1. NAME OF THE MEDICINAL PRODUCT

VIRACEPT 250 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Refer to Section 5.1 Pharmacodynamic properties.

4.2 Posology and method of administration

VIRACEPT tablets are administered orally and should be ingested with food.

Patients older than 13 years: the recommended dosage of VIRACEPT tablets is 1250 mg (five 250 mg tablets) twice a day (BID) or 750 mg (three 250 mg tablets) three times a day (TID) by mouth.

The efficacy of the BID regimen has been evaluated versus the TID regimen primarily in patients naïve to protease inhibitors (see section 5.1, pharmacodynamic properties).

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

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

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

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

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

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

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

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

4.3 Contraindications

Hypersensitivity to nelfinavir or to any of the excipients.

Nelfinavir is contraindicated in breast-feeding women.

VIRACEPT should not be administered concurrently with medicinal products with narrow therapeutic windows and which are substrates of CYP3A4. Co-administration may result in competitive inhibition of the metabolism of these medicinal products and create the potential for serious and/or life-threatening adverse events such as cardiac arrhythmias (e.g., terfenadine, astemizole, cisapride, amiodarone, quinidine, pimozide), prolonged sedation or respiratory depression (e.g., triazolam, midazolam), or other events (e.g., ergot derivatives).

VIRACEPT must not be given with rifampicin. Rifampicin decreases nelfinavir plasma AUC by 82 %.

See also 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 4.5 Interactions with other medicinal products and other forms of interaction).

4.4 Special warnings and special precautions for use

Caution should be used when administering VIRACEPT to patients with impaired renal or hepatic function (see section 4.2).

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

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

The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A4 for metabolism, thus concomitant use of VIRACEPT with simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. Caution must also be exercised if VIRACEPT is used concurrently with atorvastatin, which is metabolised to a lesser extent by

CYP3A4. In this situation a reduced dose of atorvastatin should be considered. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5 Interaction with other medicinal products and other forms of interaction).

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

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

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

Combination antiretroviral therapy, including regimens containing a protease inhibitor, is associated with redistribution of body fat in some patients. Protease inhibitors are also associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance and hyperglycaemia. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to measurement of serum lipids and blood glucose. The mechanisms of these events and long-term consequences, such as an increased risk of cardiovascular disease, are currently unknown.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Nelfinavir is metabolised in part via the cytochrome P450 3A system (CYP3A). Caution should be used when co-administering medicinal products that induce CYP3A or potentially toxic medicinal products which are themselves metabolised by CYP3A. Based on *in vitro* data, nelfinavir is unlikely to inhibit other cytochrome P450 isoforms at concentrations in the therapeutic range.

Other antiretrovirals:

Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs):

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

Other Protease Inhibitors (PIs)

Ritonavir: administration of a single 750 mg dose of nelfinavir following 3 doses of ritonavir 500 mg BID resulted in a 152 % increase in nelfinavir plasma area under the plasma concentration-time curve (AUC) and a 156 % increase in the elimination half-life of nelfinavir. Administration of a single 500 mg dose of ritonavir following six doses of nelfinavir 750 mg TID resulted in minimal increase (8 %) in ritonavir plasma AUC. The safety of this combination has not been established.

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

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

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

Non-nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs):

Efavirenz: Co-administration of efavirenz with nelfinavir increased nelfinavir AUC by 20 % with no change in efavirenz AUC. A dose adjustment is not needed when efavirenz is administered with VIRACEPT.

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

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

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

Co-administration of nelfinavir 750 mg TID and rifabutin 300 mg once a day results in a 32 % decrease in nelfinavir plasma AUC and a 207 % increase in rifabutin plasma AUC (see also Section 4.4). Co-administration of nelfinavir 750 mg TID with half the standard dose of rifabutin 150 mg once a day resulted in a 32% decrease in nelfinavir plasma AUC and an 83% increase in rifabutin plasma AUC. Dosage reduction of rifabutin to 150 mg once a day is necessary when nelfinavir 750 mg TID and rifabutin are co-administered.

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

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

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

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

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

Other potential interactions: Nelfinavir increases terfenadine plasma concentrations; therefore, VIRACEPT should not be administered concurrently with terfenadine because of the potential for serious and/or life-threatening cardiac arrhythmias. Because similar interactions are likely with astemizole and cisapride, VIRACEPT should also not be administered concurrently with these drugs. Although specific studies have not been done, potent sedatives metabolised by CYP3A, such as triazolam or midazolam, should not be co-administered with VIRACEPT due to the potential for prolonged sedation. For other compounds that are substrates for CYP3A (e.g., calcium channel blockers, including bepridil, ergot derivatives including ergotamine and dihydroergotamine, immunosuppressants including tacrolimus and cyclosporin, sildenafil and pimozide) plasma concentrations may be elevated when co-administered with VIRACEPT; therefore, patients should be monitored for toxicities associated with such medicinal products.

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

4.6 Pregnancy and lactation

No treatment-related adverse effects were seen in animal reproductive toxicity studies in rats at doses providing systemic exposure comparable to that observed with the clinical dose. Clinical experience

in pregnant women is lacking. Until additional data become available, VIRACEPT should be given during pregnancy only after special consideration.

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 influence on the ability to drive and use machines.

4.8 Undesirable effects

The safety of VIRACEPT 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. Over 4000 patients ≥ 13 years in the expanded access programmes received nelfinavir at a dose of 750 mg TID. The majority of adverse events were of mild intensity. The most frequently reported adverse event among patients receiving VIRACEPT at the recommended doses was diarrhoea.

Across the two phase III, double-blind studies adverse reactions of moderate to severe intensity reported by investigators as at least possibly related to VIRACEPT or of unknown relationship in ≥ 2 % of patients treated with the 750 mg TID dose of nelfinavir (n = 200) in combination with nucleoside analogues (for 24 weeks) included the following undesirable effects: diarrhoea (25.9 %), flatulence (2.5 %), nausea (4.5 %), and rash (3.0 %). Safety data up to 48 weeks is available from 554 patients in the study comparing 1250 mg nelfinavir BID (n=344) versus 750 mg nelfinavir TID (n=210), each in combination with lamivudine and stavudine. The incidence of adverse reactions of moderate to severe intensity reported by investigators as at least possibly related to VIRACEPT or of unknown relationship in ≥ 2 % of patients treated was similar for the BID and TID arms: diarrhoea (21.2 % versus 18.2 %), nausea (2.9 % versus 3.3 %) and rash (1.7 % versus 1.4 %).

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

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

Combination antiretroviral therapy, including regimens containing a protease inhibitor, is associated with redistribution of body fat in some patients, including loss of peripheral subcutaneous fat, increased intra-abdominal fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump). Protease inhibitors are also associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance and hyperglycaemia.

The following additional adverse reactions have been reported in the post-marketing experience: increased spontaneous bleeding in patients with haemophilia; new onset diabetes mellitus, or exacerbation of existing diabetes mellitus; abdominal pain, abdominal distension and vomiting; pancreatitis/increased amylase; hypersensitivity reactions including bronchospasm, fever, pruritus,

facial oedema and rash (maculopapular or bullous); hepatitis, abnormal liver enzymes and jaundice when nelfinavir is used in combination with other antiretroviral agents..

Increased CPK, myalgia, myositis and rarely, rhabdomyolysis have been reported with protease inhibitors, particularly in combination with nucleoside analogues.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiviral agent, ATC code: J05A E04

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

Antiviral activity *in vitro*: the antiviral activity of nelfinavir *in vitro* has been demonstrated in both HIV acute and chronic infections in lymphoblastoid cell lines, peripheral blood lymphocytes and monocytes/macrophages. Nelfinavir was found to be active against a broad range of laboratory strains and clinical isolates of HIV-1 and the HIV-2 strain ROD. The EC_{95} (95 % effective concentration) of nelfinavir ranged from 7 to 111 nM (mean of 58 nM). Nelfinavir demonstrated additive to synergistic effects against HIV in combination with reverse transcriptase inhibitors zidovudine (ZDV), lamivudine (3TC), didanosine (ddI), zalcitabine (ddC) and stavudine (d4T) without enhanced cytotoxicity.

Resistance: HIV isolates with reduced susceptibility to nelfinavir have been selected *in vitro*. Genotypic analysis of a variant which exhibited a nine-fold decrease in sensitivity showed a unique substitution of an aspartic acid (D) to an asparagine (N) in HIV protease at amino acid residue 30 (D30N). Genotypic changes in HIV protease genes obtained from 58 patients enrolled in phase I/II trials were also evaluated. Consistent with the *in vitro* results, the predominant change observed was the D30N substitution. In a subset of these patients followed for up to 44 weeks, this substitution was maintained. Mutations described for other protease inhibitors were either never observed (G48V, V82F/T, I84V) or only rarely (3 of 55 patients) observed (L90M). Sequence analyses were performed on the protease genes derived at 16 weeks from randomly selected patients who received nelfinavir either alone (n = 64) or in combination with ZDV and 3TC (n = 49) in pivotal trials. The incidence of genotypic resistance to nelfinavir at 16 weeks was significantly reduced when nelfinavir was used in combination with ZDV and 3TC (6 %), compared to monotherapy (56 %).

Cross-resistance to other antivirals: cross-resistance between nelfinavir and reverse transcriptase inhibitors is unlikely because of the different enzyme targets involved. HIV isolates resistant to nucleoside analogues and non-nucleoside reverse transcriptase inhibitors remain susceptible *in vitro* to nelfinavir. The potential for HIV cross-resistance to other protease inhibitors has been explored with nelfinavir. Six clinical isolates containing the D30N substitution showed no change in sensitivity to saquinavir, ritonavir, indinavir or 141W94 *in vitro*. This lack of cross-resistance was confirmed with an HIV recombinant virus containing the D30N substitution; the recombinant virus exhibited a

reduced sensitivity to nelfinavir, yet retained full sensitivity to the other protease inhibitors. In addition, in patients previously treated with ritonavir, indinavir and/or saquinavir five of fourteen clinical isolates with reduced susceptibility to one or more of these protease inhibitors were susceptible to nelfinavir.

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.

A randomised open-label study compared the HIV RNA suppression of nelfinavir 1250 mg BID versus nelfinavir 750 mg TID in protease inhibitor 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.

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. Trough drug exposures remain at least twenty fold greater than the mean IC95 throughout the dosing interval for both regimens. The clinical relevance of relating *in vitro* measures to drug potency and clinical outcome has not been established.

The absolute bioavailability of VIRACEPT has not been determined.

Effect of food on gastrointestinal absorption: maximum plasma concentrations and area under the plasma concentration-time curve were consistently 2 to 3-fold higher under fed conditions compared to fasting. The increased plasma concentrations with food were independent of fat content of the meals.

Distribution: in both animals and humans, the estimated volumes of distribution (2-7 l/kg) exceeded total body water, suggesting extensive penetration of nelfinavir into tissues. Although no studies have been conducted in humans, studies with a single 50 mg/kg dose of ^{14}C-nelfinavir in rats showed that concentrations in the brain were lower than in other tissues, but exceeded the *in vitro* EC_{95} for antiviral activity. Nelfinavir in serum is extensively protein-bound (≥ 98 %).

Metabolism: unchanged nelfinavir comprised 82-86 % of the total plasma radioactivity after a single oral 750 mg dose of ^{14}C-nelfinavir. One major and several minor oxidative metabolites were found in plasma. The major oxidative metabolite has *in vitro* antiviral activity equal to the parent drug. The plasma levels of this metabolite are approximately 25 % of the total plasma nelfinavir-related concentration. *In vitro*, multiple cytochrome P-450 isoforms including CYP3A, CYP2C19/C9 and CYP2D6 are responsible for metabolism of nelfinavir.

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

<u>Pharmacokinetics in special clinical situations:</u>

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

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

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

There are no data available in the elderly.

Pharmacokinetics in patients with liver impairment:

Pharmacokinetics of nelfinavir after a single dose of 750 mg was studied in patients with liver impairment and healthy volunteers. A 49 %-69 % increase was observed in AUC of nelfinavir in the hepatically impaired groups with impairment (Child-Turcotte Classes A to C) compared to the healthy group. Specific dose recommendations for nelfinavir cannot be made based on the results of this study.

5.3 Preclinical safety data

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: The oral administration of 1000 mg/kg/day to rats for two years 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 adenoma. Chronic nelfinavir treatment of rats has been demonstrated to produce effects consistent with enzyme induction, which predisposed rats, but not humans, to thyroid neoplasms. The weight of evidence indicates that nelfinavir is unlikely to be a carcinogen in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

VIRACEPT tablets are provided in HDPE plastic bottles fitted with HDPE child resistant closures with polyethylene liners. A cotton wad is included in each bottle containing 180 or 270 tablets. Not all pack sizes may be marketed.

6.6 Instructions for use and handling <, and disposal>

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
40 Broadwater Road
Welwyn Garden City
Hertfordshire AL7 3AY
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/054/002-EU/1/97/054/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22.1.1998

10. DATE OF REVISION OF THE TEXT

10.9.2002