding in patients with haemophilia.

Gastrointestinal disorders:
*Rare (≥ 0.01 % - ≤ 0.1 %)*: abdominal distension,
*Uncommon (≥ 0.1 % - ≤ 1 %):* vomiting, pancreatitis/increased amylase.

Skin and subcutaneous tissue disorders:
*Uncommon - rare (≥ 0.01 % - ≤ 1 %)*: Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).
*Very rare (≤ 0.01 %), including isolated reports*: Erythema multiforme.

Musculoskeletal and connective tissue disorders:
*Rare (≥ 0.01 % - ≤ 0.1 %)*: Increased CPK, myalgia, myositis and rhabdomyolysis have been reported with PIs, particularly in combination with nucleoside analogues.

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactaemia (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

### 4.9 Overdose

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

Overdoses of nelfinavir could theoretically be associated with prolongation of the QT-interval of the ECG (see also section 5.3). Monitoring of overdosed patients is warranted.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiviral agent, ATC code: J05A E04

**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 reversibly binds to the active site of HIV protease and prevents cleavage of the polyproteins resulting in the formation of immature non-infectious viral particles.

**Antiviral activity *in vitro***: the antiviral activity of nelfinavir *in vitro* has been demonstrated in both HIV acute and chronic infections in lymphoblastoid cell lines, peripheral blood lymphocytes and monocytes/macrophages. Nelfinavir was found to be active against a broad range of 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 (mean of 58 nM). Nelfinavir demonstrated additive to synergistic effects against HIV in combination with reverse transcriptase inhibitors zidovudine (ZDV), lamivudine (3TC), didanosine (ddI), zalcitabine (ddC) and stavudine (d4T) without enhanced cytotoxicity.

**Drug Resistance***:* HIV isolates with reduced susceptibility to nelfinavir have been selected *in vitro*. HIV isolates from selected patients treated with nelfinavir alone or in combination with reverse transcriptase inhibitors were monitored for phenotypic (n=19) and genotypic (n=195, 157 of which were assessable) changes in clinical trials over a period of 2 to 82 weeks. One or more viral protease mutations at amino acid positions 30, 35, 36, 46, 71, 77 and 88 were detected in > 10 % of patients with assessable isolates. Of 19 patients for whom both phenotypic and genotypic analyses were performed on clinical isolates, 9 patients isolates showed reduced susceptibility (5- to 93-fold) to nelfinavir *in vitro*. Isolates from all 9 patients possessed one or more mutations in the viral protease gene. Amino acid position 30 appeared to be the most frequent mutation site.

The overall incidence of the D30N mutation in the viral protease of assessable isolates (n=157) from patients receiving nelfinavir monotherapy or nelfinavir in combination with zidovudine and lamivudine or stavudine was 54.8 %. The overall incidence of other mutations associated with primary PI resistance was 9.6 % for the L90M substitution where as substitutions at 48, 82 and 84 were not observed.

**Cross resistance**: HIV isolates obtained from 5 patients during nelfinavir therapy showed a 5- to 93-fold decrease in nelfinavir susceptibility *in vitro* when compared to matched baseline isolates but did not demonstrate a concordant decrease in susceptibility to indinavir, ritonavir, saquinavir or amprenavir *in vitro*. Conversely, following ritonavir therapy, 6 of 7 clinical isolates with decreased ritonavir susceptibility (8- to 113-fold) *in vitro* compared to baseline also exhibited decreased susceptibility to nelfinavir *in vitro* (5- to 40 fold). An HIV isolate obtained from a patient receiving saquinavir therapy showed decreased susceptibility to saquinavir (7- fold) but did not demonstrate a concordant decrease in susceptibility to nelfinavir. Cross-resistance between nelfinavir and reverse transcriptase inhibitors is unlikely because different enzyme targets are involved. Clinical isolates (n=5) with decreased susceptibility to zidovudine, lamivudine, or nevirapine remain fully susceptible to nelfinavir *in vitro*.

**Clinical pharmacodynamic data:** treatment with nelfinavir alone or in combination with other antiretroviral agents has been documented to reduce viral load and increase CD4 cell counts in HIV-1 seropositive patients. Decreases in HIV RNA observed with nelfinavir monotherapy were less pronounced and of shorter duration. The effects of nelfinavir (alone or combined with other antiretroviral agents) on biological markers of disease activity, CD4 cell count and viral RNA, were evaluated in several studies involving HIV-1 infected patients.

The efficacy of the BID regimen has been evaluated versus the TID regimen with VIRACEPT 250 mg tablets primarily in patients naïve to PIs. A randomised open-label study compared the HIV RNA suppression of nelfinavir 1250 mg BID versus nelfinavir 750 mg TID in PI naïve patients also receiving stavudine (30-40 mg BID) and lamivudine (150 mg BID).

| **Proportion of patients with HIV RNA below LOQ (sensitive and ultrasensitive assays) at Week 48** | | | | |
|---|---|---|---|---|
| **Assay** | **Analysis** | **Viracept BID (%)** | **Viracept TID (%)** | **95% CI** |
| Sensitive | Observed data | 135/164 (82%) | 146/169 (86%) | (-12, +4) |
| | LOCF | 145/200 (73%) | 161/206 (78%) | (-14, +3) |
| | ITT (NC = F) | 135/200 (68%) | 146/206 (71%) | (-12, +6) |
| Ultrasensitive | Observed data | 114/164 (70%) | 125/169 (74%) | (-14, +5) |
| | LOCF | 121/200 (61%) | 136/206 (66%) | (-15, +4) |

| | | | | |
|---|---|---|---|---|
| | ITT (NC = F) | 114/200 (57%) | 125/206 (61%) | (-13, +6) |

*LOCF= Last observation carried forward*
*ITT = Intention to Treat*
*NC = F: non-completers = failures*

The BID regimen produced statistically significantly higher peak nelfinavir plasma levels versus the TID regimen. Small, non-statistically significant differences were observed in other pharmacokinetic parameters with no trend favouring one regimen over the other. Although study 542 showed no statistically significant differences between the two regimens in efficacy in a predominantly antiretroviral naïve patient population, the significance of these findings for antiretroviral experienced patients is unknown.

In a study of 297 HIV-1 seropositive patients receiving zidovudine and lamivudine plus nelfinavir (2 different doses) or zidovudine and lamivudine alone, the mean baseline CD4 cell count was 288 cells/$mm^3$ and the mean baseline plasma HIV RNA was 5.21 $log_{10}$ copies/ml (160,394 copies/ml). The mean decrease in plasma HIV RNA using a PCR assay (< 400 copies/ml) at 24 weeks was 2.33 $log_{10}$ in patients receiving combination therapy with nelfinavir 750 mg TID, compared to 1.34 $log_{10}$ in patients receiving zidovudine and lamivudine alone. At 24 weeks, the percentage of patients whose plasma HIV RNA levels had decreased to below the limit of detection of the assay (< 400 copies/ml) were 81 % and 8 % for the groups treated with nelfinavir 750 mg TID plus zidovudine and lamivudine or zidovudine and lamivudine, respectively. Mean CD4 cell counts at 24 weeks were increased by 150 and 95 cells/$mm^3$ for the groups treated with nelfinavir 750 mg TID plus zidovudine and lamivudine or zidovudine and lamivudine, respectively. At 48 weeks, approximately 75 % of the patients treated with nelfinavir 750 mg TID plus zidovudine and lamivudine remained below the level of detection of the assay (< 400 copies/ml); mean increase in CD4 cell counts was 198 cells/$mm^3$ at 48 weeks in this group.

No important differences in safety or tolerability were observed between the BID and TID dosing groups, with the same proportion of patients in each arm experiencing adverse events of any intensity, irrespective of relationship to trial medication.

Plasma levels of certain HIV-1 protease inhibitors, which are metabolized predominantly by CYP3A4, can be increased by the co-administration of low-dose ritonavir, which is an inhibitor of this metabolism. Treatment paradigms for several protease inhibitors, which are subject to this interaction, require the co-administration of low-dose ritonavir ('boosting') in order to enhance plasma levels and optimize antiviral efficacy. Plasma levels of nelfinavir, which is metabolized predominantly by CYP2C19 and only partially by CYP3A4, are not greatly increased by coadministration with ritonavir, and therefore co-administration of nelfinavir with low-dose ritonavir does not appear to be beneficial. Two studies have compared the safety and efficacy of nelfinavir (unboosted) with ritonavir- boosted protease inhibitors, each in combination with other antiretroviral agents.

Study M98-863 is a randomised, double blind trial of 653 antiretroviral-naïve patients investigating lopinavir/ritonavir (400/100 mg BID n=326) compared to nelfinavir (750mg TID n=327), each in combination with lamivudine (150 mg twice daily) and stavudine (40 mg twice daily). Median baseline HIV-1 RNA was 4.98 log10 copies/ml and 5.01 log10 copies/ml in the nelfinavir and lopinavir/ritonavir treatment groups respectively. Median baseline CD4+ cell count was 232 cells/mm3 in both groups. At week 48, 63% nelfinavir and 75% lopinavir/ritonavir patients had HIV-1 RNA < 400 copies/ml, whereas 52% nelfinavir and 67% lopinavir/ritonavir patients had HIV-1 RNA <50 copies/ml (intent-to-treat, missing = failure). The mean increase from baseline in CD4+ cell count at week 48 was 195 cells/mm3 and 207 cells/mm3 in the nelfinavir and lopinavir/ritonavir groups respectively. Through 48 weeks of therapy, a statistically significantly higher proportion of patients in the lopinavir/ritonavir arm had HIV-1 RNA < 50 copies/ml compared to the nelfinavir arm.

Study APV30002 is a randomised, open-label trial of 649 antiretroviral treatment naïve patients with advanced HIV-disease, investigating fosamprenavir/ritonavir (1400mg/200mg QD n=322) compared to nelfinavir (1250mg BID n=327), each in combination with lamivudine (150 mg twice daily) and abacavir (300 mg twice daily). Median baseline HIV-1 RNA was 4.8 log10 copies/ml in both treatment groups. Median baseline CD4+ cell counts were 177 and 166 x106 cells/l for the nelfinavir

and fosamprenavir/ritonavir groups respectively. At week 48, non-inferiority was shown with 68% of patients in the group treated with nelfinavir and 69% patients treated with fosamprenavir/ritonavir having plasma HIV-1 RNA <400 copies/ml whereas 53% in the nelfinavir and 55% in the fosamprenavir/ritonavir patients had HIV-1 RNA <50 copies/ml (intent-to-treat, rebound/discontinuation = failure). The median increase from baseline in CD4+ cell count over 48 weeks was 207 cells/mm3 and 203 cells/mm3 in the nelfinavir and fosamprenavir/ritonavir groups respectively. The virological failure was greater in the nelfinavir group (17%) than in the fosamprenavir/ritonavir group (7%). Treatment emergent NRTI resistance was significantly less frequent with fosamprenavir/ritonavir compared to nelfinavir (13% versus 57%; $p<0.001$).

## 5.2 Pharmacokinetic properties

The pharmacokinetic properties of nelfinavir have been evaluated in healthy volunteers and HIV-infected patients. No substantial differences have been observed between healthy volunteers and HIV-infected patients.

**Absorption**: after single or multiple oral doses of 500 to 750 mg (two to three 250 mg tablets) with food, peak nelfinavir plasma concentrations were typically achieved in 2 to 4 hours. After multiple dosing with 750 mg every 8 hours for 28 days (steady-state), peak plasma concentrations ($C_{max}$) averaged 3-4 µg/ml and plasma concentrations prior to the next dose (trough) were 1-3 µg/ml. A greater than dose-proportional increase in nelfinavir plasma concentrations was observed after single doses; however, this was not observed after multiple dosing.

A pharmacokinetic study in HIV-positive patients compared multiple doses of 1250 mg twice daily (BID) with multiple doses of 750 mg three times daily (TID) for 28 days. Patients receiving VIRACEPT BID (n=10) achieved nelfinavir $C_{max}$ of 4.0 ± 0.8 µg/ml and morning and evening trough concentrations of 2.2 ± 1.3 µg/ml and 0.7 ± 0.4 µg/ml, respectively. Patients receiving VIRACEPT TID (n=11) achieved nelfinavir peak plasma concentrations ($C_{max}$) of 3.0 ± 1.6 µg/ml and morning and evening trough concentrations of 1.4 ± 0.6 µg/ml and 1.0 ± 0.5 µg/ml, respectively. 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 precise 8- or 12-hour intervals.

The pharmacokinetics of nelfinavir are similar during BID and TID administration. In patients, the nelfinavir $AUC_{0-24}$ with 1250 mg BID administration was 52.8 ± 15.7 µg·h/ml (n=10) and with 750 mg TID administration was 43.6 ± 17.8 µg·h/ml (n=11). Trough drug exposures remain at least twenty fold greater than the mean IC95 throughout the dosing interval for both regimens. The clinical relevance of relating *in vitro* measures to drug potency and clinical outcome has not been established. A greater than dose-proportional increase in nelfinavir plasma concentrations was observed after single doses; however, this was not observed after multiple dosing.

The absolute bioavailability of VIRACEPT has not been determined.

**Effect of food on gastrointestinal absorption**: maximum plasma concentrations and area under the plasma concentration-time curve were consistently 2 to 3-fold higher under fed conditions compared to fasting. The increased plasma concentrations with food were independent of fat content of the meals. The effect of meal content on nelfinavir exposure was investigated in a study using the 250 mg film-coated tablets formulation. Steady state nelfinavir AUC and $C_{max}$ were respectively 15 % and 20 % higher when doses followed a 800 kcal/50 % fat meal compared to those following a light meal (350 kcal/33 % fat), suggesting that meal content has less effect on nelfinavir exposures during multiple dosing than would be anticipated based on data from single dose studies.

**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 were lower than in other tissues, but exceeded the *in vitro* $EC_{95}$ for antiviral activity. Nelfinavir in serum is extensively protein-bound (≥ 98 %).

**Metabolism:** unchanged nelfinavir comprised 82-86 % of the total plasma radioactivity after a single oral 750 mg dose of $^{14}$C-nelfinavir. *In vitro*, multiple cytochrome P-450 isoforms including CYP3A, CYP2C19/C9 and CYP2D6 are responsible for metabolism of nelfinavir. One major and several minor oxidative metabolites were found in plasma.

The major oxidative metabolite, M8 (*tert-butyl* hydroxy nelfinavir), has *in vitro* antiviral activity equal to the parent drug and its formation is catalysed by the polymorphic cytochrome CYP2C19. The further degradation of M8 appears to be catalysed by CYP3A4. In subjects with normal CYP2C19 activity, plasma levels of this metabolite are approximately 25 % of the total plasma nelfinavir-related concentration. It is expected that in CYP2C19 poor metabolisers or in patients receiving concomitantly strong CYP2C19 inhibitors (see section 4.5), nelfinavir plasma levels would be elevated whereas levels of *tert-butyl* hydroxy nelfinavir would be negligible or non-measurable. Limited clinical data suggest that patients with very low or non-measurable plasma concentrations of the metabolite and elevated concentrations of nelfinavir do not show a reduced virological response or a different safety profile when compared with the whole study population.

**Elimination:** oral clearance estimates after single doses (24-33 l/h) and multiple doses (26-61 l/h) indicate that nelfinavir exhibits medium to high hepatic bioavailability. The terminal half-life in plasma was typically 3.5 to 5 hours. The majority (87 %) of an oral 750 mg dose containing $^{14}$C-nelfinavir was recovered in the faeces; total faecal radioactivity consisted of nelfinavir (22 %) and numerous oxidative metabolites (78 %). Only 1-2 % of the dose was recovered in urine, of which unchanged nelfinavir was the major component.

**Pharmacokinetics in special clinical situations:**

***Pharmacokinetics in children and the elderly:*** in children between the ages of 2 and 13 years, the clearance of orally administered nelfinavir is approximately 2 to 3 times higher than in adults, with large intersubject variability. Administration of VIRACEPT oral powder or film-coated tablets with food at a dose of approximately 25-30 mg/kg TID achieves steady-state plasma concentrations similar to adult patients receiving 750 mg TID.

In an open prospective study, the pharmacokinetics of BID and TID VIRACEPT regimens in 18 HIV infected children aged 2-14 years were investigated. Children weighing less than 25 kg received 30-37 mg/kg nelfinavir TID or 45-55 mg/kg nelfinavir BID. Children over 25 kg received 750 mg TID or 1250 mg BID.

The $C_{min}$, $C_{max}$ and $AUC_{0-24}$ were all significantly higher with the BID regimen compared with the TID regimen. In addition, in twice daily application, 14 out of 18 (78 %) and 11 out of 18 (61 %) reached $C_{min}$ values of 1-3 µg/ml and $C_{max}$ values of 3-4 µg/ml, whereas in TID application only 4 out of 18 (22 %) and 7 out of 18 (39 %) reached these values.

There are no data available in the elderly.

***Pharmacokinetics in patients with liver impairment:***

Pharmacokinetics of nelfinavir after a single dose of 750 mg 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 with impairment (Child-Turcotte Classes A to C) compared to the healthy group. Specific dose recommendations for nelfinavir cannot be made based on the results of this study.

## 5.3 Preclinical safety data

During *in vitro* studies, cloned human cardiac potassium channels (hERG) were inhibited by high concentrations of nelfinavir and its active metabolite M8. hERG potassium channels were inhibited by 20 % at nelfinavir and M8 concentrations that are about four- to five-fold and seventy-fold, respectively, above the average free therapeutic levels in humans. By contrast, no effects suggesting prolongation of the QT-interval of the ECG were observed at similar doses in dogs or in isolated cardiac tissue. The clinical relevance of these *in vitro* data is unknown. However, based on data from

products known to prolong the QT-interval, a block of hERG potassium channels of > 20 % may be clinically relevant. Therefore the potential for QT prolongation should be considered in cases of overdose (see section 4.9).

**Acute and chronic toxicity:** oral acute and chronic toxicity studies were conducted in the mouse (500 mg/kg/day), rat (up to 1,000 mg/kg/day) and monkey (up to 800 mg/kg/day). There were increased liver weights and dose-related thyroid follicular cell hypertrophy in rats. Weight loss and general physical decline was observed in monkeys together with general evidence of gastrointestinal toxicity.

**Mutagenicity**: *in vitro* and *in vivo* studies with and without metabolic activation have shown that nelfinavir has no mutagenic or genotoxic activity.

**Carcinogenicity:** Two year oral carcinogenicity studies with nelfinavir mesilate were conducted in mice and rats. In mice, administration of up to 1000 mg/kg/day did not result in any evidence for an oncogenic effect. In rats administration of 1000 mg/kg/day resulted in increased incidences of thyroid follicular cell adenoma and carcinoma, relative to those for controls. Systemic exposures were 3 to 4 times those for humans given therapeutic doses. Administration of 300 mg/kg/day resulted in an increased incidence of thyroid follicular cell adenoma. Chronic nelfinavir treatment of rats has been demonstrated to produce effects consistent with enzyme induction, which predisposed rats, but not humans, to thyroid neoplasms. The weight of evidence indicates that nelfinavir is unlikely to be a carcinogen in humans.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Each tablet contains the following excipients:

*Tablet core:*
Calcium silicate,
Crospovidone,
Magnesium stearate,
Indigo carmine (E132) as powder.

*Tablet coat:*
Hypromellose,
Glycerol triacetate.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf-life

3 years.

### 6.4 Special precautions for storage

Store in the original container. Do not store above 30°C.

### 6.5 Nature and contents of container

VIRACEPT film-coated tablets are provided in HDPE plastic bottles containing either 270 or 300 tablets, fitted with HDPE child resistant closures with polyethylene liners. Not all pack sizes may be marketed.

### 6.6 Instructions for use, handling and disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/054/004 - EU/1/97/054/005

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

5.3.2001 – 19.7.2001 / 3.2.2003

## 10. DATE OF REVISION OF THE TEXT

# ANNEX II

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OF THE MARKETING AUTHORISATION**

## A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

F. Hoffmann-La Roche Ltd.
Grenzacherstr. 124
CH-4070 Basel
Switzerland

Name and address of the manufacturer responsible for batch release

VIRACEPT 50 mg/g oral powder, VIRACEPT 250 mg tablets :

Hoffmann-La Roche AG
Emil-Barell-Strasse 1
D-79639 Grenzach-Wyhlen
Germany

VIRACEPT 250 mg film-coated tablets:

Roche Farma S.A.
C/Severo Ochoa 13
Polígono Ind. de Leganés
E-28914 Leganés
Spain.

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2.)

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING**

**Outer carton text/Bottle label text**

## 1. NAME OF THE MEDICINAL PRODUCT

Viracept 50 mg/g oral powder
Nelfinavir

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gram of oral powder contains 58.45 mg of nelfinavir mesilate, equivalent to 50 mg of nelfinavir as free base.

## 3. LIST OF EXCIPIENTS

Also contains sweetener aspartame (E951), natural and artificial flavourings and other constituents.

## 4. PHARMACEUTICAL FORM AND CONTENTS

144 g Oral powder

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not reconstitute in the bottle

Refer to the package leaflet before use

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

Store in the original container

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/054/001

## 13. MANUFACTURER'S BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING**

**Outer carton text/Bottle label text**

## 1. NAME OF THE MEDICINAL PRODUCT

Viracept 250 mg tablets
Nelfinavir

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 292.25 mg of nelfinavir mesilate, equivalent to 250 mg nelfinavir as free base.

## 3. LIST OF EXCIPIENTS

Also contains colourant indigocarmine (E132) and other constituents.

## 4. PHARMACEUTICAL FORM AND CONTENTS

270 tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Refer to the package leaflet before use

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

Store in the original container

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

## 12. MARKETING AUTHORISATION

EU/1/97/054/003

## 13. MANUFACTURER'S BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING**

**Outer carton text/Bottle label text**

## 1. NAME OF THE MEDICINAL PRODUCT

Viracept 250 mg film-coated tablets
Nelfinavir

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 292.25 mg of nelfinavir mesilate, equivalent to 250 mg nelfinavir as free base.

## 3. LIST OF EXCIPIENTS

Also contains colourant indigocarmine (E132) and other constituents.

## 4. PHARMACEUTICAL FORM AND CONTENTS

270 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Refer to the package leaflet before use

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

Store in the original container

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/01/097/054/004

## 13. MANUFACTURER'S BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING**

**Outer carton text/Bottle label text**

## 1. NAME OF THE MEDICINAL PRODUCT

Viracept 250 mg film-coated tablets
Nelfinavir

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 292.25 mg of nelfinavir mesilate, equivalent to 250 mg nelfinavir as free base.

## 3. LIST OF EXCIPIENTS

Also contains colourant indigocarmine (E132) and other constituents.

## 4. PHARMACEUTICAL FORM AND CONTENTS

300 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Refer to the package leaflet before use

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

Store in the original container

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/054/005

## 13. MANUFACTURER'S BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

# B. PACKAGE LEAFLET

# PACKAGE LEAFLET

**Read all of this leaflet carefully before you start taking this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

**In this leaflet**:

1. What VIRACEPT is and what it is used for
2. Before you take VIRACEPT
3. How to take VIRACEPT
4. Possible side effects
5. Storing VIRACEPT
6. Further information


VIRACEPT 50 mg/g oral powder
Nelfinavir

The active substance is nelfinavir. VIRACEPT 50 mg/g oral powder contains 58.45 mg of nelfinavir mesilate corresponding to 50 mg of nelfinavir (as free base) per gram of powder.

The other ingredients are microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hydroxypropyl methylcellulose, aspartame (E951), sucrose palmitate, and natural and artificial flavour.

**Marketing Authorisation Holder:**
Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

**Manufacturer:**
Hoffmann-La Roche AG
Emil-Barell-Str. 1
D-79639 Grenzach-Wyhlen
Germany

## 1. WHAT VIRACEPT IS AND WHAT IT IS USED FOR

50 mg/g oral powder.

VIRACEPT 50 mg/g oral powder is provided in plastic bottles containing 144 g of oral powder with a 1 gram (white) and a 5 gram (blue) plastic scoop.

VIRACEPT is an antiviral agent. It is a member of a class of medicinal products called protease inhibitors. 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 that contains HIV particles or by sexual contact with an infected individual.

VIRACEPT should be taken in combination with other medicines that are active against HIV. These medicines, including VIRACEPT, are called antiretroviral agents. These combinations have been shown to reduce the number of HIV particles in the blood and to increase circulating CD4 cells (the type of white blood cell that is particularly reduced in numbers by HIV, leading to an increased risk of many types of infections).

## 2. BEFORE YOU TAKE VIRACEPT

**Do not take VIRACEPT:**
- if you are allergic to nelfinavir or to any of the other ingredients.
- if you take a medicine that contains any of the following: terfenadine, astemizole, cisapride, amiodarone, quinidine, pimozide, triazolam, midazolam, ergot derivatives (sometimes used to treat migraine), rifampicin, or herbal preparations containing St. John's wort *(Hypericum perforatum)*.

**Take special care with VIRACEPT:**
VIRACEPT 50 mg/g oral powder contains aspartame as a sweetening agent. Aspartame provides a source of phenylalanine and, therefore, may not be suitable for persons with phenylketonuria.

You should know that VIRACEPT is not a cure for HIV infection and that you may continue to develop infections or other illnesses associated with HIV disease. 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.

Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

Consult your doctor if you have diabetes because an increase in severity of existing diabetes has been rarely reported in patients receiving protease inhibitors (see also section 4 of this leaflet).

Consult your doctor if you have haemophilia because there have been rare reports of increased bleeding while taking this treatment or another protease inhibitor (see also section 4 of this leaflet).

**Children:**
The safety and activity of VIRACEPT in children below the age of 3 years is not yet known.

**Patients with kidney disease:**
There are not sufficient data available on patients with this condition taking VIRACEPT. Consult your doctor if you have kidney disease.

**Patients with liver disease:**
Please speak with your doctor if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require blood tests for control of liver function.

**Taking VIRACEPT with food and drink:**

To obtain the full benefit of VIRACEPT, the powder form of VIRACEPT must be taken by mouth, with a meal.

VIRACEPT 50 mg/g oral powder may be mixed with water, milk, formula, soy formula, soy milk, dietary supplements, or pudding. It is recommended that VIRACEPT 50 mg/g oral powder mixed in these media be used within 6 hours. VIRACEPT 50 mg/g oral powder should not be mixed with orange juice, apple juice, apple sauce or other liquids or foods that are acidic due to taste. Do not add water to bottles of VIRACEPT 50 mg/g oral powder.

**Pregnancy:**
It is not known whether VIRACEPT is harmful to an unborn baby when taken by a pregnant woman. If you are pregnant, you should take VIRACEPT only if your doctor decides it is clearly needed. Inform your doctor if you are pregnant or intend to become pregnant.

**Breast-feeding:**
You should not breast-feed while taking VIRACEPT. It is recommended that HIV-infected women should not breast-feed their infants to avoid transmission of HIV. Inform your doctor if you are breast-feeding or intend to breast-feed. Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines:**
VIRACEPT has no or very little effect on the ability to drive and use machines.

**Taking other medicines:**
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Patients taking VIRACEPT must not take products containing St. John's wort (*Hypericum perforatum)* as this may result in the loss of therapeutic effect and development of resistance. Other drugs that *cannot be taken* with VIRACEPT include rifampicin (used for treating bacterial infections), terfenadine or astemizole (commonly used to treat allergy symptoms), cisapride (for heart burn or problems with the digestive system), amiodarone or quinidine (used to treat an irregular heart beat), triazolam or midazolam (used to relieve anxiety and/or trouble with sleeping), ergot derivatives (used to treat migraine), and pimozide (for psychiatric problems).

VIRACEPT *can be taken* with most medicines that are commonly used in HIV infection but special care is needed with some of these and also with some other medicines. This is because the actions of VIRACEPT or the other medicines can be affected if they are taken together.

Consult your doctor if you are taking the following medicines. In some cases, their use with VIRACEPT is not usually recommended. In other cases increased monitoring and/or a change in the dose of these medicines or of VIRACEPT may be needed:
ritonavir, indinavir, saquinavir and delavirdine (used in the treatment of HIV infection),
rifabutin (used for treating bacterial infections),
birth control pills (may not prevent pregnancy when given with VIRACEPT so other birth control methods should be used),
calcium channel blockers including bepridil (for the treatment of heart conditions),
immunosuppressants including tacrolimus and ciclosporin,
sildenafil (for male impotence),
statins (used to lower lipid levels in the blood),
phenobarbital, phenytoin or carbamazepine (used in the treatment of epilepsy),
methadone (used in the treatment of opiate dependence).

Clinically important drug interactions would not be expected with the following medicines but the possibility cannot be excluded: amprenavir, efavirenz and nevirapine (used in the treatment of HIV infection); ketoconazole, itraconazole and fluconazole (used for treating fungal infections); erythromycin and clarithromycin (used for treating bacterial infections); fluoxetine, paroxetine, imipramine and amitriptyline (used in the treatment of depression), omeprazole and lansoprazole (used

in the treatment of gastrointestinal ulcers), diazepam (used to relieve anxiety and/or trouble with sleeping).

## 3. HOW TO TAKE VIRACEPT

Always take VIRACEPT exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. The usual doses are described below. Please observe these instructions for use, otherwise you will not fully benefit from VIRACEPT.

There are two scoops provided in the box, a white 1 gram scoop and a blue 5 gram scoop. You should measure out a level scoop of powder by using the handle of the second scoop to scrape off the extra powder (see picture below).

For those patients who are unable to take tablets:

**For adults and children older than 13 years**, the recommended dose of VIRACEPT 50 mg/g oral powder can be taken **either** twice a day (BID) **or** three times a day (TID) with the following dosage:

| **Dose to be taken by adults and children older than 13 years** | | | | | |
|---|---|---|---|---|---|
| **Dosage regimen** | **Blue Scoop** 5 gram | | **White Scoop** 1 gram | | **Total grams of Powder per dose** |
| Twice daily **or** | 5 | plus | 0 | | 25 |
| Three times daily | 3 | plus | 0 | | 15 |

**For children, aged 3 to 13 years**, the recommended dose of VIRACEPT oral powder is **either** 50-55 mg /kg if given twice daily (BID) **or** 25-30 mg per kg of body weight if given three times daily (TID).

The following table shows the dose that should be given to **children, if giving VIRACEPT twice daily (BID).**

| **Dose to be given two times a day to children aged 3 to 13** | | | | | |
|---|---|---|---|---|---|
| **Body Weight of the patient** | **Blue Scoop** 5 gram | | **White Scoop** 1 gram | | **Total grams of Powder per dose** |
| 7.5 to 8.5 kg | 1 | plus | 3 | | 8 g |
| 8.5 to 10.5 kg | 2 | | - | | 10 g |
| 10.5 to 12 kg | 2 | plus | 2 | | 12 g |
| 12 to 14 kg | 2 | plus | 4 | | 14 g |
| 14 to 16 kg | 3 | plus | 1 | | 16 g |
| 16 to 18 kg | 3 | plus | 3 | | 18 g |
| 18 to 22 kg | 4 | plus | 1 | | 21 g |

| | | | |
|---|---|---|---|
| over 22 kg | 5 | - | 25 g |

The following table shows the dose that should be given to **children, if giving VIRACEPT three times daily (TID).**

| **Dose to be administered three times a day to children aged 3 to 13** | | | | |
|---|---|---|---|---|
| **Body Weight of the patient** | **Blue Scoop** 5 gram | | **White Scoop** 1 gram | **Total grams of Powder per dose** |
| 7.5 to 8.5 kg | - | | 4 | 4 g |
| 8.5 to 10.5 kg | 1 | | - | 5 g |
| 10.5 to 12 kg | 1 | plus | 1 | 6 g |
| 12 to 14 kg | 1 | plus | 2 | 7 g |
| 14 to 16 kg | 1 | plus | 3 | 8 g |
| 16 to 18 kg | 1 | plus | 4 | 9 g |
| 18 to 23 kg | 2 | plus | - | 10 g |
| over 23 kg | 3 | | - | 15 g |

The powder form of VIRACEPT must be taken by mouth with a meal.

VIRACEPT 50 mg/g oral powder may be mixed with water, milk, formula, soy formula, soy milk, dietary supplements, or pudding. It is recommended that VIRACEPT 50 mg/g oral powder mixed in these media be used within 6 hours. VIRACEPT 50 mg/g oral powder should not be mixed with orange juice, apple juice, apple sauce or other liquids or foods that are acidic due to taste. Do not add water to bottles of VIRACEPT 50 mg/g oral powder.

VIRACEPT 250 mg tablets are generally recommended for adults and older children. For younger children able to take tablets, VIRACEPT tablets may be administered instead of the oral powder. See Package Leaflet for VIRACEPT tablets.

**If you take more VIRACEPT than you should:**
If you realise you have taken more VIRACEPT than you should have, contact your doctor right away. If you cannot reach your doctor, go to the nearest emergency room and take your VIRACEPT powder with you. Among other symptoms, very large doses of VIRACEPT might cause disturbances in the heart rhythm.

**If you forget to take VIRACEPT:**
Take the next dose as soon as you remember and then carry on as before. Do not take a double dose to make up for forgotten individual doses.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, VIRACEPT can have side effects.

In clinical trials with VIRACEPT 250 mg tablets, either taken as 1250 mg two times daily or 750 mg three times daily, the most frequently reported side effect (in more than one in ten patients) was diarrhoea. The commonest moderate or severe side effects (in approximately one in four to one in fifty patients) were:
- diarrhoea,
- wind,
- feeling sick,
- rash,
- low numbers of a particular type of white blood cell that fights infections (neutrophils),

- abnormal results from blood tests that measure how the liver is working and
- abnormal results from a blood test that measures how muscle tissue is working.

Other side effects that have been experienced with VIRACEPT are described below.

***Uncommon (in more than one in a thousand but less than one in a hundred persons):***
Allergic reactions including difficulty in breathing, fever, itching, swelling of the face and skin rashes that can sometimes form blisters,
being sick,
inflammation of the pancreas. Sometimes there are no symptoms of this and the problem appears only in blood tests.

***Rare (in more than one in ten thousand but less than one in a thousand persons):***
Inflammation of the liver, sometimes with jaundice (yellowing of the skin and eyes),
swelling of the belly.
New onset diabetes mellitus, high blood sugar or an increase in severity of existing diabetes mellitus has been rarely reported in patients receiving protease inhibitors. In some of these the high blood sugar was severe and in some cases also associated with ketoacidosis (change in metabolite levels in the blood). Many of these patients had additional medical conditions, some of which required therapy with agents that have been associated with the development of diabetes or high blood sugar.

In patients with haemophilia type A and B (patients who have blood clotting problems), there have been rare reports of increased bleeding while taking this treatment or another protease inhibitor. Should this happen to you, seek immediate advice from your doctor.

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (’buffalo hump’). The cause and long-term health effects of these conditions are not known at this time. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin.

There have been rare reports of muscle pain, tenderness or weakness, particularly with combination antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions these muscle problems have been serious causing muscle degeneration (rhabdomyolysis).

If you experience any side effects that are not in this leaflet, please tell your doctor or pharmacist. Also, tell your doctor if you have any severe or unusual symptoms or if any side effect that you think you may have gets worse or persists.

## 5. STORING VIRACEPT

Keep out of the reach and sight of children.

Do not store above 30°C.

Store in the original container.

Do not use after the expiry date stated on the label and carton.

**If you have any further questions please consult your doctor or pharmacist.**

## 6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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**This leaflet was last approved on {date}**

**PACKAGE LEAFLET**

**Read all of this leaflet carefully before you start taking this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

**In this leaflet**:

1. What VIRACEPT is and what it is used for
2. Before you take VIRACEPT
3. How to take VIRACEPT
4. Possible side effects
5. Storing VIRACEPT
6. Further information


VIRACEPT 250 mg tablets
Nelfinavir

The active substance is nelfinavir. VIRACEPT 250 mg tablets contain 292.25 mg of nelfinavir mesilate corresponding to 250 mg of nelfinavir (as free base).

The other ingredients are calcium silicate, crospovidone, magnesium stearate, indigo carmine (E132), as powder.

**Marketing Authorisation Holder:**
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6 Falcon Way
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Welwyn Garden City
AL7 1TW
United Kingdom

**Manufacturer:**
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Emil-Barell-Str. 1
D-79639 Grenzach-Wyhlen
Germany

## 1. WHAT VIRACEPT IS AND WHAT IT IS USED FOR

250 mg tablets.

VIRACEPT 250 mg tablets are provided in plastic bottles containing 270 tablets.

VIRACEPT is an antiviral agent. It is a member of a class of medicinal products called protease inhibitors. 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 that contains HIV particles or by sexual contact with an infected individual.

VIRACEPT should be taken in combination with other medicines that are active against HIV. These medicines, including VIRACEPT, are called antiretroviral agents. These combinations have been shown to reduce the number of HIV particles in the blood and to increase circulating CD4 cells (the type of white blood cell that is particularly reduced in numbers by HIV, leading to an increased risk of many types of infections).

## 2. BEFORE YOU TAKE VIRACEPT

**Do not take VIRACEPT:**
- if you are allergic to nelfinavir or to any of the other ingredients.
- if you take a medicine that contains any of the following: terfenadine, astemizole, cisapride, amiodarone, quinidine, pimozide, triazolam, midazolam, ergot derivatives (sometimes used to treat migraine), rifampicin, or herbal preparations containing St. John's wort *(Hypericum perforatum)*.

**Take special care with VIRACEPT:**
You should know that VIRACEPT is not a cure for HIV infection and that you may continue to develop infections or other illnesses associated with HIV disease. 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.

Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

Consult your doctor if you have diabetes because an increase in severity of existing diabetes has been rarely reported in patients receiving protease inhibitors (see also section 4 of this leaflet).

Consult your doctor if you have haemophilia because there have been rare reports of increased bleeding while taking this treatment or another protease inhibitor (see also section 4 of this leaflet).

**Children:**
The safety and activity of VIRACEPT in children below the age of 3 years is not yet known.

**Patients with kidney disease:**
There are not sufficient data available on patients with this condition taking VIRACEPT. Consult your doctor if you have kidney disease.

**Patients with liver disease:**
Please speak with your doctor if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require blood tests for control of liver function.

**Taking VIRACEPT with food and drink:**
To obtain the full benefit of VIRACEPT, the tablets should be taken with a meal.

**Pregnancy:**

It is not known whether VIRACEPT is harmful to an unborn baby when taken by a pregnant woman. If you are pregnant, you should take VIRACEPT only if your doctor decides it is clearly needed. Inform your doctor if you are pregnant or intend to become pregnant.

**Breast-feeding:**
You should not breast-feed while taking VIRACEPT. It is recommended that HIV-infected women should not breast-feed their infants to avoid transmission of HIV. Inform your doctor if you are breast-feeding or intend to breast-feed. Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines:**
VIRACEPT has no or very little effect on the ability to drive and use machines.

**Taking other medicines:**
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Patients taking VIRACEPT must not take products containing St. John's wort (*Hypericum perforatum)* as this may result in the loss of therapeutic effect and development of resistance. Other drugs that *cannot be taken* with VIRACEPT include rifampicin (used for treating bacterial infections), terfenadine or astemizole (commonly used to treat allergy symptoms), cisapride (for heart burn or problems with the digestive system), amiodarone or quinidine (used to treat an irregular heart beat), triazolam or midazolam (used to relieve anxiety and/or trouble with sleeping), ergot derivatives (used to treat migraine), and pimozide (for psychiatric problems).

VIRACEPT *can be taken* with most medicines that are commonly used in HIV infection but special care is needed with some of these and also with some other medicines. This is because the actions of VIRACEPT or the other medicines can be affected if they are taken together.

Consult your doctor if you are taking the following medicines. In some cases, their use with VIRACEPT is not usually recommended. In other cases increased monitoring and/or a change in the dose of these medicines or of VIRACEPT may be needed: ritonavir, indinavir, saquinavir and delavirdine (used in the treatment of HIV infection),
rifabutin (used for treating bacterial infections),
birth control pills (may not prevent pregnancy when given with VIRACEPT so other birth control methods should be used),
calcium channel blockers including bepridil (for the treatment of heart conditions),
immunosuppressants including tacrolimus and ciclosporin,
sildenafil (for male impotence),
statins (used to lower lipid levels in the blood),
phenobarbital, phenytoin or carbamazepine (used in the treatment of epilepsy),
methadone (used in the treatment of opiate dependence).

Clinically important drug interactions would not be expected with the following medicines but the possibility cannot be excluded: amprenavir, efavirenz and nevirapine (used in the treatment of HIV infection); ketoconazole, itraconazole and fluconazole (used for treating fungal infections); erythromycin and clarithromycin (used for treating bacterial infections); fluoxetine, paroxetine, imipramine and amitriptyline (used in the treatment of depression), omeprazole and lansoprazole (used in the treatment of gastrointestinal ulcers), diazepam (used to relieve anxiety and/or trouble with sleeping).

## 3. HOW TO TAKE VIRACEPT

Always take VIRACEPT exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. The usual doses are described below. Please observe these instructions for use, otherwise you will not fully benefit from VIRACEPT.

The tablet form of VIRACEPT must be taken by mouth. VIRACEPT tablets should be swallowed whole and should be taken with a meal.

**For adults and children older than 13 years**, the recommended dose of VIRACEPT 250 mg tablets is 1250 mg given as five 250 mg tablets twice daily (BID) or 750 mg given as three 250 mg tablets three times daily (TID).

**For children, aged 3 to 13 years**, the recommended dose is **either** 50-55 mg/kg body weight if VIRACEPT is taken twice daily (BID) **or** 25-30 mg per kg of body weight if VIRACEPT is taken three times daily (TID) as follows:

**If you are receiving VIRACEPT tablets twice a day**

| Body Weight (kg) | Number of tablets twice daily* |
|---|---|
| 18 to < 22 | 4 |
| ≥ 22 | 5 |

**If you are receiving VIRACEPT tablets three times a day**

| Body Weight (kg) | Number of tablets three times daily* |
|---|---|
| 18 to < 23 | 2 |
| ≥ 23 | 3 |

*see Package Leaflet for VIRACEPT oral powder for patients less than 18 kg body weight.

For adults or children unable to take tablets, VIRACEPT 50 mg/g oral powder may be administered (see Package Leaflet for VIRACEPT 50 mg/g oral powder).

**If you take more VIRACEPT than you should:**
If you realise you have taken more VIRACEPT than you should have, contact your doctor right away. If you cannot reach your doctor, go to the nearest emergency room and take your VIRACEPT tablets with you. Among other symptoms, very large doses of VIRACEPT might cause disturbances in the heart rhythm.

**If you forget to take VIRACEPT:**
Take the next dose as soon as you remember and then carry on as before. Do not take a double dose to make up for forgotten individual doses.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, VIRACEPT can have side effects.

In clinical trials with VIRACEPT 250 mg tablets, either taken as 1250 mg two times daily or 750 mg three times daily, the most frequently reported side effect (in more than one in ten patients) was diarrhoea
The commonest moderate or severe side effects (in approximately one in four to one in fifty patients) were:
- diarrhoea,
- wind,
- feeling sick,
- rash,
- low numbers of a particular type of white blood cell that fights infections (neutrophils),
- abnormal results from blood tests that measure how the liver is working and
- abnormal results from a blood test that measures how muscle tissue is working.

Other side effects that have been experienced with VIRACEPT are described below.

***Uncommon (in more than one in a thousand but less than one in a hundred persons):***

Allergic reactions including difficulty in breathing, fever, itching, swelling of the face and skin rashes that can sometimes form blisters,
being sick,
inflammation of the pancreas. Sometimes there are no symptoms of this and the problem appears only in blood tests.

***Rare (in more than one in ten thousand but less than one in a thousand persons):***
Inflammation of the liver, sometimes with jaundice (yellowing of the skin and eyes),
swelling of the belly.
New onset diabetes mellitus, high blood sugar or an increase in severity of existing diabetes mellitus has been rarely reported in patients receiving protease inhibitors. In some of these the high blood sugar was severe and in some cases also associated with ketoacidosis (change in metabolite levels in the blood). Many of these patients had additional medical conditions, some of which required therapy with agents that have been associated with the development of diabetes or high blood sugar.

In patients with haemophilia type A and B (patients who have blood clotting problems), there have been rare reports of increased bleeding while taking this treatment or another protease inhibitor. Should this happen to you, seek immediate advice from your doctor.

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (’buffalo hump’). The cause and long-term health effects of these conditions are not known at this time. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin.

There have been rare reports of muscle pain, tenderness or weakness, particularly with combination antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions these muscle problems have been serious causing muscle degeneration (rhabdomyolysis).

If you experience any side effects that are not in this leaflet, please tell your doctor or pharmacist. Also, tell your doctor if you have any severe or unusual symptoms or if any side effect that you think you may have gets worse or persists.

## 5. STORING VIRACEPT

Keep out of the reach and sight of children.

Do not store above 30°C.

Store in the original container.

Do not use after the expiry date stated on the label and carton.

**If you have any further questions please consult your doctor or pharmacist.**

## 6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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**This leaflet was last approved on {date}**

**PACKAGE LEAFLET**

**Read all of this leaflet carefully before you start taking this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

**In this leaflet**:

1. What VIRACEPT is and what it is used for
2. Before you take VIRACEPT
3. How to take VIRACEPT
4. Possible side effects
5. Storing VIRACEPT
6. Further information


VIRACEPT 250 mg film-coated tablets
Nelfinavir

The active substance is nelfinavir. VIRACEPT 250 mg film-coated tablets contain 292.25 mg of nelfinavir mesilate corresponding to 250 mg of nelfinavir (as free base).

The other ingredients are calcium silicate, crospovidone, magnesium stearate, indigo carmine (E132), as powder, hypromellose and glycerol triacetate.

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**Manufacturer:**
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Spain.

## 1. WHAT VIRACEPT IS AND WHAT IT IS USED FOR

VIRACEPT 250 mg film-coated tablets are provided in plastic bottles containing 270 or 300 film-coated tablets. Both pack sizes may not be available.

VIRACEPT is an antiviral agent. It is a member of a class of medicinal products called protease inhibitors. 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 that contains HIV particles or sexual contact with an infected individual.

VIRACEPT should be taken in combination with other medicines that are active against HIV. These medicines, including VIRACEPT, are called antiretroviral agents. These combinations have been shown to reduce the number of HIV particles in the blood and to increase circulating CD4 cells (the type of white blood cell that is particularly reduced in numbers by HIV, leading to an increased risk of many types of infections).

## 2. BEFORE YOU TAKE VIRACEPT

**Do not take VIRACEPT:**
- if you are allergic to nelfinavir or to any of the other ingredients.
- if you take a medicine that contains any of the following: terfenadine, astemizole, cisapride, amiodarone, quinidine, pimozide, triazolam, midazolam, ergot derivatives (sometimes used to treat migraine), rifampicin, or herbal preparations containing St. John's wort *(Hypericum perforatum)*.

**Take special care with VIRACEPT:**
You should know that VIRACEPT is not a cure for HIV infection and that you may continue to develop infections or other illnesses associated with HIV disease. 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.

Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

Consult your doctor if you have diabetes because an increase in severity of existing diabetes has been rarely reported in patients receiving protease inhibitors (see also section 4 of this leaflet).

Consult your doctor if you have haemophilia because there have been rare reports of increased bleeding while taking this treatment or another protease inhibitor (see also section 4 of this leaflet).

**Children:**
The safety and activity of VIRACEPT in children below the age of 3 years is not yet known.

**Patients with kidney disease:**
There are not sufficient data available on patients with this condition taking VIRACEPT. Consult your doctor if you have kidney disease.

**Patients with liver disease:**
Please speak with your doctor if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require blood tests for control of liver function.

**Taking VIRACEPT with food and drink:**
To obtain the full benefit of VIRACEPT, the VIRACEPT film-coated tablets should be taken with a meal.

**Pregnancy:**

It is not known whether VIRACEPT is harmful to an unborn baby when taken by a pregnant woman. If you are pregnant, you should take VIRACEPT only if your doctor decides it is clearly needed. Inform your doctor if you are pregnant or intend to become pregnant.

**Breast-feeding:**
You should not breast-feed while taking VIRACEPT. It is recommended that HIV-infected women should not breast-feed their infants to avoid transmission of HIV. Inform your doctor if you are breast-feeding or intend to breast-feed. Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines:**
VIRACEPT has no or very little effect on the ability to drive and use machines.

**Taking other medicines:**
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Patients taking VIRACEPT must not take products containing St. John's wort (*Hypericum perforatum)* as this may result in the loss of therapeutic effect and development of resistance. Other drugs that *cannot be taken* with VIRACEPT include rifampicin (used for treating bacterial infections), terfenadine or astemizole (commonly used to treat allergy symptoms), cisapride (for heart burn or problems with the digestive system), amiodarone or quinidine (used to treat an irregular heart beat), triazolam or midazolam (used to relieve anxiety and/or trouble with sleeping), ergot derivatives (used to treat migraine), and pimozide (for psychiatric problems).

VIRACEPT *can be taken* with most medicines that are commonly used in HIV infection but special care is needed with some of these and also with some other medicines. This is because the actions of VIRACEPT or the other medicines can be affected if they are taken together.

Consult your doctor if you are taking the following medicines. In some cases, their use with VIRACEPT is not usually recommended. In other cases increased monitoring and/or a change in the dose of these medicines or of VIRACEPT may be needed: ritonavir, indinavir, saquinavir and delavirdine (used in the treatment of HIV infection),
rifabutin (used for treating bacterial infections),
birth control pills (may not prevent pregnancy when given with VIRACEPT so other birth control methods should be used),
calcium channel blockers including bepridil (for the treatment of heart conditions),
immunosuppressants including tacrolimus and ciclosporin; sildenafil (for male impotence),
statins (used to lower lipid levels in the blood),
phenobarbital, phenytoin or carbamazepine (used in the treatment of epilepsy),
methadone (used in the treatment of opiate dependence).

Clinically important drug interactions would not be expected with the following medicines but the possibility cannot be excluded: amprenavir, efavirenz and nevirapine (used in the treatment of HIV infection); ketoconazole, itraconazole and fluconazole (used for treating fungal infections); erythromycin and clarithromycin (used for treating bacterial infections); fluoxetine, paroxetine, imipramine and amitriptyline (used in the treatment of depression), omeprazole and lansoprazole (used in the treatment of gastrointestinal ulcers), diazepam (used to relieve anxiety and/or trouble with sleeping).

## 3. HOW TO TAKE VIRACEPT

Always take VIRACEPT exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. The usual doses are described below. Please observe these instructions for use, otherwise you will not fully benefit from VIRACEPT.

The tablet form of VIRACEPT must be taken by mouth. VIRACEPT film-coated tablets should be swallowed whole and should be taken with a meal.

**For adults and children older than 13 years**, the recommended dose of VIRACEPT 250 mg film-coated tablets is 1250 mg given as five 250 mg tablets twice daily (BID) or 750 mg given as three 250 mg tablets three times daily (TID).

**For children, aged 3 to 13 years**, the recommended dose is **either** 50-55 mg/kg body weight if VIRACEPT is taken twice daily (BID) **or** 25-30 mg per kg of body weight if VIRACEPT is taken three times daily (TID) as follows:

**If you are receiving VIRACEPT film-coated tablets twice a day**

| Body Weight (kg) | Number of film-coated tablets twice daily* |
|---|---|
| 18 to < 22 | 4 |
| ≥ 22 | 5 |

**If you are receiving VIRACEPT film-coated tablets three times a day**

| Body Weight (kg) | Number of film-coated tablets three times daily* |
|---|---|
| 18 to < 23 | 2 |
| ≥ 23 | 3 |

*see Package Leaflet for VIRACEPT oral powder for patients less than 18 kg body weight.

For adults or children unable to take tablets, VIRACEPT 50 mg/g oral powder may be administered (see Package Leaflet for VIRACEPT 50 mg/g oral powder).

**If you take more VIRACEPT than you should:**
If you realise you have taken more VIRACEPT than youshould have, contact your doctor right away. If you cannot reach your doctor, go to the nearest emergency room and take your VIRACEPT tablets with you. Among other symptoms, very large doses of VIRACEPT might cause disturbances in the heart rhythm.

**If you forget to take VIRACEPT:**
Take the next dose as soon as you remember and then carry on as before. Do not take a double dose to make up for forgotten individual doses.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, VIRACEPT can have side effects.

In clinical trials with VIRACEPT 250 mg tablets, either taken as 1250 mg two times daily or 750 mg three times daily, the most frequently reported side effect (in more than one in ten patients) was diarrhoea.
The commonest moderate or severe side effects (in approximately one in four to one in fifty patients) were:
- diarrhoea,
- wind,
- feeling sick,
- rash,
- low numbers of a particular type of white blood cell that fights infections (neutrophils),
- abnormal results from blood tests that measure how the liver is working and
- abnormal results from a blood test that measures how muscle tissue is working.

Other side effects that have been experienced with VIRACEPT are described below.

***Uncommon (in more than one in a thousand but less than one in a hundred persons):***
Allergic reactions including difficulty in breathing, fever, itching, swelling of the face and skin rashes that can sometimes form blisters,
being sick,
inflammation of the pancreas. Sometimes there are no symptoms of this and the problem appears only in blood tests.

***Rare (in more than one in ten thousand but less than one in a thousand persons):***
Inflammation of the liver, sometimes with jaundice (yellowing of the skin and eyes),
swelling of the belly.
New onset diabetes mellitus, high blood sugar or an increase in severity of existing diabetes mellitus has been rarely reported in patients receiving protease inhibitors. In some of these the high blood sugar was severe and in some cases also associated with ketoacidosis (change in metabolite levels in the blood). Many of these patients had additional medical conditions, some of which required therapy with agents that have been associated with the development of diabetes or high blood sugar.

In patients with haemophilia type A and B (patients who have blood clotting problems), there have been rare reports of increased bleeding while taking this treatment or another protease inhibitor. Should this happen to you, seek immediate advice from your doctor.

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (’buffalo hump’). The cause and long-term health effects of these conditions are not known at this time. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin.

There have been rare reports of muscle pain, tenderness or weakness, particularly with combination antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions these muscle problems have been serious causing muscle degeneration (rhabdomyolysis).

If you experience any side effects that are not in this leaflet, please tell your doctor or pharmacist. Also, tell your doctor if you have any severe or unusual symptoms or if any side effect that you think you may have gets worse or persists.

## 5. STORING VIRACEPT

Keep out of the reach and sight of children.

Do not store above 30°C.

Store in the original container.

Do not use after the expiry date stated on the label and carton.

**If you have any further questions please consult your doctor or pharmacist.**

## 6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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**This leaflet was last approved on {date}**