**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

VIRACEPT 50 mg/g oral powder.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The bottle contains 144 g of oral powder. Each gram of oral powder contains nelfinavir mesilate corresponding to 50 mg of nelfinavir.

Excipients:
- Contains sucrose palmitate: 10.0 mg per gram of oral powder. 10.0 mg of sucrose palmitate, which is an ester, theoretically corresponds to maximally 5.9 mg of sucrose when fully hydrolysed.
- Contains aspartame (E951): 20.0 mg of aspartame per gram of oral powder.
- Contains potassium: 50.0 mg of dibasic potassium phosphate corresponding to 22.5 mg of potassium per gram of oral powder.

See section 4.4

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Oral powder.
White to off-white amorphous 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 is administered orally and 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 (twice daily) regimen has been evaluated versus the TID (three times daily) regimen primarily in patients naïve to PIs (see section 5.1)

*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 – 35 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 in kg** | **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 in kg** | **Blue Scoop** 5 gram | | **White Scoop** 1 gram | | **Total grams of Powder per dose** |
| 7.5 to 8.5 kg | 1 | | | | 5 g |
| 8.5 to 10.5 kg | 1 | plus | 1 | | 6 g |
| 10.5 to 12 kg | 1 | plus | 2 | | 7 g |
| 12 to 14 kg | 1 | plus | 3 | | 8 g |
| 14 to 16 kg | 2 | | | | 10 g |
| 16 to 18 kg | 2 | plus | 1 | | 11 g |
| 18 to 22 kg | 2 | plus | 3 | | 13 g |
| over 22 kg | 3 | | | | 15 g |

The oral powder may be mixed with a small amount of water, milk, formula, soy formula, soy milk, dietary supplements, or pudding. Once mixed, the entire contents must be consumed in order to obtain the full dose. If the mixture is not consumed immediately, it must be stored under refrigeration, but storage must not exceed 6 hours. Acidic food or juice (e.g., orange juice, apple juice or apple sauce) are not recommended to be used in combination with VIRACEPT, because the combination may result in a bitter taste. VIRACEPT oral powder should not be reconstituted with water in its original container.

Renal and hepatic impairment: there are no data specific for HIV positive patients with renal impairment and therefore specific dosage recommendations cannot be made (see section 4.4). 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, orally administered midazolam (for caution on parenterally administered midazolam, see section 4.5), ergot derivatives, lovastatin and simvastatin, alfuzosin, and sildenafil when used for treatment of pulmonary arterial hypertension, (for the use of sildenafil and other PDE-5 inhibitors in patients with erectile dysfunction, see section 4.5)].

Potent inducers of CYP3A (e.g., rifampicin, phenobarbital and carbamazepine) reduce nelfinavir plasma concentrations.
Co- administration with rifampicin is contra-indicated due to a reduction in exposure to nelfinavir. Physicians should not use potent inducers of CYP 3A4 in combination with Viracept and should consider using alternatives when a patient is taking VIRACEPT (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).

VIRACEPT should not be co-administered with omeprazole due to a reduction in exposure to nelfinavir and its active metabolite M8 (Tert-butyl hydroxy nelfinavir). This may lead to a loss of virologic response and possible resistance to VIRACEPT (see section 4.5).

## 4.4 Special warnings and 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.

*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. The use of nelfinavir in

patients with moderate hepatic impairment has not been studied. In the absence of such studies, caution should be exercised, as increases in nelfinavir levels and/or increases in liver enzymes may occur.
Patients with hepatic impairment should not be given colchicine with VIRACEPT.

*Osteonecrosis:* Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

*Renal impairment:* Since nelfinavir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodiaylisis or peritoneal dialysis. Therefore, no special precautions or dose adjustments are required in these patients.
Patients with renal impairment should not be given colchicine with VIRACEPT.

*Diabetes mellitus and hyperglycaemia*: New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving PIs. In some of those 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.

*Patients with haemophilia*: 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.

*Lipodystrophy:* Combination antiretroviral therapy has been associated with the redistribution of body fat (acquired 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).

*PDE5 inhibitors:* particular caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction in patients receiving VIRACEPT. Co-administration of VIRACEPT with these medicinal products is expected to increase their concentrations and may result in associated adverse events such as hypotension, syncope, visual changes and prolonged erection (see section 4.5). Concomitant use of sildenafil prescribed for the treatment of pulmonary arterial hypertension with VIRACEPT is contraindicated (see section 4.3).

***HMG-CoA reductase inhibitors (statins):*** HMG-CoA reductase inhibitors may interact with protease inhibitors and increase the risk of myopathy, including rhabdomyolysis. Concomitant use of protease inhibitors with lovastatin or simvastatin is contraindicated. Other HMG-CoA reductase inhibitors may also interact with protease inhibitors and should be used with caution.

*Excipients:* VIRACEPT oral powder contains aspartame (E951) as a sweetening agent. Aspartame provides a source of phenylalanine and, therefore, may not be suitable for persons with phenylketonuria.
VIRACEPT oral powder contains potassium.

VIRACEPT oral powder also contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltese insufficiency should not take this medicine.
See section 2 and 6.1 for further information on excipients.

Concurrent administration of salmeterol with VIRACEPT is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.

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

Nelfinavir is primarily metabolised via the cytochrome P450 isoenzymes CYP3A4 and CYP2C19 (see section 5.2). Nelfinavir is also an inhibitor of CYP 3A4. Based on *in vitro* data, nelfinavir is unlikely to inhibit other cytochrome P450 isoforms at concentrations in the therapeutic range.

*Combination with other medicinal products:* Caution is advised whenever VIRACEPT is co-administered with agents that are inducers or inhibitors and/or substrates of CYP3A4; such combinations may require dose adjustment (see also sections 4.3 and 4.8).

*Substrates for CYP3A4:* Co-administration is contraindicated with the following agents that are substrates for CYP3A4 and that have narrow therapeutic windows:
terfenadine, astemizole, cisapride, amiodarone, quinidine, ergot derivatives, pimozide, oral midazolam, triazolam, alfuzosin, and sildenafil when used to treat pulmonary arterial hypertension (see section 4.3).

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.

For other substrates of CYP3A4 a dose reduction or consideration of an alternative may be required (Table 1).
Coadministration of nelfinavir with fluticasone proprionate may increase plasma concentrations of fluticasone propionate. Consider alternatives that are not metabolised by CYP3A4 such as beclomethasone.
Concomitant use of trazodone and nelfinavir may increase plasma concentrations of trazodone and a lower dose of trazodone should be considered.

Coadministration of nelfinavir with simvastatin or lovastatin may result in significant increases in simvastatin and lovastatin plasma concentrations and is contraindicated (see section 4.3). Consider alternatives that are not substrates of CYP3A4 such as pravastatin or fluvastatin.Other HMG-CoA reductase inhibitors may also interact with protease inhibitors and should be used with caution.
Concurrent administration of salmeterol with VIRACEPT is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Coadministration of warfarin and VIRACEPT may affect concentrations of warfarin. It is recommended that the international normalized ratio (INR) be monitored carefully during treatment with VIRACEPT, especially when commencing therapy.

*Metabolic enzyme inducers:* Potent inducers of CYP3A4 (e.g., rifampicin, pehnobarbital and carbamazepine) may reduce nelfianvir plasma concentrations and their coadministration is contraindicated (see section 4.3). Caution should be used when co-administering other agents that induce CYP3A4 Plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally and should therefore not be coadministered with nelfinavir. Parenteral midazolam should be coadministered with nelfinavir in an intensive care unit to ensure close clinical monitoring. Dose adjustment for midazolam should be considered if more than a single dose is administered (Table 1)

*Metabolic enzyme inhibitors:*Co-administration of nelfinavir with inhibitors of CYP2C19 (e.g., fluconazole, fluoxetine, paroxetine, 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.

Interactions of nelfinavir with selected compounds that describe the impact of nelfinavir on the pharmacokinetics of the co-administered compound and the impact of other drugs on pharmacokinetics of nelfinavir are listed in Table 1.

**Table 1: Interactions and dose recommendations with other medical products**

| **Medicinal product by therapeutic areas (dose of nelfinavir used in study)** | **Effects on drug levels % Change** | **Recommendations concerning coadministration** |
|---|---|---|
| ***NRTIs*** | | |
| | | Clinically significant interactions have not been observed between nelfinavir and nucleoside analogues. 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. |
| ***Protease Inhibitors*** | | |
| Ritonavir 500 mg single dose (nelfinavir 750 mg tid 6 days) | Ritonavir AUC ↔<br>Ritonavir Cmax ↔<br>Nelfinavir concentrations not measured | No dosage adjustment for needed for either product |
| Ritonavir 500 mg BID, 3 doses (nelfinavir 750 single dose) | Ritonavir concentrations not measured<br>Nelfinavir AUC ↑ 152 % | No dosage adjustment for needed for either product |
| Ritonavir 100 mg or 200 mg BID (nelfinavir 1250 mg BID morning administration) | Ritonavir concentrations not measured<br>Nelfinavir AUC ↑ 20%<br>M8 metabolite AUC ↑ 74% | 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. |
| Ritonavir 100 mg or 200 mg BID (nelfinavir 1250 mg BID evening administration) | Ritonavir concentrations not measured<br>Nelfinavir AUC ↑ 39 %<br>M8 metabolite AUC ↑ 86% | |
| Indinavir 800 mg single dose (nelfinavir 750 mg TID X 7 days) | Indinavir AUC ↑ 51%<br>Indinavir Cmax ↔<br>Nelfinavir concentrations not measured | The safety of the combination indinavir + nelfinavir has not been established |
| Indinavir 800 mg Q8H X 7 days (nelfinavir 750 mg single dose) | Indinavir concentrations not measured<br>Nelfinavir AUC ↑ 83% | |
| Saquinavir 1200 mg single dose (nelfinavir 750 mg TID X 4 days) | Saquinavir AUC ↑ 392%<br>Nelfinavir concentrations not measured | |

| **Medicinal product by therapeutic areas (dose of nelfinavir used in study)** | **Effects on drug levels % Change** | **Recommendations concerning coadministration** |
|---|---|---|
| Saquinavir 1200 mg TID (nelfinavir 750 mg single dose) | Saquinavir concentrations not measured<br>Nelfinavir AUC ↑ 30% | |
| Amprenavir 800 mg TID (nelfinavir 750 mg TID) | Amprenavir AUC ↔<br>Amprenavir Cmin ↑ 189 %<br>Nelfinavir AUC ↔ | No dosage adjustment for needed for either product |
| ***Non-nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)*** | | |
| Efavirenz 600 mg QD (Nelfinavir 750 mg TID) | Efavirenz AUC ↔<br>Nelfinavir AUC ↓ 20 % | No dosage adjustment for needed for either product |
| Delavirdine 400 mg TID (Nelfinavir 750 mg TID) | Delavirdine AUC ↓ 31 %<br>Nelfinavir AUC ↑ 107 % | Safety of combination not established; combination not recommended |
| Nevirapine | | Dose adjustment is not needed when nevirapine is administered with nelfinavir. |
| ***Anti infective Agents*** | | |
| Rifabutin 300 mg QD (Nelfinavir 750 mg TID) | Rifabutin AUC ↑ 207 %<br>Nelfinavir AUC ↓ 32 % | Dosage reduction of rifabutin to 150 mg QD is necessary when nelfinavir 750 mg TID or 1250 mg BID and rifabutin are co-administered. |
| Rifabutin 150 mg QD (Nelfinavir 750 mg TID) | Rifabutin AUC ↑ 83 %<br>Nelfinavir AUC ↓ 23 % | Dosage reduction of rifabutin to 150 mg QD is necessary when nelfinavir 750 mg TID or 1250 mg BID and rifabutin are co-administered |
| Rifampicin 600 mg qd x 7 days (Nelfinavir 750 mg q8h x 5-6 days) | Rifampicin concentrations not measured<br>Nelfinavir AUC ↓82% | Concomitant use of rifampicin is contraindicated with nelfinavir |
| Ketoconazole | Ketoconazole concentrations not measured<br>Nelfinavir AUC ↑35% | Coadministration of nelfinavir and a strong inhibitor of CYP3A, ketoconazole, resulted in a 35 % increase in nelfinavir plasma AUC.The changes in nelfinavir concentrations are not considered clinically significant and no dose adjustment is needed when ketoconazole and nelfinavir are co-administered. |
| ***Oral Contraceptives*** | | |
| 17 α-Ethinyl estradiol 35 µg qd x 15 days<br>(Nelfinavir 750 mg q8h x 7 days) | Ethinyl estradiol AUC ↓47%<br>Nelfinavir concentrations not measured | Contraceptives with ethinyl estradiol should not be coadministered with nelfinavir. Alternative contraceptive measures should be considered. |
| Norethindrone 0.4 mg qd x 15 days<br>(Nelfinavir 750 mg q8h x 7 days) | Norethindrone AUC ↓18%<br>Nelfinavir concentrations not measured | Contraceptives with norethindrone should not be coadministered with nelfinavir. Alternative contraceptive measures should be considered. |

| Medicinal product by therapeutic areas (dose of nelfinavir used in study) | Effects on drug levels % Change | Recommendations concerning coadministration |
|---|---|---|
| ***HMG-CoA reductase inhibitors (Statins)*** | | |
| | | Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicinal products with nelfinavir is not recommended. |
| Simvastatin or lovastatin(Nelfinavir 1250 mg bid) | Simvastatin AUC ↑ 505%<br>Nelfinavir AUC ↔<br>concentrations not measured | Combination of simvastatin or lovastatin and nelfinavir is contraindicated (see contraindication) |
| Atorvastatin 10 mg qd (Nelfinavir 1250 mg bid) | Atorvastatin AUC ↑ 74 %<br>Nelfinavir AUC concentrations not measured | Atorvastatin is less dependent on CYP3A4 for metabolism. When used with nelfinavir, the lowest possible dose of atorvastatin should be administered. |
| Pravastatin, fluvastatin, rosuvastatin | | The metabolism of pravastatin, and fluvastatin is not dependent on CYP3A4, and interactions are not expected withnelfinavir. If treatment with HMG-CoA reductase inhibitors is indicated in combination with nelfinavir, pravastatin or fluvastatin are recommended. Rosuvastatin may also be administered with nelfinavir but patients should be monitored. |
| ***Anticonvulsants*** | | |
| Phenytoin 300 mg qd x 7 days (Nelfinavir 1250 mg bid x 14 days) | Phenytoin AUC ↓29%<br>Free Phenytoin ↓28% | No dose adjustment for nelfinavir is recommended. Nelfinavir may lead to decreased AUC of phenytoin; therefore phenytoin concentrations should be monitored during concomitant use with nelfinavir. |
| ***Proton Pump Inhibitors*** | | |
| Omeprazole 20 mg bid x 4 days administered 30 minutes before nelfinavir (Nelfinavir 1250 mg bid x 4 days) | Omeprazole concentrations not measured<br>Nelfinavir AUC ↓36%<br>Nelfinavir Cmax ↓37%<br>Nelfinavir Cmin ↓39%<br>M8 metabolite AUC ↓92%<br>M8 metabolite Cmax ↓ 89%<br>M8 metabolite Cmin ↓ 75% | Omeprazole should not be co-administered with nelfinavir. The absorption of nelfinavir may be reduced in situations where the gastric pH is increased irrespective of cause. Co-administration of nelfinavir with omeprazole may lead to a loss of virologic response and therefore concomitant use is contra-indicated. Caution is recommended when nelfinavir is co-administered with other proton pump inhibitors |

| Medicinal product by therapeutic areas (dose of nelfinavir used in study) | Effects on drug levels % Change | Recommendations concerning coadministration |
|---|---|---|
| ***Sedatives/Anxiolytics*** | | |
| Midazolam | No drug interaction study has been performed for the co-administration of nelfinavir with benzodiazepines. | Midazolam is extensively metabolised by CYP3A4. Co-administration of midazolam with nelfinavir may cause a large increase in the concentration of this benzodiazepine. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore nelfinavir should not be co-administered with orally administered midazolam. If nelfinavir is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered |
| ***H1 Receptor Antagonists, 5-HT Agonists*** | | |
| Terfenadine, astemizole, cisapride | Nelfinavir increases terfenadine plasma concentrations. Similar interactions are likely with astemizole and cisapride. | Nelfinavir must not be administered concurrently with terfenadine, astemizole or cisapride because of the potential for serious and/or life-threatening cardiac arrhythmias. |
| ***Endothelin receptor antagonists*** | | |
| Bosentan | Not studied. Concomitant use of bosentan and nelfinavir may increase plasma levels of bosentan. | When administered concomitantly with nelfinavir, the patient's tolerability of bosentan should be monitored. |
| ***Analgesics*** | | |
| Methadone 80 mg – 21 mg qd > 1 month (Nelfinavir 1250mg bid x 8 days | Methadone AUC ↓47% | 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 combination may experience withdrawal symptoms and require an upward adjustment of the methadone dose. Methadone AUC may be decreased when co-administered with nelfinavir; therefore upward adjustment of methadone dose may be required during concomitant use with nelfinavir. |

| Medicinal product by therapeutic areas (dose of nelfinavir used in study) | Effects on drug levels % Change | Recommendations concerning coadministration |
|---|---|---|
| ***Inhaled/nasal steroid*** | | |
| Fluticasone | ↑ Fluticasone | Concomitant use of fluticasone propionate and VIRACEPT may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, that are not metabolised by CYP3A4, such as beclometasone, particularly for long-term use. |
| ***Antidepressants*** | | |
| Trazodone | ↑ Trazodone | Concomitant use of trazodone and VIRACEPT may increase plasma concentrations of trazodone. The combination should be used with caution and a lower dose of trazodone should be considered. |
| ***PDE-5 inhibitors for the treatment of pulmonary arterial hypertension (PAH)*** | | |
| Tadalafil | Not studied. Concomitant use of tadalafil and nelfinavir may increase plasma levels of tadalafil. | Co-administration of tadalafil for the treatment of pulmonary arterial hypertension with VIRACEPT is not recommended. |
| Sildenafil | Not studied. Concomitant use of sildenafil and nelfinavir may increase plasma levels of sildenafil. | Sildenafil is contraindicated when coadministered with VIRACEPT (see contraindications). |
| ***PDE-5 inhibitors for the treatment of erectile dysfunction (ED)*** | | |
| Tadalafil | Not studied. Concomitant use of tadalafil and nelfinavir may increase plasma levels of tadalafil. | Use with increased monitoring for adverse events associated with increased exposure to tadalafil. |
| Sildenafil | Not studied. Concomitant use of sildenafil and nelfinavir may increase plasma levels of sildenafil. | Sildenafil at a starting dose not exceeding 25 mg in 48 hours. Use with increased monitoring for adverse events associated with increased exposure to sildenafil. |
| Vardenafil | Not studied. Concomitant use of vardenafil and nelfinavir may increase plasma levels of vardenafil. | Use with increased monitoring for adverse events associated with increased exposure to vardenafil. |
| ***Antigout preparation*** | | |
| Colchicine | Not studied. Concomitant use of colchicine and nelfinavir may increase plasma levels of colchicine. | A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with nelfinavir is required. Patients with renal or hepatic impairment should not be given colchicine with nelfinavir (see section 4.4). |

| Medicinal product by therapeutic areas (dose of nelfinavir used in study) | Effects on drug levels % Change | Recommendations concerning coadministration |
|---|---|---|
| ***Herbal Products*** | | |
| St. John's wort | 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 nelfinavir. 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 nelfinavir may need adjusting. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment. |

↑ Indicates increase, ↓ indicates decrease, ↔ indicates minimal change (< 10 %).

## 4.6 Fertility, pregnancy and lactation

No treatment-related adverse reactions 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

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 following adverse events with an at least possible relationship to nelfinavir (i.e. adverse reactions) were reported most frequently: diarrhoea, nausea, and rash. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions from clinical trials with nelfinavir

Adverse reactions in clinical studies are summarised in Table 2. The list also includes marked laboratory abnormalities that have been observed with nelfinavir (at 48 weeks).

**Table 2: Incidences of Adverse Reactions and marked laboratory abnormalities from the phase II and phase III studies. (Very common (≥ 10 %); common (≥ 1 % and < 10 %)**

| ***Body System*** **Frequency of Reaction** | Adverse Reactions |
|---|---|
| Grades 3&4 | All Grades |
| *Gastrointestinal disorders* | |
| Very common | Diarrhoea |
| Common | Nausea, flatulence, |
| *Skin and subcutaneous tissue disorders* | |
| Common | Rash |
| *Investigations* | |
| Common | Increased alanine aminotransferase, increased aspartate aminotransferase, neutropenia, blood creatinine phosphokinase increased, neutrophil count decreased |

Children and neonates:
A total of approximately 400 patients received nelfinavir in paediatric treatment trials (Studies 524, 556, PACTG 377/725, and PENTA-7) for up to 96 weeks. The adverse reaction profile seen during paediatric clinical trials was similar to that for adults. Diarrhoea was the most commonly reported adverse event in children. Neutropenia/leukopenia was the most frequently observed laboratory abnormality. During these trials less than 13% of patients in total discontinued treatment due to adverse events.

Post-marketing experience with nelfinavir
Serious and non-serious adverse reactions from post-marketing spontaneous reports (where nelfinavir was taken as the sole protease inhibitor or in combination with other antiretroviral therapy), not mentioned previously in section 4.8, for which a causal relationship to nelfinavir cannot be excluded, are summarised below. As these data come from the spontaneous reporting system, the frequency of the adverse reactions is not confirmed.

*Immune system disorders:*
*Uncommon (≥ 0.1 % - ≤ 1 %)*: hypersensitivity including bronchospasm, pyrexia, pruritus, facial oedema and rash maculo-papular or dermatitis bullous.

*Metabolism and nutrition disorders:*
*Uncommon - rare (≥ 0.01 % - ≤ 1 %)*: Combination antiretroviral therapy has been associated with redistribution of body fat (Lipodystrophy aquired) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (lipohypertrophy buffalo hump).
*Rare (≥ 0.01 % - ≤ 0.1 %)*: new onset diabetes mellitus, or exacerbation of existing diabetes mellitus.

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

*Hepatobiliary disorders:*
*Rare (≥ 0.01 % - ≤ 0.1 %)*: hepatitis, hepatic enzymes increased and jaundice when nelfinavir is used in combination with other antiretroviral agents.

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

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

*Skin and subcutaneous tissue disorders:*
*Very rare (≤ 0.01 %), including isolated reports*: Erythema multiforme.

*Paediatric population*:
Additional adverse reactions have been reported in the post-marketing experience and are listed below. As these data come from the spontaneous reporting system, the frequency of the adverse reactions is unknown: hypertriglyceridemia, anaemia, blood lactic acid increased, and pneumonia.

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as blood triglycerides increased, blood cholesterol increased, insulin resistance, hyperglycaemia and hyperlactaemia. The frequency of this is unknown (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. The frequency of this is unknown (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:direct acting antivirals, ATC code: J05AE04.

*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.

*Resistance:* Viral escape from nelfinavir can occure via viral protease mutations at amino acid positions 30, 88 and 90.

*In vitro:* 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.

*Cross resistance in vitro*: 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*.

*In vivo:* 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.

*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 metabolised 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 optimise antiviral efficacy. Plasma levels of nelfinavir, which is metabolised predominantly by CYP2C19 and only partially by CYP3A4, are not greatly increased by co-administration with ritonavir, and therefore nelfinavir does not require co-administration with low-dose ritonavir.. 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 (750 mg 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 log$^{10}$ copies/ml and 5.01 log$^{10}$ copies/ml in the nelfinavir and lopinavir/ritonavir treatment groups respectively. Median baseline CD4+ cell count was 232 cells/mm$^3$ 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/mm$^3$ and 207 cells/mm$^3$ 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 (1400 mg/200 mg QD n=322) compared to nelfinavir (1250 mg 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 log$^{10}$ copies/ml in both treatment groups. Median baseline CD4+ cell counts were 177 and 166 x10$^6$ 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/mm$^3$ and 203 cells/mm$^3$ 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 $IC_{95}$ 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 Oral Absorption*
Food increases nelfinavir exposure and decreases nelfinavir pharmacokinetic variability relative to the fasted state. In one study, healthy volunteers received a single dose of 1250 mg of VIRACEPT (5x 250 mg tablets) under fasted or fed conditions (three meals with different caloric and fat contents). In a second study, healthy volunteers received single doses of 1250 mg VIRACEPT (5 x 250 mg tablets) under fasted or fed conditions (two meals with different fat content). The results from the two studies are summarized below.

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

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

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

| Number of Kcal | % Fat | Number of Subjects | AUC fold increase | $C_{max}$ fold increase | Increase in $T_{max}$ (hr) |
|---|---|---|---|---|---|
| 500 | 20 | n=22 | 3.1 | 2.5 | 1.8 |
| 500 | 50 | n=22 | 5.1 | 3.8 | 2.1 |

Nelfinavir exposure increases with increasing calorie or fat content of meals taken with VIRACEPT.

*Distribution:* Nelfinavir in serum is extensively protein-bound (≥ 98 %). The estimated volumes of distribution in both animals and humans is 2-7 l/kg which exceeded total body water and suggests extensive penetration of nelfinavir into tissues.

*Metabolism:* *In vitro* studies demonstrated that multiple cytochrome P-450 isoforms including CYP3A, CYP2C19/C9 and CYP2D6 are responsible for the 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.

*Elimination:* oral clearance estimates after single doses (24-36 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 populations:*

*Children:*
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 at a dose of approximately 25-30 mg/kg TID with food achieves steady-state plasma concentrations that are similar to those achieved in adult patients receiving 750 mg TID.

The pharmacokinetics of nelfinavir have been investigated in 5 studies in paediatric patients from birth to 13 years of age. Patients received VIRACEPT either three times daily or twice daily with food or with meals. The dosing regimens and associated $AUC_{24}$ values are summarized below.

**Summary of Steady-state AUC24 of nelfinavir in Paediatric Studies**

| Protocol No. | Dosing Regimen[1] | N[2] | Age | Food taken with Viracept | AUC24 (mg.hr/L) Arithmetic mean ± SD |
|---|---|---|---|---|---|
| **AG1343-524** | **20 (19-28) mg/kg TID** | **14** | **2-13 years** | Powder with milk, formula, pudding, or water, as part of a light meal or tablet taken with a light meal | **56.1 ± 29.8** |
| **PACTG-725** | **55 (48-60) mg/kg BID** | **6** | **3-11 years** | With food | **101.3 ± 56.1** |
| **PENTA 7** | **40 (34-43) mg/kg TID** | **4** | **2-9 months** | With milk | **33.8 ± 8.9** |
| **PENTA 7** | **75 (55-83) mg/kg BID** | **12** | **2-9 months** | With milk | **37.2 ± 19.2** |
| **PACTG-353** | **40 (14-56) mg/kg BID** | **10** | **6 weeks** | Powder with water, milk, formula, soy formula, soy milk, or dietary supplements | **44.1 ± 27.4** |
| | | | **1 week** | | **45.8 ± 32.1** |

[1] Protocol specified dose (actual dose range)
[2] N: number of subjects with evaluable pharmacokinetic results
$C_{trough}$ values are not presented in the table because they are not available from all studies

Pharmacokinetic data are also available for 86 patients (age 2 to 12 years) who received VIRACEPT 25-35 mg/kg TID in Study AG1343-556. The pharmacokinetic data from Study AG1343-556 were more variable than data from other studies conducted in the paediatric population; the 95% confidence interval for $AUC_{24}$ was 9 to 121 mg.hr/L.

Overall, use of VIRACEPT in the paediatric population is associated with highly variable drug exposure. The reason for this high variability is not known but may be due to inconsistent food intake in paediatric patients.

*Elderly:*
There are no data available in the elderly.

*Hepatic impairment:*
The multiple dose pharmacokinetics of nelfinavir have not been studied in HIV-positive patients with hepatic insufficiency.
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. A second study evaluated the steady state pharmacokinetics of nelfinavir (1250 mg twice daily for 2 weeks) in adult HIV-seronegative subjects with mild (Child-Pugh A; n=6) or moderate (Child-Pugh B; n=6) hepatic impairment. Compared to control subjects with normal hepatic function, the AUC and $C_{max}$ of nelfinavir were not significantly different in subjects with mild impairment but were increased by 62% and 22%, respectively, in subjects with moderate hepatic impairment.

### 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
- natural and artificial flavour

### 6.2 Incompatibilities

This medicinal product must 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 Special precautions for disposal and other handling

There are two scoops provided in the box, a white 1 gram scoop and a blue 5 gram scoop.

1. Measure out a level scoop of powder by using the handle of the second scoop to scrape off the extra powder.
2. mix powder with water, milk, formula, soy milk, dietary supplements or pudding
3. do not mix powder with acidic food or juice
4. powder mixed in the media as described under 2 is recommended to be used within 6 hours

## 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

Date of first authorisation: 22 January 1998
Date of latest renewal: 23 January 2008

## 10. DATE OF REVISION OF THE TEXT

## 1. NAME OF THE MEDICINAL PRODUCT

VIRACEPT 250 mg film-coated tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains nelfinavir mesilate corresponding to 250 mg of nelfinavir.

Excipients:
For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Blue, oblong biconvex 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 is administered orally and should always be ingested with food (see section 5.2).

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

*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 – 35 mg/kg body weight** per dose.

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

| **Dose to be administered two times a day to children aged 3 to 13** | |
|---|---|
| **Body weight of the patient in kg** | **Number of VIRACEPT 250 mg film-coated tablets per dose*** |
| 18 to 22 kg | 4 |
| over 22 kg | 5 |

The recommended dose of VIRACEPT film-coated tablets to be administered **TID to children aged 3 to 13 years** is shown in the table below. **Children with weights between 10.5–12 kg, 12–14 kg and 18–22 kg will receive a different number of tablets with each meal.** The table provides a schedule assuring that the appropriate total daily dose of Viracept is taken each day based on the child's weight.

The prescriber should advise the caregiver to carefully monitor increases in weight of the child to ensure that the appropriate total daily dose is taken. The prescriber should also advise the caregiver about the importance of adhering to the dosing instructions and that the appropriate number of tablets should be taken at each dose with a meal.

| **Dose to be administered three times a day to children aged 3 to 13** | | | | |
|---|---|---|---|---|
| **Body weight of the patient in kg** | **Recommended number of tablets at each meal** | | | **Total number of tablets per day** |
| | **Number of tablets at breakfast** | **Number of tablets at lunch** | **Number of tablets at dinner** | |
| 7.5 to 8.5 kg | 1 | 1 | 1 | 3 |
| 8.5 to 10.5 kg | 1 | 1 | 1 | 3 |
| **10.5 to 12 kg*** | **2** | **1** | **1** | **4** |
| **12 to 14 kg*** | **2** | **1** | **2** | **5** |
| 14 to 16 kg | 2 | 2 | 2 | 6 |
| 16 to 18 kg | 2 | 2 | 2 | 6 |
| **18 to 22 kg*** | **3** | **2** | **2** | **7** |
| over 22 kg | 3 | 3 | 3 | 9 |

* Children with these weights will be given an uneven number of tablets during the day. The virologic and immunologic responses should be monitored to assure these children achieve response to therapy.

For patients unable to swallow the tablets, VIRACEPT tablets may be dispersed in a half cup of water while thoroughly stirring with a spoon. Once dispersed, the cloudy bluish liquid should be thoroughly mixed and consumed immediately. The glass should be rinsed with a half cup of water and the rinse should be swallowed to ensure that the entire dose is consumed.

Acidic food or juice (e.g. orange juice, apple juice or apple sauce) are not recommended to be used in combination with VIRACEPT, because the combination may result in a bitter taste. The VIRACEPT suspension should be taken with a meal.

The prescriber should assure that the caregiver understands the importance of monitoring adherence and the appropriate method to prepare and administer Viracept tablets to children in each weight band.

Renal and hepatic impairment: there are no data specific for HIV positive patients with renal impairment and therefore specific dosage recommendations cannot be made (see section 4.4). 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, orally administered midazolam (for caution on parenterally administered midazolam, see section 4.5), ergot derivatives, lovastatin and simvastatin, alfuzosin, and sildenafil when used for treatment of

pulmonary arterial hypertension hypertension (for the use of sildenafil and other PDE-5 inhibitors in patients with erectile dysfunction, see section 4.5)].

Potent inducers of CYP3A (e.g., rifampicin, phenobarbital and carbamazepine) reduce nelfinavir plasma concentrations.
Co- administration with rifampicin is contra-indicated due to a reduction in exposure to nelfinavir. Physicians should not use potent inducers of CYP 3A4 in combination with Viracept and should consider using alternatives when a patient is taking VIRACEPT (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).

VIRACEPT should not be co-administered with omeprazole due to a reduction in exposure to nelfinavir and its active metabolite M8 (Tert-butyl hydroxy nelfinavir). This may lead to a loss of virologic response and possible resistance to VIRACEPT (see section 4.5).

## 4.4 Special warnings and 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.

*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. The use of nelfinavir in patients with moderate hepatic impairment has not been studied. In the absence of such studies, caution should be exercised, as increases in nelfinavir levels and/or increases in liver enzymes may occur.
Patients with hepatic impairment should not be given colchicine with VIRACEPT.

*Osteonecrosis:* Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

*Renal Impairment*: Since nelfinavir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodiaylisis or peritoneal dialysis. Therefore, no special precautions or dose adjustments are required in these patients.
Patients with renal impairment should not be given colchicine with VIRACEPT.

*Diabetes mellitus and hyperglycaemia:* 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.

*Patients with haemophilia:* 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.

*Lipodystrophy:* Combination antiretroviral therapy has been associated with the redistribution of body fat (acquired 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).

*PDE5 inhibitors:* particular caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction in patients receiving VIRACEPT. Co-administration of VIRACEPT with these medicinal products is expected to increase their concentrations and may result in associated adverse events such as hypotension, syncope, visual changes and prolonged erection (see section 4.5). Concomitant use of sildenafil prescribed for the treatment of pulmonary arterial hypertension with VIRACEPT is contraindicated (see section 4.3).

***HMG-CoA reductase inhibitors (statins):*** HMG-CoA reductase inhibitors may interact with protease inhibitors and increase the risk of myopathy, including rhabdomyolysis. Concomitant use of protease inhibitors with lovastatin or simvastatin is contraindicated. Other HMG-CoA reductase inhibitors may also interact with protease inhibitors and should be used with caution.

Concurrent administration of salmeterol with VIRACEPT is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.

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

Nelfinavir is primarily metabolised via the cytochrome P450 isoenzymes CYP3A4 and CYP2C19 (see section 5.2). Nelfinavir is also an inhibitor of CYP 3A4. Based on *in vitro* data, nelfinavir is unlikely to inhibit other cytochrome P450 isoforms at concentrations in the therapeutic range.

*Combination with other medicinal products:* Caution is advised whenever VIRACEPT is co-administered with agents that are inducers or inhibitors and/or substrates of CYP3A4; such combinations may require dose adjustment (see also sections 4.3 and 4.8).

*Substrates for CYP3A:* Co-administration is contraindicated with the following agents that are substrates for CYP3A4 and that have narrow therapeutic windows terfenadine, astemizole, cisapride, amiodarone, quinidine, ergot derivatives, pimozide, oral midazolam, triazolam, alfuzosin, and sildenafil when used to treat pulmonary arterial hypertension (see section 4.3).

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.

For other substrates of CYP3A4 a dose reduction or consideration of an alternative may be required (Table 1).
Coadministration of nelfinavir with fluticasone proprionate may increase plasma concentrations of fluticasone propionate. Consider alternatives that are not metabolised by CYP3A4 such as beclomethasone.
Concomitant use of trazodone and nelfinavir may increase plasma concentrations of trazodone and a lower dose of trazodone should be considered.

Coadministration of nelfinavir with simvastatin or lovastatin may result in significant increases in simvastatin and lovastatin plasma concentrations and is contraindicated (see section 4.3). Consider alternatives that are not substrates of CYP3A4 such as pravastatin or fluvastatin. Other HMG-CoA reductase inhibitors may also interact with protease inhibitors and should be used with caution .

Concurrent administration of salmeterol with VIRACEPT is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Coadministration of warfarin and VIRACEPT may affect concentrations of warfarin. It is recommended that the international normalized ratio (INR) be monitored carefully during treatment with VIRACEPT, especially when commencing therapy.

*Metabolic enzyme inducers:* Potent inducers of CYP3A4 (e.g., rifampicin, phenobarbital and carbamazepine) may reduce nelfianvir plasma concentrations and their coadministration is contraindicated (see section 4.3). Caution should be used when co-administering other agents that induce CYP3A4.
Plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally and should therefore not be coadministered with nelfinavir. Parenteral midazolam should be coadministered with nelfinavir in an intensive care unit to ensure close clinical monitoring. Dose adjustment for midazolam should be considered if more than a single dose is administered (Table 1)

*Metabolic enzyme inhibitors:* Co-administration of nelfinavir with inhibitors of CYP2C19 (e.g., fluconazole, fluoxetine, paroxetine, 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.

Interactions of nelfinavir with selected agents that describe the impact of nelfinavir on the pharmacokinetics of the co-administered compound and the impact of other drugs on pharmacokinetics of nelfinavir are listed in Table 1.

**Table 1: Interactions and dose recommendations with other medical products**

| Medicinal product by therapeutic areas (dose of nelfinavir used in study) | Effects on drug levels % Change | Recommendations concerning coadministration |
|---|---|---|
| | | |
| ***NRTIs*** | | |
| | | Clinically significant interactions have not been observed between nelfinavir and nucleoside analogues. 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. |
| ***Protease Inhibitors*** | | |
| Ritonavir 500 mg single dose (nelfinavir 750 mg tid 6 days) | Ritonavir AUC ↔<br>Ritonavir Cmax ↔<br>Nelfinavir concentrations not measured | No dosage adjustment for needed for either product |
| Ritonavir 500 mg BID, 3 doses (nelfinavir 750 single dose) | Ritonavir concentrations not measured<br>Nelfinavir AUC ↑ 152 % | No dosage adjustment for needed for either product |
| Ritonavir 100 mg or 200 mg BID (nelfinavir 1250 mg BID morning administration) | Ritonavir concentrations not measured<br>Nelfinavir AUC ↑ 20%<br>M8 metabolite AUC ↑ 74% | 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. |
| Ritonavir 100 mg or 200 mg BID (nelfinavir 1250 mg BID evening administration) | Ritonavir concentrations not measured<br>Nelfinavir AUC ↑ 39 %<br>M8 metabolite AUC ↑ 86% | |
| Indinavir 800 mg single dose (nelfinavir 750 mg TID X 7 days) | Indinavir AUC ↑ 51%<br>Indinavir Cmax ↔<br>Nelfinavir concentrations not measured | The safety of the combination indinavir + nelfinavir has not been established |
| Indinavir 800 mg Q8H X 7 days (nelfinavir 750 mg single dose) | Indinavir concentrations not measured<br>Nelfinavir AUC ↑ 83% | |
| Saquinavir 1200 mg single dose (nelfinavir 750 mg TID X 4 days) | Saquinavir AUC ↑ 392%<br>Nelfinavir concentrations not measured | |
| Saquinavir 1200 mg TID (nelfinavir 750 mg single dose) | Saquinavir concentrations not measured<br>Nelfinavir AUC ↑ 30% | |
| Amprenavir 800 mg TID (nelfinavir 750 mg TID) | Amprenavir AUC ↔<br>Amprenavir Cmin ↑ 189 %<br>Nelfinavir AUC ↔ | No dosage adjustment for needed for either product |
| ***Non-nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)*** | | |
| Efavirenz 600 mg QD (Nelfinavir 750 mg TID) | Efavirenz AUC ↔<br>Nelfinavir AUC ↓ 20 % | No dosage adjustment for needed for either product |

| Medicinal product by therapeutic areas (dose of nelfinavir used in study) | Effects on drug levels % Change | Recommendations concerning coadministration |
|---|---|---|
| Delavirdine 400 mg TID (Nelfinavir 750 mg TID) | Delavirdine AUC ↓ 31 %<br>Nelfinavir AUC ↑ 107 % | Safety of combination not established; combination not recommended |
| Nevirapine | | Dose adjustment is not needed when nevirapine is administered with nelfinavir. |
| ***Anti infective Agents*** | | |
| Rifabutin 300 mg QD (Nelfinavir 750 mg TID) | Rifabutin AUC ↑ 207 %<br>Nelfinavir AUC ↓ 32 % | Dosage reduction of rifabutin to 150 mg QD is necessary when nelfinavir 750 mg TID or 1250 mg BID and rifabutin are co-administered. |
| Rifabutin 150 mg QD (Nelfinavir 750 mg TID) | Rifabutin AUC ↑ 83 %<br>Nelfinavir AUC ↓ 23 % | Dosage reduction of rifabutin to 150 mg QD is necessary when nelfinavir 750 mg TID or 1250 mg BID and rifabutin are co-administered |
| Rifampicin 600 mg qd x 7 days (Nelfinavir 750 mg q8h x 5-6 days) | Rifampicin concentrations not measured<br>Nelfinavir AUC ↓82% | Concomitant use of rifampicin is contraindicated with nelfinavir |
| Ketoconazole | Ketoconazole concentrations not measured<br>Nelfinavir AUC ↑35% | Coadministration of nelfinavir and a strong inhibitor of CYP3A, ketoconazole, resulted in a 35 % increase in nelfinavir plasma AUC.The changes in nelfinavir concentrations are not considered clinically significant and no dose adjustment is needed when ketoconazole and nelfinavir are co-administered. |
| ***Oral Contraceptives*** | | |
| 17 α-Ethinyl estradiol 35 µg qd x 15 days (Nelfinavir 750 mg q8h x 7 days) | Ethinyl estradiol AUC ↓47%<br>Nelfinavir concentrations not measured | Contraceptives with ethinyl estradiol should not be coadministered with nelfinavir. Alternative contraceptive measures should be considered. |
| Norethindrone 0.4 mg qd x 15 days (Nelfinavir 750 mg q8h x 7 days) | Norethindrone AUC ↓18%<br>Nelfinavir concentrations not measured | Contraceptives with norethindrone should not be coadministered with nelfinavir. Alternative contraceptive measures should be considered. |
| ***HMG-CoA reductase inhibitors (Statins)*** | | |
| | | Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicinal products with nelfinavir is not recommended. |

| **Medicinal product by therapeutic areas (dose of nelfinavir used in study)** | **Effects on drug levels % Change** | **Recommendations concerning coadministration** |
|---|---|---|
| Simvastatin or lovastatin (Nelfinavir 1250 mg bid) | Simvastatin AUC ↑ 505 %<br>Nelfinavir AUC ↔<br>concentrations not measured | Combination of simvastatin or lovastatin and nelfinavir is contraindicated (see contraindication). |
| Atorvastatin 10 mg qd (Nelfinavir 1250 mg bid) | Atorvastatin AUC ↑ 74 %<br>Nelfinavir AUC concentrations not measured | Atorvastatin is less dependent on CYP3A4 for metabolism. When used with nelfinavir, the lowest possible dose of atorvastatin should be administered. |
| Pravastatin, fluvastatin, rosuvastatin | | The metabolism of pravastatin and fluvastatinis not dependent on CYP3A4, and interactions are not expected with nelfinavir. If treatment with HMG-CoA reductase inhibitors is indicated in combination with nelfinavir, pravastatin or fluvastatin are recommended. Rosuvastatin may also be administered with nelfinavir but patients should be monitored. |
| ***Anticonvulsants*** | | |
| Phenytoin 300 mg qd x 7 days (Nelfinavir 1250 mg bid x 14 days) | Phenytoin AUC ↓29%<br>Free Phenytoin ↓28% | No dose adjustment for nelfinavir is recommended. Nelfinavir may lead to decreased AUC of phenytoin; therefore phenytoin concentrations should be monitored during concomitant use with nelfinavir. |
| ***Proton Pump Inhibitors*** | | |
| Omeprazole 20 mg bid x 4 days administered 30 minutes before nelfinavir (Nelfinavir 1250 mg bid x 4 days) | Omeprazole concentrations not measured<br>Nelfinavir AUC ↓36%<br>Nelfinavir Cmax ↓37%<br>Nelfinavir Cmin ↓39%<br>M8 metabolite AUC ↓92%<br>M8 metabolite Cmax ↓ 89%<br>M8 metabolite Cmin ↓ 75% | Omeprazole should not be co-administered with nelfinavir. The absorption of nelfinavir may be reduced in situations where the gastric pH is increased irrespective of cause. Co-administration of nelfinavir with omeprazole may lead to a loss of virologic response and therefore concomitant use is contra-indicated. Caution is recommended when nelfinavir is co-administered with other proton pump inhibitors |

| Medicinal product by therapeutic areas (dose of nelfinavir used in study) | Effects on drug levels % Change | Recommendations concerning coadministration |
|---|---|---|
| ***Sedatives/Anxiolytics*** | | |
| Midazolam | No drug interaction study has been performed for the co-administration of nelfinavir with benzodiazepines. | Midazolam is extensively metabolised by CYP3A4. Co-administration of midazolam with nelfinavir may cause a large increase in the concentration of this benzodiazepine. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore nelfinavir should not be co-administered with orally administered midazolam. If nelfinavir is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered |
| ***H1 Receptor Antagonists, 5-HT Agonists*** | | |
| Terfenadine, astemizole, cisapride | Nelfinavir increases terfenadine plasma concentrations. Similar interactions are likely with astemizole and cisapride. | Nelfinavir must not be administered concurrently with terfenadine, astemizole or cisapride because of the potential for serious and/or life-threatening cardiac arrhythmias. |
| ***Endothelin receptor antagonists*** | | |
| Bosentan | Not studied. Concomitant use of bosentan and nelfinavir may increase plasma levels of bosentan. | When administered concomitantly with nelfinavir, the patient's tolerability of bosentan should be monitored. |
| ***Analgesics*** | | |
| Methadone 80 mg ± 21 mg qd > 1 month<br>(Nelfinavir 1250mg bid x 8 days | Methadone AUC ↓47% | 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 combination may experience withdrawal symptoms and require an upward adjustment of the methadone dose.<br>Methadone AUC may be decreased when co-administered with nelfinavir; therefore upward adjustment of methadone dose may be required during concomitant use with nelfinavir. |

| Medicinal product by therapeutic areas (dose of nelfinavir used in study) | Effects on drug levels % Change | Recommendations concerning coadministration |
|---|---|---|
| ***Inhaled/nasal steroid*** | | |
| ↑Fluticasone | ↑ Fluticasone | Concomitant use of fluticasone propionate and VIRACEPT may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, that are not metabolised by CYP3A4, such as beclometasone, particularly for long-term use. |
| ***Antidepressants*** | | |
| Trazodone | ↑ Trazodone | Concomitant use of trazodone and VIRACEPT may increase plasma concentrations of trazodone. The combination should be used with caution and a lower dose of trazodone should be considered. |
| ***PDE-5 inhibitors for the treatment of pulmonary arterial hypertension (PAH)*** | | |
| Tadalafil | Not studied. Concomitant use of tadalafil and nelfinavir may increase plasma levels of tadalafil. | Co-administration of tadalafil for the treatment of pulmonary arterial hypertension with Viracept is not recommended. |
| Sildenafil | Not studied. Concomitant use of sildenafil and nelfinavir may increase plasma levels of sildenafil. | Sildenafil is contraindicated when coadministered with VIRACEPT (see contraindications). |
| ***PDE-5 inhibitors for the treatment of erectile dysfunction (ED)*** | | |
| Tadalafil | Not studied. Concomitant use of tadalafil and nelfinavir may increase plasma levels of tadalafil. | Use with increased monitoring for adverse events associated with increased exposure to tadalafil. |
| Sildenafil | Not studied. Concomitant use of sildenafil and nelfinavir may increase plasma levels of sildenafil. | Sildenafil at a starting dose not exceeding 25 mg in 48 hours. Use with increased monitoring for adverse events associated with increased exposure to sildenafil. |
| Vardenafil | Not studied. Concomitant use of vardenafil and nelfinavir may increase plasma levels of vardenafil | Use with increased monitoring for adverse events associated with increased exposure to vardenafil. |
| ***Antigout preparation*** | | |
| Colchicine | Not studied. Concomitant use of colchicine and nelfinavir may increase plasma levels of colchicine | A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with nelfinavir is required. Patients with renal or hepatic impairment should not be given colchicine with nelfinavir (see section 4.4). |

| Medicinal product by therapeutic areas (dose of nelfinavir used in study) | Effects on drug levels % Change | Recommendations concerning coadministration |
|---|---|---|
| ***Herbal Products*** | | |
| *St. John's wort* | 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 nelfinavir. 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 nelfinavir may need adjusting. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment. |

↑ Indicates increase, ↓ indicates decrease, ↔ indicates minimal change (< 10 %)

## 4.6 Fertility, pregnancy and lactation

No treatment-related adverse reactions 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

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 following adverse events with an at least possible relationship to nelfinavir (i.e. adverse reactions) were reported most frequently: diarrhoea, nausea, and rash. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions from clinical trials with nelfinavir

Adverse reactions in clinical studies are summarised in Table 2. The list also includes marked laboratory abnormalities that have been observed with nelfinavir (at 48 weeks).

**Table 2: Incidences of Adverse Reactions and marked laboratory abnormalities from the phase II and phase III studies. (Very common (≥ 10 %); common (≥ 1 % and < 10 %)**

| ***Body System*** **Frequency of Reaction** | Adverse Reactions |
|---|---|
| Grades 3&4 | All Grades |
| *Gastrointestinal disorders* | |
| Very common | Diarrhoea |
| Common | Nausea, flatulence, |
| *Skin and subcutaneous tissue disorders* | |
| Common | Rash |
| *Investigations* | |
| Common | Increased alanine aminotransferase, increased aspartate aminotransferase, neutropenia, blood creatinine phosphokinase increased, neutrophil count decreased |

Children and neonates:
A total of approximately 400 patients received nelfinavir in paediatric treatment trials (Studies 524, 556, PACTG 377/725, and PENTA-7) for up to 96 weeks. The adverse reaction profile seen during paediatric clinical trials was similar to that for adults. Diarrhoea was the most commonly reported adverse event in children. Neutropenia/leukopenia was the most frequently observed laboratory abnormality. During these trials less than 13% of patients in total discontinued treatment due to adverse events.

Post-marketing experience with nelfinavir
Serious and non-serious adverse reactions from post-marketing spontaneous reports (where nelfinavir was taken as the sole protease inhibitor or in combination with other antiretroviral therapy), not mentioned previously in section 4.8, for which a causal relationship to nelfinavir cannot be excluded, are summarised below. As these data come from the spontaneous reporting system, the frequency of the adverse reactions is not confirmed.

*Immune system disorders:*
*Uncommon (≥ 0.1 % - ≤ 1 %)*: hypersensitivity including bronchospasm, pyrexia, pruritus, facial oedema and rash maculo-papular or dermatitis bullous.

*Metabolism and nutrition disorders:*
*Uncommon - rare (≥ 0.01 % - ≤ 1 %)*: Combination antiretroviral therapy has been associated with redistribution of body fat (Lipodystrophy acquired) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (lypohypertrophy buffalo hump).
*Rare (≥ 0.01 % - ≤ 0.1 %)*: new onset diabetes mellitus, or exacerbation of existing diabetes mellitus.

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

*Hepatobiliary disorders:*
*Rare (≥ 0.01 % - ≤ 0.1 %)*: hepatitis, hepatic enzymes increased and jaundice when nelfinavir is used in combination with other antiretroviral agents.

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

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

*Skin and subcutaneous tissue disorders:*
*Very rare (≤ 0.01 %), including isolated reports*: Erythema multiforme.

*Paediatric population*:
Additional adverse reactions have been reported in the post-marketing experience and are listed below. As these data come from the spontaneous reporting system, the frequency of the adverse reactions is unknown: hypertriglyceridemia, anaemia, blood lactic acid increased, and pneumonia.

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as blood triglycerides increased, blood cholesterol increased, insulin resistance, hyperglycaemia and hyperlactaemia. The frequency of this is unknown (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. The frequency of this is unknown (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: direct acting antivirals, ATC code: J05AE04

*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.

*Resistance:* Viral escape from nelfinavir can occur via viral protease mutations at amino acid positions 30, 88 and 90.

*In vitro:* 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.

*Cross resistance in vitro:* 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*.

*In vivo:* 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.

*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 metabolised 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 optimise antiviral efficacy. Plasma levels of nelfinavir, which is metabolised predominantly by CYP2C19 and only partially by CYP3A4, are not greatly increased by co-administration with ritonavir, and therefore nelfinavir does not require co-administration with low-dose ritonavir . 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 (750 mg 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 $log^{10}$ copies/ml and 5.01 $log^{10}$ copies/ml in the nelfinavir and lopinavir/ritonavir treatment groups respectively. Median baseline CD4+ cell count was 232 cells/$mm^3$ 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/$mm^3$ and 207 cells/$mm^3$ 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 (1400 mg/200 mg QD n=322) compared to nelfinavir (1250 mg 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 $log^{10}$ copies/ml in both treatment groups. Median baseline CD4+ cell counts were 177 and 166 $x10^6$ 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/$mm^3$ and 203 cells/$mm^3$ 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 $IC_{95}$ 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 Oral Absorption*
Food increases nelfinavir exposure and decreases nelfinavir pharmacokinetic variability relative to the fasted state. In one study, healthy volunteers received a single dose of 1250 mg of VIRACEPT (5x 250 mg tablets) under fasted or fed conditions (three meals with different caloric and fat contents). In a second study, healthy volunteers received single doses of 1250 mg VIRACEPT (5 x 250 mg tablets) under fasted or fed conditions (two meals with different fat content). The results from the two studies are summarized below.

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

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

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

| Number of Kcal | % Fat | Number of Subjects | AUC fold increase | $C_{max}$ fold increase | Increase in $T_{max}$ (hr) |
|---|---|---|---|---|---|
| 500 | 20 | n=22 | 3.1 | 2.5 | 1.8 |
| 500 | 50 | n=22 | 5.1 | 3.8 | 2.1 |

Nelfinavir exposure increases with increasing calorie or fat content of meals taken with VIRACEPT.

*Distribution:* Nelfinavir in serum is extensively protein-bound (≥ 98 %). The estimated volumes of distribution in both animals and humans is 2-7 l/kg which exceeded total body water and suggests extensive penetration of nelfinavir into tissues.

*Metabolism:* *In vitro* studies demonstrated that multiple cytochrome P-450 isoforms including CYP3A, CYP2C19/C9 and CYP2D6 are responsible for the 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.

*Elimination:* oral clearance estimates after single doses (24-36 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 specialpopulations:*

*Children:*
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 at a dose of approximately 25-30 mg/kg TID with food achieves steady-state plasma concentrations that are similar to those achieved in adult patients receiving 750 mg TID.

The pharmacokinetics of nelfinavir have been investigated in 5 studies in paediatric patients from birth to 13 years of age. Patients received VIRACEPT either three times daily or twice daily with food or with meals. The dosing regimens and associated $AUC_{24}$ values are summarized below.

**Summary of Steady-state AUC24 of nelfinavir in Paediatric Studies**

| Protocol No. | Dosing Regimen[1] | N[2] | Age | Food taken with Viracept | AUC24 (mg.hr/L) Arithmetic mean ± SD |
|---|---|---|---|---|---|
| **AG1343-524** | **20 (19-28) mg/kg TID** | **14** | **2-13 years** | Powder with milk, formula, pudding, or water, as part of a light meal or tablet taken with a light meal | **56.1 ± 29.8** |
| **PACTG-725** | **55 (48-60) mg/kg BID** | **6** | **3-11 years** | With food | **101.3 ± 56.1** |
| **PENTA 7** | **40 (34-43) mg/kg TID** | **4** | **2-9 months** | With milk | **33.8 ± 8.9** |
| **PENTA 7** | **75 (55-83) mg/kg BID** | **12** | **2-9 months** | With milk | **37.2 ± 19.2** |
| **PACTG-353** | **40 (14-56) mg/kg BID** | **10** | **6 weeks** | Powder with water, milk, formula, soy formula, soy milk, or dietary supplements | **44.1 ± 27.4** |
| | | | **1 week** | | **45.8 ± 32.1** |

[1] Protocol specified dose (actual dose range)
[2] N: number of subjects with evaluable pharmacokinetic results
$C_{trough}$ values are not presented in the table because they are not available from all studies

Pharmacokinetic data are also available for 86 patients (age 2 to 12 years) who received VIRACEPT 25-35 mg/kg TID in Study AG1343-556. The pharmacokinetic data from Study AG1343-556 were more variable than data from other studies conducted in the paediatric population; the 95% confidence interval for $AUC_{24}$ was 9 to 121 mg.hr/L.

Overall, use of VIRACEPT in the paediatric population is associated with highly variable drug exposure. The reason for this high variability is not known but may be due to inconsistent food intake in paediatric patients.

*Elderly:*
There are no data available in the elderly.

*Hepatic impairment:*
The multiple dose pharmacokinetics of nelfinavir have not been studied in HIV-positive patients with hepatic insufficiency.
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 group (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.
A second study evaluated the steady state pharmacokinetics of nelfinavir (1250 mg twice daily for 2 weeks) in adult HIV-seronegative subjects with mild (Child-Pugh A; n=6) or moderate (Child-Pugh B; n=6) hepatic impairment. Compared to control subjects with normal hepatic function, the AUC and $C_{max}$ of nelfinavir were not significantly different in subjects with mild impairment but were increased by 62% and 22%, respectively in subjects with moderate hepatic impairment.

## 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 Special precautions for disposal and other handling

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

Date of first authorisation: 22 January 1998
Date of latest renewal: 23 January 2008

## 10. DATE OF REVISION OF THE TEXT

# ANNEX II

**A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OF THE MARKETING AUTHORISATION**

## A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

VIRACEPT 50 mg/g oral powder

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

VIRACEPT 250 mg film-coated tablets:

Roche Pharma AG
Emil-Barell-Strasse 1
D-79639 Grenzach-Whylen
Germany

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.)

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1, dated 30 July 2007 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

PSUR: The Marketing Authorisation Holder will submit yearly PSURs.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

**A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON TEXT**

**1. NAME OF THE MEDICINAL PRODUCT**

Viracept 50 mg/g oral powder
Nelfinavir

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

The bottle contains 144 g of oral powder. Each gram of oral powder contains nelfinavir mesilate corresponding to 50 mg of nelfinavir.

**3. LIST OF EXCIPIENTS**

Also contains sweetener aspartame (E951), sucrose palmitate, potassium, natural and artificial flavourings and other constituents. See the Package Leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

**144 g Oral powder**

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

Oral use
Read the package leaflet before 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**

**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. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

viracept 50 mg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**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 50 mg of nelfinavir (as mesilate).

## 3. LIST OF EXCIPIENTS

Also contains E95, sucrose palmitate, potassium.

## 4. PHARMACEUTICAL FORM AND CONTENTS

**144 g**

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

Oral use
Read the package leaflet before 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**

## 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**

'Logo'

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/97/054/001

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON 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
Read the package leaflet before 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**

**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. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

viracept 250 mg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**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 250 mg of nelfinavir (as mesilate).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

270 film-coated tablets

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

Oral use
Read the package leaflet before 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

## 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**

'Logo'

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/01/097/054/004

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON 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
Read the package leaflet before 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**

**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

## 16. INFORMATION IN BRAILLE

viracept 250 mg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**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 250 mg of nelfinavir (as mesilate).

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

300 film-coated tablets

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

Oral use
Read the package leaflet before 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**

**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**

'Logo'

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/97/054/005

**13. MANUFACTURER'S BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**B. PACKAGE LEAFLET**

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**VIRACEPT 50 mg/g oral powder**
Nelfinavir

**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 any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious or troublesome, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet:**




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

**What Viracept is**
Viracept contains a medicine called nelfinavir, which is a 'protease inhibitor'. This belongs to a group of medicines called 'anti-retrovirals'.

**What Viracept is used for**
Viracept is used with other 'anti-retroviral' medicines to:
- Work against the Human Immunodeficiency Virus (HIV). It helps to reduce the number of HIV particles in your blood.
- Increase the number of some cells in your blood that help fight infection. These are called CD4 white blood cells. They are particularly reduced in numbers when you have HIV infection. This can lead to an increased risk of many types of infections.

Viracept is not a cure for HIV infection. You may continue to get infections or other illnesses due to your HIV. Treatment with Viracept does not stop you giving HIV to others through contact with blood or sexual contact. Therefore you must keep taking appropriate precautions to avoid giving the virus to others when you are taking Viracept.

## 2. BEFORE YOU TAKE VIRACEPT

**Do not take Viracept if:**
- You are allergic to nelfinavir or to any of the other ingredients (listed in Section 6 'Further information').
- You are taking any of the medicines listed in the first part of Section 2 'Taking other medicines', 'Do not take Viracept'.

Do not take Viracept if any of the above apply to you.

**Take special care with Viracept**
Check with your doctor or pharmacist before taking Viracept if:
- You have kidney problems.
- You have high blood sugar (diabetes).
- You have a rare blood problem which runs in families called 'haemophilia'.
- You have liver disease caused by hepatitis B or C. Your doctor may wish to carry out regular blood tests.

If any of the above apply to you, or if you are not sure, talk to your doctor or pharmacist before you take Viracept.

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

**Body fat**
Combination anti-retroviral 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. Contact your doctor if you notice changes in body fat.

**Signs of previous infections**
In some patients with advanced HIV infection 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.

**Bone disease (osteonecrosis)**
Some patients taking combination anti-retroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination anti-retroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor immediately.

**Taking other medicines**
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines that you buy without a prescription and herbal medicines. This is because Viracept can affect the way some other medicines work. Also some other medicines can affect the way Viracept works.

**Do not take Viracept** and tell your doctor or pharmacist if you are taking any of the following medicines:
- Medicines made from ergot such as cabergoline, ergotamine or lisuride (for Parkinson's disease or migraine)
- Herbal preparations containing St. John's Wort (for depression or improving your mood)
- Rifampicin (for tuberculosis (TB))
- Terfenadine or astemizole (for allergy)
- Pimozide (used for mental health problems)
- Amiodarone or quinidine (for an uneven heart beat)
- Phenobarbital or carbamazepine (for fits or epilepsy)
- Triazolam or oral midazolam taken by mouth (for anxiety or to help you sleep)
- Cisapride (for heart burn or problems with your digestive system)

- Omeprazole (for ulcers in your stomach or gut)
- Alfuzosin (for benign prostatic hyperplasia (BPH))
- Sildenafil (for pulmonary arterial hypertension (PAH))
- Simvastatin or lovastatin (for lowering blood cholesterol)

Do not take Viracept and tell your doctor or pharmacist if any of these apply to you. If you are not sure, talk to your doctor or pharmacist before taking Viracept.

**Tell your doctor or pharmacist** if you are taking any of the following medicines:
- Any other medicines for HIV infection such as ritonavir, indinavir, saquinavir and delavirdine, amprenavir, efavirenz or nevirapine
- Oral contraceptives (the pill). Viracept can stop the pill from working, so you should use other contraception methods (such as condoms) while you are taking Viracept.
- Calcium channel blockers such as bepridil (for heart problems)
- Immunosuppressant medicines such as tacrolimus or ciclosporin
- Medicines that lower stomach acid such as lansoprazole
- Fluticasone (for hay fever)
- Phenytoin (for fits or epilepsy)
- Methadone (for drug dependence)
- Sildenafil (for getting or keeping an erection)
- Tadalafil (for pulmonary arterial hypertension (PAH), or for getting or keeping an erection)
- Vardenafil (for pulmonary arterial hypertension (PAH), or for getting or keeping an erection)
- Ketoconazole, itraconazole or fluconazole (for fungal infections)
- Rifabutin, erythromycin or clarithromycin (for bacterial infections)
- Midazolam given by injection or diazepam (for anxiety or to help you sleep)
- Fluoxetine, paroxetine, imipramine, amitriptyline or trazodone (for depression)
- Atorvastatinor other statins(for lowering blood cholesterol)
- Salmeterol (for asthma or chronic obstructive pulmonary disease (COPD))
- Warfarin (for lowering the chance of blood clots in your body)
- Colchicine (for gout-flares or Mediterranean fever)
- Bosentan (for pulmonary arterial hypertension (PAH)

)
If any of the above apply to you, or if you are not sure, talk to your doctor or pharmacist before you take Viracept.

**Taking Viracept with food and drink**
Take Viracept with a meal. This helps your body to get the full benefit from your medicine**.**

**Pregnancy, contraception and breast-feeding**
- Talk to your doctor before you take Viracept if you are pregnant or planning to become pregnant.
- Do not breast-feed while taking Viracept because HIV may be passed to the baby.
- Viracept can stop oral contraceptives (the pill) from working, so you should use other contraception methods (such as condoms) while you are taking Viracept.
- Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**
Viracept is not likely to affect you being able to drive or use any tools or machines.

**Important information about some of the ingredients of Viracept**
- This medicine contains sucrose, which is a type of sugar. If you have been told by your doctor that you cannot tolerate or digest some sugars (have an intolerance to some sugars), talk to your doctor before taking this medicine. Each dose contains up to 5.9 milligrams of sucrose, which should be taken into account in patients with diabetes mellitus.

- This medicine contains aspartame, which is a source of phenylalanine. This may be harmful for people with phenylketonuria.
- This medicine is essentially 'potassium-free' as it contains less than 1 mmol (39 milligrams) of potassium per dose.

If any of the above apply to you, or if you are not sure, talk to your doctor or pharmacist before you take Viracept.

## 3. HOW TO TAKE VIRACEPT

Always take Viracept exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure. The usual doses are described below. Follow the instructions carefully to get the most benefit from Viracept.

Viracept powder is for people who cannot take tablets. Viracept tablets are generally recommended for adults and older children. For younger children able to take tablets, Viracept tablets may be taken instead of the oral powder. If you want to take the tablets instead please see the Package Leaflet for Viracept 250 mg tablets.

**How to prepare Viracept**
Two measuring scoops are provided in the medicine box:
- White 1 gram (1g) scoop.
- Blue 5 gram (5g) scoop.

Measure out a level scoop of powder. You can use the handle of the second scoop to scrape off the extra powder and make your scoop level (see picture below).

- You can mix the powder with a small amount of water, milk, baby formula, soy formula, soy milk, dietary liquid supplements or pudding.
- If you mix the powder, but do not take it straight away you can store it for up to 6 hours in a refrigerator.
- Do not mix the powder with orange juice, apple sauce or other acidic liquids or foods. This may give your medicine a bitter taste.
- Do not add liquid to the powder in its original container

**Taking this medicine**
- **Take Viracept with a meal. This helps your body to get the full benefit from your medicine.**
- Take all the mixture you make each time. This will make sure that you get the right amount of your medicine.
- Take all your doses at the right time each day. This helps make your medicine work as well as it can.
- Do not stop taking this medicine without talking to your doctor first.

**How much to take**

**Adults and children older than 13 years**

Viracept powder can be taken either two or three times a day with a meal. Table 1 below shows the usual doses.

**Table 1**

| Dose to be taken by adults and children older than 13 years | | | |
|---|---|---|---|
| How often you take it | Number of scoops Blue Scoop (5 g) | White Scoop (1 g) | How much you take each time (in grams) |
| Two times a day | 5 | - | 25 g |
| Three times a day | 3 | - | 15 g |

**Children aged 3 to 13 years**

For children aged 3 to 13 years, the recommended dose of Viracept powder is based on their body weight. You will either give the medicine to your child two or three times a day with a meal.

The different ways are shown in separate tables below.

- **Table 2:** if you give the medicine **two times a day**, you will give 50-55 mg nelfinavir each time for each kg of body weight.
- **Table 3:** if you give the medicine **three times a day**, you will give 25-35 mg nelfinavir each time for each kg of body weight.

**Table 2**

| Dose to be given **two times a day** to children aged 3 to 13 | | | | | |
|---|---|---|---|---|---|
| Body weight of your child | Number of scoops Blue Scoop (5 g) | | White Scoop (1 g) | | How much to give each time (in grams) |
| 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 |

**Table 3**

| Dose to be given **three times a day** to children aged 3 to 13 | | | | | |
|---|---|---|---|---|---|
| Body weight of your child | Number of scoops Blue Scoop (5 g) | | White Scoop (1 g) | | How much to give each time (in grams) |
| 7.5 to 8.5 kg | 1 | | | | 5 g |
| 8.5 to 10.5 kg | 1 | plus | 1 | | 6 g |
| 10.5 to 12 kg | 1 | plus | 2 | | 7 g |
| 12 to 14 kg | 1 | plus | 3 | | 8 g |
| 14 to 16 kg | 2 | | | | 10 g |
| 16 to 18 kg | 2 | plus | 1 | | 11 g |
| 18 to 22 kg | 2 | plus | 3 | | 13 g |
| over 22 kg | 3 | | | | 15 g |

**If you take more Viracept than you should**
If you take more Viracept than you should, talk to a doctor or pharmacist or go to a hospital straight away. Take the medicine pack with you. Among other things, very large doses of Viracept might cause problems with your heart rhythm.

**If you forget to take Viracept**
If you forget to take a dose, take it as soon as you remember it.
- However if it is nearly time for your next dose, skip the missed dose.
- Do not take a double dose to make up for a forgotten dose.

**If you stop taking Viracept**
Do not stop taking this medicine without talking to your doctor first. Take all your doses at the right time each day. This helps make your medicine work as well as it can.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Viracept can have side effects, although not everybody gets them. The following side effects may happen with this medicine.

**Contact your doctor straight away if you notice any of the following side effects:**
- **Allergic reactions.** The signs may include difficulty in breathing, fever, itching, swelling of the face and skin rashes that can sometimes form blisters.
- **Increased bleeding if you have haemophilia.** If you have haemophilia type A or B, in rare cases your bleeding may increase.
- **Bone disease (osteonecrosis).** The signs may include joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. Some patients taking combination anti-retroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone).
- **Infection.** In some patients with advanced HIV infection 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 of the above, contact your doctor straight away.

**Other possible side effects, where you should talk to your doctor**
If you get any of the side effects on this list, or if you notice any side effects not listed in this leaflet, please tell your doctor.

**Very common (affect more than 1 in 10 people):**
- Diarrhoea.

**Common (affect less than 1 in 10 people):**
- Rash.
- Wind.
- Feeling sick.
- Low numbers of a type of white blood cell that fights infections (neutrophils).
- Abnormal results from blood tests that measure how well your liver or muscles are working.

**Uncommon (affect less than 1 in 100 people):**
- Being sick.
- Pancreatitis. The signs include severe pains in your stomach that spread to your back.
- Combination anti-retroviral 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.

**Rare (affect less than 1 in 1000 people):**
- Yellow skin or eyes. This could be a sign of a liver problem such as hepatitis or jaundice.
- A severe form of rash (erythema multiforme).
- Swelling of your belly (abdomen).
- High blood sugar (diabetes) or diabetes get worse.
- There have been rare reports of muscle pain, tenderness or weakness, particularly with combination anti-retroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions these muscle problems have been serious causing muscle degeneration (rhabdomyolysis).

**Other side effects which have also been reported:**
- Combination anti-retroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin.
- Low numbers of red blood cells (anaemia).
- Lung disease (pneumonia).
- Cases of diabetes mellitus or increased blood sugar levels have been reported in patients receiving this treatment or another protease inhibitor.

**Side effects in children**
About 400 children (aged from 0 to 13 years) received Viracept in clinical trials. The side effects seen in children are similar to those seen in adults. The most commonly reported side effect in children is diarrhoea. The side effects only rarely resulted into having to stop taking Viracept.

## 5. HOW TO STORE VIRACEPT

- Keep out of the reach and sight of children.
- Do not use after the expiry date stated on the label and carton.
- Do not store above 30°C.
- Store in the original container.
- The mixed solution can be stored for up to 6 hours in a refrigerator.

## 6. FURTHER INFORMATION

**What Viracept contains**

- The active substance in Viracept is nelfinavir. Each gram of oral powder contains an amount of nelfinavir mesilate that makes 50 mg of nelfinavir.
- The other ingredients are microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hydroxypropyl methylcellulose, aspartame (E951), sucrose palmitate, and natural and artificial flavour.

**What Viracept looks like and contents of the pack**

Viracept 50 mg/g oral powder is a white to off-white powder. It is supplied in plastic bottles with plastic child resistant lids. Each bottle contains 144 grams of powder and is supplied with a 1 gram scoop (white) and a 5 gram scoop (blue).

**Marketing Authorisation Holder and Manufacturer**

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

**Manufacturer**

Roche Pharma AG
Emil-Barell-Str. 1
D-79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
N.V. Roche S.A.
Tél/Tel: +32 (0) 2 525 82 11

**България**
Рош България ЕООД
Тел: +359 2 818 44 44

**Česká republika**
Roche s. r. o.
Tel: +420 - 2 20382111

**Danmark**
Roche a/s
Tlf: +45 - 36 39 99 99

**Deutschland**
Roche Pharma AG
Tel: +49 (0) 7624 140

**Luxembourg/Luxemburg**
(Voir/siehe Belgique/Belgien)

**Magyarország**
Roche (Magyarország) Kft.
Tel: +36 - 23 446 800

**Malta**
(See United Kingdom)

**Nederland**
Roche Nederland B.V.
Tel: +31 (0) 348 438050

**Norge**
Roche Norge AS
Tlf: +47 - 22 78 90 00

**Eesti**
Roche Eesti OÜ
Tel: + 372 - 6 177 380

**Ελλάδα**
Roche (Hellas) A.E.
Τηλ: +30 210 61 66 100

**España**
Roche Farma S.A.
Tel: +34 - 91 324 81 00

**France**
Roche
Tél: +33 (0) 1 47 61 40 00

**Ireland**
Roche Products (Ireland) Ltd.
Tel: +353 (0) 1 469 0700

**Ísland**
Roche a/s
c/o Icepharma hf
Sími: +354 540 8000

**Italia**
Roche S.p.A.
Tel: +39 - 039 2471

**Κύπρος**
Γ.Α.Σταμάτης & Σια Λτδ.
Τηλ: +357 – 22 25 72 00

**Latvija**
Roche Latvija SIA
Tel: +371 – 6 7039831

**Lietuva**
UAB "Roche Lietuva"
Tel: +370 5 2546799

**Österreich**
Roche Austria GmbH
Tel: +43 (0) 1 27739

**Polska**
Roche Polska Sp.z o.o.
Tel: +48 - 22 345 18 88

**Portugal**
Roche Farmacêutica Química, Lda
Tel: +351 - 21 425 70 00

**România**
Roche România S.R.L.
Tel: +40 21 206 47 01

**Slovenija**
Roche farmacevtska družba d.o.o.
Tel: +386 - 1 360 26 00

**Slovenská republika**
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

**Suomi/Finland**
Roche Oy
Puh/Tel: +358 (0) 10 554 500

**Sverige**
Roche AB
Tel: +46 (0) 8 726 1200

**United Kingdom**
Roche Products Ltd.
Tel: +44 (0) 1707 366000



**This leaflet was last approved in** {MM/YYYY}**.**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/. There are also links to other websites about rare diseases and treatments.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**VIRACEPT 250 mg film-coated tablets**
Nelfinavir

**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 any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious or troublesome, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet:**




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

**What Viracept is**
Viracept contains a medicine called nelfinavir, which is a 'protease inhibitor'. This belongs to a group of medicines called 'anti-retrovirals'.

**What Viracept is used for**
Viracept is used with other 'anti-retroviral' medicines to:
- Work against the Human Immunodeficiency Virus (HIV). It helps to reduce the number of HIV particles in your blood.
- Increase the number of some cells in your blood that help fight infection. These are called CD4 white blood cells. They are particularly reduced in numbers when you have HIV infection. This can lead to an increased risk of many types of infections.

Viracept is not a cure for HIV infection. You may continue to get infections or other illnesses due to your HIV. Treatment with Viracept does not stop you giving HIV to others through contact with blood or sexual contact. Therefore you must keep taking appropriate precautions to avoid giving the virus to others when you are taking Viracept.

## 2. BEFORE YOU TAKE VIRACEPT

**Do not take Viracept if:**
- You are allergic to nelfinavir or to any of the other ingredients (listed in Section 6 'Further information').
- You are taking any of the medicines listed in the first part of Section 2 'Taking other medicines', 'Do not take Viracept'.

Do not take Viracept if any of the above apply to you.

**Take special care with Viracept**
Check with your doctor or pharmacist before taking Viracept if:
- You have kidney problems.
- You have high blood sugar (diabetes).
- You have a rare blood problem which runs in families called 'haemophilia'.
- You have liver disease caused by hepatitis B or C. Your doctor may wish to carry out regular blood tests.

If any of the above apply to you, or if you are not sure, talk to your doctor or pharmacist before you take Viracept.

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

**Body fat**
Combination anti-retroviral 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. Contact your doctor if you notice changes in body fat.

**Signs of previous infections**
In some patients with advanced HIV infection 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.

**Bone disease (osteonecrosis)**
Some patients taking combination anti-retroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination anti-retroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor immediately.

**Taking other medicines**
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines that you buy without a prescription and herbal medicines. This is because Viracept can affect the way some other medicines work. Also some other medicines can affect the way Viracept works.

**Do not take Viracept** and tell your doctor or pharmacist if you are taking any of the following medicines:
- Medicines made from ergot such as cabergoline, ergotamine or lisuride (for Parkinson's disease or migraine)
- Herbal preparations containing St. John's Wort (for depression or improving your mood)
- Rifampicin (for tuberculosis (TB))
- Terfenadine or astemizole (for allergy)
- Pimozide (used for mental health problems)
- Amiodarone or quinidine (for an uneven heart beat)
- Phenobarbital or carbamazepine (for fits or epilepsy)
- Triazolam or oral midazolam taken by mouth (for anxiety or to help you sleep)
- Cisapride (for heart burn or problems with your digestive system)

- Omeprazole (for ulcers in your stomach or gut)
- Alfuzosin (for benign prostatic hyperplasia (BPH))
- Sildenafil (for pulmonary arterial hypertension (PAH))
- Simvastatin or lovastatin (for lowering blood cholesterol)

Do not take Viracept and tell your doctor or pharmacist if any of these apply to you. If you are not sure, talk to your doctor or pharmacist before taking Viracept.

**Tell your doctor or pharmacist** if you are taking any of the following medicines:
- Any other medicines for HIV infection such as ritonavir, indinavir, saquinavir and delavirdine, amprenavir, efavirenz or nevirapine
- Oral contraceptives (the pill). Viracept can stop the pill from working, so you should use other contraception methods (such as condoms) while you are taking Viracept.
- Calcium channel blockers such as bepridil (for heart problems)
- Immunosuppressant medicines such as tacrolimus or ciclosporin
- Medicines that lower stomach acid such as lansoprazole
- Fluticasone (for hay fever)
- Phenytoin (for fits or epilepsy)
- Methadone (for drug dependence)
- Sildenafil (for getting or keeping an erection)
- Tadalafil (for pulmonary arterial hypertension (PAH), or for getting or keeping an erection)
- Vardenafil (for pulmonary arterial hypertension (PAH), or for getting or keeping an erection)
- Ketoconazole, itraconazole or fluconazole (for fungal infections)
- Rifabutin, erythromycin or clarithromycin (for bacterial infections)
- Midazolam given by injection or diazepam (for anxiety or to help you sleep)
- Fluoxetine, paroxetine, imipramine, amitriptyline or trazodone (for depression)
- Atorvastatin or other statins (for lowering blood cholesterol)
- Salmeterol (for asthma or chronic obstructive pulmonary disease (COPD)
- Warfarin (for lowering the chance of blood clots in your body)
- Colchicine (for gout-flares or Mediterranean fever)
- Bosentan (for pulmonary arterial hypertension (PAH))

If any of the above apply to you, or if you are not sure, talk to your doctor or pharmacist before you take Viracept.

**Taking Viracept with food and drink**
Take Viracept with a meal. This helps your body to get the full benefit from your medicine**.**

**Pregnancy, contraception and breast-feeding**
- Talk to your doctor before you take Viracept if you are pregnant or planning to become pregnant.
- Do not breast-feed while taking Viracept because HIV may be passed to the baby.
- Viracept can stop oral contraceptives (the pill) from working, so you should use other contraception methods (such as condoms) while you are taking Viracept.
- Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**
Viracept is not likely to affect you being able to drive or use any tools or machines.

## 3. HOW TO TAKE VIRACEPT

Always take Viracept exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure. The usual doses are described below. Follow the instructions carefully to get the most benefit from Viracept.

The Viracept tablets must be taken by mouth. They should be swallowed whole and taken with a meal. For adults or children unable to take tablets, Viracept tablets may be put into water and taken as follows:

- Put the tablets in a half cup of water and stir with a spoon.
- Once the tablet is dispersed, mix the cloudy bluish liquid thoroughly and take immediately.
- Rinse the glass with a half cup of water and swallow the rinse to ensure all of the dose is taken.

Acidic food or juice (such as orange juice, apple juice or apple sauce) are not recommended to be taken with Viracept because together they may have a bitter taste.

Alternatively, Viracept 50 mg/g oral powder may be taken instead. If you want to take the powder instead please see the Package Leaflet for Viracept 50 mg/g oral powder.

**Taking this medicine**

- **Take Viracept with a meal. This helps your body to get the full benefit from your medicine.**
- Take all your doses at the right time each day. This helps make your medicine work as well as it can.
- Do not stop taking this medicine without talking to your doctor first.

**How much to take**

**Adults and children older than 13 years**

Viracept tablets can be taken either two or three times a day with a meal. Table 1 below shows the usual doses.

**Table 1**

| Dose to be taken by adults and children older than 13 years | | |
|---|---|---|
| How often you take it | Number of tablets | How much you take each time (in milligrams) |
| Two times a day | 5 | 1250 mg |
| Three times a day | 3 | 750 mg |

**Children aged 3 to 13 years**

For children aged 3 to 13 years, the recommended dose of Viracept tablets is based on their body weight. Carefully monitor the increase in weight of your child to ensure the appropriate total daily dose is taken.

- When your child weighs 18 kg or more, you may provide the tablets either two or three times a day.
- When your child weighs 18 kg or less, you must provide the tablets three times a day.

The different ways are shown in separate tables below.

- **Table 2:** if you give the medicine **two times a day** (for children who weigh 18 kg or more), you will give 50-55 mg nelfinavir each time for each kg of body weight.

- **Table 3:** if you give the medicine **three times a day**, you will give 25-35 mg nelfinavir each time for each kg of body weight, **except for children who weigh from 10.5 to 12 kg, from 12 to 14 kg and from 18 to 22 kg**. These children will be given a different number of tablets with each meal. The table also shows the recommended total number of Viracept tablets that children will be given each day based on their weight.

**Table 2**

| Dose to be given **two times a day** to children aged 3 to 13 who weigh more than 18 kg | |
|---|---|
| Body weight of your child | Number of tablets |
| 18 to 22 kg | 4 |
| over 22 kg | 5 |

**Table 3**

| Dose to be given **three times a day** to children aged 3 to 13 who weigh more than 7.5 kg | | | | |
|---|---|---|---|---|
| Body weight of your child | Recommended number of tablets given at each meal | | | **Total number of tablets per day** |
| | Number of tablets at breakfast | Number of tablets at lunch | Number of tablets at dinner | |
| 7.5 to 8.5 kg | 1 | 1 | 1 | **3** |
| 8.5 to 10.5 kg | 1 | 1 | 1 | **3** |
| **10.5 to 12 kg*** | **2** | **1** | **1** | **4** |
| **12 to 14 kg*** | **2** | **1** | **2** | **5** |
| 14 to 16 kg | 2 | 2 | 2 | **6** |
| 16 to 18 kg | 2 | 2 | 2 | **6** |
| **18 to 22 kg*** | **3** | **2** | **2** | **7** |
| over 22 kg | 3 | 3 | 3 | **9** |

*** Children with these weights will be given an uneven number of tablets during the day. Your doctor should monitor the number of HIV particles and the number of CD4 white blood cells in your child's blood to assure the medicine works as well as it can.**

It is very important that the correct number of tablets be taken at each dose. You should monitor your child to assure that the recommended number of tablets are taken at each dose with meals, for each weight band.

**If you take more Viracept than you should**
If you take more Viracept than you should, talk to a doctor or pharmacist or go to a hospital straight away. Take the medicine pack with you. Among other things, very large doses of Viracept might cause problems with your heart rhythm.

**If you forget to take Viracept**
If you forget to take a dose, take it as soon as you remember it.
- However if it is nearly time for your next dose, skip the missed dose.
- Do not take a double dose to make up for a forgotten dose.

**If you stop taking Viracept**
Do not stop taking this medicine without talking to your doctor first. Take all your doses at the right time each day. This helps make your medicine work as well as it can.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Viracept can have side effects, although not everybody gets them. The following side effects may happen with this medicine.

**Contact your doctor straight away if you notice any of the following side effects:**

- **Allergic reactions.** The signs may include difficulty in breathing, fever, itching, swelling of the face and skin rashes that can sometimes form blisters.
- **Increased bleeding if you have haemophilia.** If you have haemophilia type A or B, in rare cases your bleeding may increase.
- **Bone disease (osteonecrosis).** The signs may include joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. Some patients taking combination anti-retroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone).
- **Infection.** In some patients with advanced HIV infection 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 of the above, contact your doctor straight away.

**Other possible side effects, where you should talk to your doctor**
If you get any of the side effects on this list, or if you notice any side effects not listed in this leaflet, please tell your doctor.

**Very common (affect more than 1 in 10 people):**
- Diarrhoea.

**Common (affect less than 1 in 10 people):**
- Rash.
- Wind.
- Feeling sick.
- Low numbers of a type of white blood cell that fights infections (neutrophils).
- Abnormal results from blood tests that measure how well your liver or muscles are working.

**Uncommon (affect less than 1 in 100 people):**
- Being sick.
- Pancreatitis. The signs include severe pains in your stomach that spread to your back.
- Combination anti-retroviral 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.

**Rare (affect less than 1 in 1000 people):**
- Yellow skin or eyes. This could be a sign of a liver problem such as hepatitis or jaundice.
- A severe form of rash (erythema multiforme).
- Swelling of your belly (abdomen).
- High blood sugar (diabetes) or diabetes get worse.
- There have been rare reports of muscle pain, tenderness or weakness, particularly with combination anti-retroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions these muscle problems have been serious causing muscle degeneration (rhabdomyolysis).

**Other side effects which have also been reported:**

- Combination anti-retroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin.
- Low numbers of red blood cells (anaemia).
- Lung disease (pneumonia).
- Cases of diabetes mellitus or increased blood sugar levels have been reported in patients receiving this treatment or another protease inhibitor.

**Side effects in children**

About 400 children (aged from 0 to 13 years) received Viracept in clinical trials. The side effects seen in children are similar to those seen in adults. The most commonly reported side effect in children is diarrhoea. The side effects only rarely resulted into having to stop taking Viracept.

## 5. HOW TO STORE VIRACEPT

- Keep out of the reach and sight of children.
- Do not use after the expiry date stated on the label and carton.
- Do not store above 30°C.
- Store in the original container.

## 6. FURTHER INFORMATION

**What Viracept contains**

- The active substance in Viracept is nelfinavir. Each tablet contains 250 mg of nelfinavir.
- The other ingredients are calcium silicate, crospovidone, magnesium stearate, indigo carmine (E132), as powder, hypromellose and glyceryl triacetate.

**What Viracept looks like and contents of the pack**

Viracept film-coated tablets is supplied in plastic bottles with plastic child resistant lid. Each bottle contains either 270 or 300 tablets. Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

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

**Manufacturer**

Roche Pharma AG
Emil-Barell-Str. 1
D-79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
N.V. Roche S.A.
Tél/Tel: +32 (0) 2 525 82 11

**България**
Рош България ЕООД
Тел: +359 2 818 44 44

**Česká republika**
Roche s. r. o.
Tel: +420 - 2 20382111

**Danmark**
Roche a/s
Tlf: +45 - 36 39 99 99

**Deutschland**
Roche Pharma AG
Tel: +49 (0) 7624 140

**Eesti**
Roche Eesti OÜ
Tel: + 372 - 6 177 380

**Ελλάδα**
Roche (Hellas) A.E.
Τηλ: +30 210 61 66 100

**España**
Roche Farma S.A.
Tel: +34 - 91 324 81 00

**France**
Roche
Tél: +33 (0) 1 47 61 40 00

**Ireland**
Roche Products (Ireland) Ltd.
Tel: +353 (0) 1 469 0700

**Ísland**
Roche a/s
c/o Icepharma hf
Sími: +354 540 8000

**Italia**
Roche S.p.A.
Tel: +39 - 039 2471

**Κύπρος**
Γ.Α.Σταμάτης & Σια Λτδ.
Τηλ: +357 – 22 25 72 00

**Luxembourg/Luxemburg**
(Voir/siehe Belgique/Belgien)

**Magyarország**
Roche (Magyarország) Kft.
Tel: +36 - 23 446 800

**Malta**
(See United Kingdom)

**Nederland**
Roche Nederland B.V.
Tel: +31 (0) 348 438050

**Norge**
Roche Norge AS
Tlf: +47 - 22 78 90 00

**Österreich**
Roche Austria GmbH
Tel: +43 (0) 1 27739

**Polska**
Roche Polska Sp.z o.o.
Tel: +48 - 22 345 18 88

**Portugal**
Roche Farmacêutica Química, Lda
Tel: +351 - 21 425 70 00

**România**
Roche România S.R.L.
Tel: +40 21 206 47 01

**Slovenija**
Roche farmacevtska družba d.o.o.
Tel: +386 - 1 360 26 00

**Slovenská republika**
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

**Suomi/Finland**
Roche Oy
Puh/Tel: +358 (0) 10 554 500

**Sverige**
Roche AB
Tel: +46 (0) 8 726 1200

**Latvija**
Roche Latvija SIA
Tel: +371 - 6 7039831

**Lietuva**
UAB “Roche Lietuva”
Tel: +370 5 2546799

**United Kingdom**
Roche Products Ltd.
Tel: +44 (0) 1707 366000

**This leaflet was last approved in** {MM/YYYY}**.**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/. There are also links to other websites about rare diseases and treatments.