ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

VIRACEPT 50 mg/g Oral Powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VIRACEPT 50 mg/g Oral Powder contains 58.45 mg of nelfinavir mesylate corresponding to 50 mg of nelfinavir (as free base) per gram of powder.

3. PHARMACEUTICAL FORM

Oral Powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VIRACEPT is indicated in combination with antiretroviral nucleoside analogues for the treatment of HIV-1 infected patients with advanced or progressive immunodeficiency.

Combinations of VIRACEPT with antiretroviral nucleoside analogues have been shown to decrease plasma viral load and to increase circulating CD4 lymphocyte counts. Clinical studies are underway to evaluate the clinical benefits of combination regimens.

Refer to Section 5.1 Pharmacodynamic properties.

4.2 Posology and method of administration

VIRACEPT 50 mg/g Oral Powder should preferably be ingested with food.

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 750 mg three times a day (TID), for patients unable to take tablets.

Patients aged 2 to 13 years: for children, the recommended starting dose is 25 - 30 mg/kg per dose, TID. 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 TID to children aged 2 to 13 years is as follows:

<table>
<thead>
<tr>
<th>Body Weight kg</th>
<th>Number of Scoops</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5 to &lt; 8.5</td>
<td>4</td>
</tr>
<tr>
<td>8.5 to &lt; 10.5</td>
<td>5</td>
</tr>
<tr>
<td>10.5 to &lt; 12</td>
<td>6</td>
</tr>
<tr>
<td>12 to &lt; 14</td>
<td>7</td>
</tr>
<tr>
<td>14 to &lt; 16</td>
<td>8</td>
</tr>
<tr>
<td>16 to &lt; 18</td>
<td>9</td>
</tr>
<tr>
<td>18 to &lt; 23</td>
<td>10</td>
</tr>
<tr>
<td>≥ 23</td>
<td>15</td>
</tr>
</tbody>
</table>
The Oral Powder may be mixed with water, milk, formula, soy formula, soy milk, dietary supplements, or pudding. It is recommended that VIRACEPT 50 mg/g Oral Powder mixed in these media be used within 6 hours. Dosing media not recommended, due to taste, includes any acidic food or juice (e.g., orange juice, apple juice or apple sauce). Do not add water to bottles of VIRACEPT 50 mg/g Oral Powder.

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

**Renal and hepatic impairment**: currently, there are no data specific for these patient populations and therefore specific dosage recommendations cannot be made. Nelfinavir is principally metabolised and eliminated by the liver. Caution should be used when administering VIRACEPT to patients with impaired renal or hepatic function.

### 4.3 Contra-indications

Hypersensitivity to nelfinavir or to any of the excipients.

VIRACEPT is contraindicated in breastfeeding 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), 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.

### 4.4 Special warnings and special precautions for use

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

The safety and activity of nelfinavir in children below the age of 2 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).

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

New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving 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.
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:** 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 VIRACEPT. 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.

**Ritonavir:** administration of a single 750 mg dose of VIRACEPT 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 VIRACEPT 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 VIRACEPT 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 VIRACEPT 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 VIRACEPT 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 VIRACEPT 750 mg TID resulted in a 392% increase in saquinavir plasma AUC.

**Metabolic enzyme inducers:** rifampicin decreases nelfinavir plasma AUC by 82%. Other potent inducers of CYP3A (e.g., phenobarbital, phenytoin, 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 VIRACEPT and rifabutin results in a 32% decrease in nelfinavir plasma AUC and an approximately 200% increase in rifabutin plasma AUC (see also Section 4.4). A dosage reduction of rifabutin to half the standard dose is necessary when VIRACEPT and rifabutin are co-administered.

**Metabolic enzyme inhibitors:** co-administration of VIRACEPT 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.

**Other potential interactions:** VIRACEPT 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
blocks) 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 VIRACEPT 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 Use during 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 breastfeed 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 breastfeeding if they are receiving VIRACEPT.

### 4.7 Effects on ability to drive and use machines

There is no indication that VIRACEPT affects the ability to drive and use machines.

### 4.8 Undesirable effects

The safety of VIRACEPT was studied in controlled clinical trials with over 800 patients, of which more than half received a dose of 750 mg TID either alone or in combination with nucleoside analogues. Over 4000 patients ≥ 13 years in the expanded access programmes received VIRACEPT at a dose of 750 mg TID. The majority of adverse events were of mild intensity. The most frequently reported adverse event among patients receiving VIRACEPT was diarrhoea.

Across the two phase III, double-blind studies adverse experiences of moderate to severe intensity reported by investigators as at least possibly related to VIRACEPT or of unknown relationship in ≥ 2% of patients treated with the 750 mg TID dose of VIRACEPT (n = 200) in combination with nucleoside analogues (for 24 weeks) included the following undesirable effects: diarrhoea (25.9%), flatulence (2.5%), nausea (4.5%), and rash (3.0%). Marked clinical laboratory abnormalities (change from grade 0 to grade 3 or 4, or change from grade 1 to grade 4) reported in ≥ 2% of patients treated with 750 mg TID of VIRACEPT (for 24 weeks) across the same studies included increased creatine kinase (3.9%), and decreased neutrophils (4.5%). Marked increases in transaminases occurred in less than 2% of patients receiving VIRACEPT at the recommended dose 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.

### 4.9 Overdose

Human experience of acute overdose with VIRACEPT is limited. There is no specific antidote for overdose with VIRACEPT. 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<sub>95</sub> (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 enzymes 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. 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.

VIRACEPT 750 mg TID in combination with one or more nucleoside analogues was consistently associated with decreases in mean plasma HIV RNA in excess of 1 log<sub>10</sub> copies/ml and increases in mean CD4 cell count of 90 - 100 cells/mm<sup>3</sup> which were sustained to at least 24 weeks. Decreases in HIV RNA observed with VIRACEPT monotherapy were less pronounced and of shorter duration.
In a study of 297 HIV-1 seropositive patients receiving zidovudine and lamivudine plus VIRACEPT (2 different doses) or zidovudine and lamivudine alone, the mean decrease in plasma HIV RNA at 24 weeks was 2.15 $\log_{10}$ in patients receiving combination therapy with VIRACEPT 750 mg TID, compared to 1.54 $\log_{10}$ 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 (<500 copies/ml) were 81% and 18% for the groups treated with VIRACEPT 750 mg TID plus zidovudine and lamivudine or zidovudine and lamivudine, respectively. Mean CD4 cell counts at 24 weeks were increased by 108 and 81 cells/mm$^3$ for the groups treated with VIRACEPT 750 mg TID plus zidovudine and lamivudine or zidovudine and lamivudine, respectively. At 48 weeks, approximately 80% of the patients treated with VIRACEPT 750 mg TID plus zidovudine and lamivudine remained below the level of detection of the assay; CD4 cell counts increased by more than 170 cells/mm$^3$ at 48 weeks in this group.

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. The absolute bioavailability 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 ($\geq$ 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.

**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. There are no data available in the elderly.
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:** carcinogenicity studies of nelfinavir are not completed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf-life

12 months

6.4 Special precautions for storage

Store in the original container at temperatures between 15-30° C.

6.5 Nature and contents of container

VIRACEPT 50 mg/g Oral Powder is provided in plastic bottles containing 144 grams of oral powder with a 1 gram polystyrene scoop.

6.6 Instructions for use and handling, and disposal (if appropriate)

Not applicable

7. MARKETING AUTHORISATION HOLDER

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

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10. DATE OF REVISION OF THE TEXT
1. **NAME OF THE MEDICINAL PRODUCT**

VIRACEPT 250 mg Tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

VIRACEPT 250 mg Tablets contain 292.25 mg of nelfinavir mesylate corresponding to 250 mg of nelfinavir (as free base).

3. **PHARMACEUTICAL FORM**

Tablets

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

VIRACEPT is indicated in combination with antiretroviral nucleoside analogues for the treatment of HIV-1 infected patients with advanced or progressive immunodeficiency.

Combinations of VIRACEPT with antiretroviral nucleoside analogues has been shown to decrease plasma viral load and to increase circulating CD4 lymphocyte counts. Clinical studies are underway to evaluate the clinical benefits of combination regimens.

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 750 mg (three 250 mg tablets) three times a day (TID) by mouth.

**Patients aged 2 to 13 years**: for children, the recommended starting dose is 25 - 30 mg/kg body weight per dose given TID. 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 TID to children aged 2 to 13 years is as follows:

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Number of Tablets*</th>
</tr>
</thead>
<tbody>
<tr>
<td>kg</td>
<td></td>
</tr>
<tr>
<td>18 to &lt; 23</td>
<td>2</td>
</tr>
<tr>
<td>≥ 23</td>
<td>3</td>
</tr>
</tbody>
</table>

* 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**: currently, there are no data specific for these patient populations and therefore specific dosage recommendations cannot be made. Nelfinavir is principally metabolised
and eliminated by the liver. Caution should be used when administering VIRACEPT to patients with impaired renal or hepatic function.
4.3 Contra-indications

Hypersensitivity to nelfinavir or to any of the excipients.

VIRACEPT is contraindicated in breastfeeding 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), 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.

4.4 Special warnings and special precautions for use

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

The safety and activity of nelfinavir in children below the age of 2 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).

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 haemarthrosis, in haemophilic 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. Haemophilic patients should therefore be made aware of the possibility of increased bleeding.

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.

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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: 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 VIRACEPT. 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.

**Ritonavir**: administration of a single 750 mg dose of VIRACEPT 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 VIRACEPT 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 VIRACEPT 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 VIRACEPT 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 VIRACEPT 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 VIRACEPT 750 mg TID resulted in a 392% increase in saquinavir plasma AUC.

**Metabolic enzyme inducers**: rifampicin decreases nelfinavir plasma AUC by 82%. Other potent inducers of CYP3A (e.g., phenobarbital, phenytoin, 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 VIRACEPT and rifabutin results in a 32% decrease in nelfinavir plasma AUC and an approximately 200% increase in rifabutin plasma AUC (see also Section 4.4). A dosage reduction of rifabutin to half the standard dose is necessary when VIRACEPT and rifabutin are coadministered.

**Metabolic enzyme inhibitors**: co-administration of VIRACEPT 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.

**Other potential interactions**: VIRACEPT 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) 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 VIRACEPT 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 Use during 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 breastfeeding if they are receiving VIRACEPT.

4.7 Effects on ability to drive and use machines

There is no indication that VIRACEPT affects the ability to drive and use machines.

4.8 Undesirable effects

The safety of VIRACEPT was studied in controlled clinical trials with over 800 patients, of which
more than half received a dose of 750 mg TID either alone or in combination with nucleoside
analogues. Over 4000 patients ≥ 13 years in the expanded access programmes received VIRACEPT
at a dose of 750 mg TID. The majority of adverse events were of mild intensity. The most frequently
reported adverse event among patients receiving VIRACEPT was diarrhoea.

Across the two phase III, double-blind studies adverse experiences of moderate to severe intensity
reported by investigators as at least possibly related to VIRACEPT or of unknown relationship in ≥
2% of patients treated with the 750 mg TID dose of VIRACEPT (n = 200) in combination with
nucleoside analogues (for 24 weeks) included the following undesirable effects: diarrhoea (25.9%),
flatulence (2.5%), nausea (4.5%), and rash (3.0%). Marked clinical laboratory abnormalities (change
from grade 0 to grade 3 or 4, or change from grade 1 to grade 4) reported in ≥ 2% of patients treated
with 750 mg TID of VIRACEPT (for 24 weeks) across the same studies included increased creatine
kinase (3.9%), and decreased neutrophils (4.5%). Marked increases in transaminases occurred in less
than 2% of patients receiving VIRACEPT at the recommended dose 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.

4.9 Overdose

Human experience of acute overdose with VIRACEPT is limited. There is no specific antidote for
overdose with VIRACEPT. 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<sub>95</sub> (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. 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.

VIRACEPT 750 mg TID in combination with one or more nucleoside analogues was consistently associated with decreases in mean plasma HIV RNA in excess of 1 log<sub>10</sub> copies/ml and increases in mean CD4 cell count of 90 - 100 cells/mm<sup>3</sup> which were sustained to at least 24 weeks. Decreases in HIV RNA observed with VIRACEPT monotherapy were less pronounced and of shorter duration.

In a study of 297 HIV-1 seropositive patients receiving zidovudine and lamivudine plus VIRACEPT (2 different doses) or zidovudine and lamivudine alone, the mean decrease in plasma HIV RNA at 24 weeks was 2.15 log<sub>10</sub> in patients receiving combination therapy with VIRACEPT 750 mg TID, compared to 1.54 log<sub>10</sub> 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 (<500 copies/ml) were 81% and 18% for the groups treated with VIRACEPT 750 mg TID plus zidovudine and lamivudine or zidovudine and lamivudine, respectively. Mean CD4 cell counts at 24 weeks were increased by 108 and 81 cells/mm<sup>3</sup> for the groups treated with VIRACEPT 750 mg TID plus zidovudine and lamivudine or zidovudine and lamivudine, respectively. At 48 weeks, approximately 80% of the patients treated with VIRACEPT 750 mg TID plus zidovudine and lamivudine remained below the level of detection of the assay; CD4 cell counts increased by more than 170 cells/mm<sup>3</sup> at 48 weeks in this group.

### 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 \((C_{\text{max}})\) 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. The absolute bioavailability 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 \(^{14}\text{C}-\text{nelfinavir}\) 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 \(^{14}\text{C}-\text{nelfinavir}\). 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 \(^{14}\text{C}-\text{nelfinavir}\) 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 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. There are no data available in the elderly.

**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:** carcinogenicity studies of nelfinavir are not completed.

**6. PHARMACEUTICAL PARTICULARS**
6.1 List of excipients

Each tablet contains calcium silicate, crospovidone, magnesium stearate, indigo carmine (E132) as powder and aluminum lake.
6.2 Incompatibilities
Not applicable

6.3 Shelf-life
18 months

6.4 Special precautions for storage
Store in the original container at temperatures between 15-30\degree C.

6.5 Nature and contents of container
VIRACEPT Tablets is provided in plastic bottles containing 180 or 270 tablets.

6.6 Instructions for use and handling, and disposal (if appropriate)
Not applicable

7. MARKETING AUTHORISATION HOLDER
Roche Registration Limited
40 Broadwater Road
Welwyn Garden City
Hertfordshire AL7 3AY
United Kingdom

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II

THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR IMPORT AND BATCH RELEASE, CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, AND SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER
A. MANUFACTURING AUTHORISATION HOLDER

Manufacturer responsible for import and batch release in the European Economic Area

Galen Limited, Seagoe Industrial Estate, Craigavon, Armagh, Northern Ireland, BT63 5UA United Kingdom

Manufacturing Authorisation issued on 1 October 1992 by the Department of Health, Medicines Control Agency, Market Towers, 1 Nine Elms Lane, Vauxhall, London SW8 5NQ.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription. (refer to the summary of product characteristics for further information)

C. SPECIFIC OBLIGATIONS

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual re-assessment of the benefit/risk profile.

- Roche Registration Limited commits to supply clinical efficacy and safety data from ongoing and/or new studies in adults and children until such time as conclusions on the long term effects of the addition of nelfinavir to dual nucleoside therapy are made possible:
  - The results from study 514 (CPCRA 042/CTN 102) will be reported as soon as they are made available by the U.S. and Canadian cooperative clinical trials groups.
  - Full reports on studies 506 and 511 following treatment of all patients for 48 weeks will be provided by 30 September 1998.
  - Further information on the Pharmacokinetics (PK) of nelfinavir in children including those of less than 2 years of age at the time of the annual re-assessment.
- Data will also be collected in the post-marketing period and reported at the time of the annual reassessment on other matters relevant to efficacy including:
  - measurements of viral load (as plasma HIV RNA) in adults and children
  - the development of viral resistance to nelfinavir during long-term combination therapy (including studies investigating long term mutations).
  - the results of switching from or to nelfinavir when resistance to one or more protease inhibitors has occurred.
A. LABELLING
144 g Oral Powder  
**VIRACEPT 50 mg/g**  
Nelfinavir

For oral administration.  
Medicinal product subject to medical prescription.  
Do not reconstitute in the bottle.

Each level measuring scoop (one gram) provides 58.45 mg of nelfinavir mesylate, equivalent to 50 mg of nelfinavir as free base. Also contains sweetener aspartame (E951), natural and artificial flavourings and other constituents.

Refer to the package leaflet before use.  
Store at temperature between 15-30° C  
Keep out of reach of children.

Marketing authorisation number: 

Marketing Authorisation Holder:  
Roche Registraction Limited  
40 Broadwater Road  
Welwyn Garden City  
Hertfordshire AL7 3AY  
United Kingdom

Batch Number:  
Expiry date:
180 Tablets

**VIRACEPT 250 mg**
Nelfinavir

For oral administration. Medicinal product subject to medical prescription.

Each tablet contains 292.25 mg of nelfinavir mesylate, equivalent to 250 mg nelfinavir as free base. Also contains colourant indigocarmine (E132) and other constituents.

Refer to the package leaflet before use.
Store at temperature between 15-30°C
Keep out of reach of children.

Marketing authorisation number:

Marketing Authorisation Holder:
Roche Registration Limited
40 Broadwater Road
Welwyn Garden City
Hertfordshire AL7 3AY
United Kingdom

Batch Number:
Expiry date:
270 Tablets  
**VIRACEPT 250 mg**  
Nelfinavir

For oral administration.  
Medicinal product subject to medical prescription.

Each tablet contains 292.25 mg of nelfinavir mesylate, equivalent to 250 mg nelfinavir as free base.  
Also contains colourant indigocarmine (E132) and other constituents.

Refer to the package leaflet before use.  
Store at temperature between 15-30°C  
Keep out of reach of children.

Marketing authorisation number:

Marketing Authorisation Holder:  
Roche Registration Limited  
40 Broadwater Road  
Welwyn Garden City  
Hertfordshire AL7 3AY  
United Kingdom

Batch Number:  
Expiry date:
B. PACKAGE LEAFLET
1. NAME OF THE MEDICINAL PRODUCT
VIRACEPT (nelfinavir) 50 mg/g Oral Powder

2. FULL STATEMENT OF THE ACTIVE SUBSTANCE AND EXCIPIENTS
What is the active substance?
VIRACEPT 50 mg/g Oral Powder contains 58.45 mg of nelfinavir mesylate corresponding to 50 mg of nelfinavir (as free base) per gram of powder.

What else does VIRACEPT contain?
The Oral Powder contains microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hydroxypropyl methylcellulose, aspartame (E951), sucrose palmitate, and natural and artificial flavour.

3. PHARMACEUTICAL FORM AND CONTENTS
50 mg/g Oral Powder

How is VIRACEPT supplied?
VIRACEPT 50 mg/g Oral Powder is provided in plastic bottles containing 144 g of oral powder with a 1 gram plastic scoop.

4. PHARMACOTHERAPEUTIC GROUP
VIRACEPT is an antiviral agent. It is a member of a class of medicinal products called protease inhibitors. It is active against the Human Immunodeficiency Virus (HIV) helping to reduce the number of HIV particles in blood.

5. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND MANUFACTURING AUTHORITY RESPONSIBLE FOR BATCH RELEASE
Who holds the marketing authorisation for VIRACEPT?
Roche Registration Limited
40 Broadwater Road
Welwyn Garden City
Hertfordshire AL7 3AY
United Kingdom

Who is responsible for the manufacture of VIRACEPT?
Galen Limited
Seagoe Industrial Estate
Craigavon, Armagh
Northern Ireland BT63 5UA
United Kingdom

6. THERAPEUTIC INDICATIONS
Why has your doctor prescribed VIRACEPT?
Your doctor has prescribed VIRACEPT for you because you have HIV infection. HIV infection is a disease spread by contact with blood or sexual contact with an infected individual.

VIRACEPT should be taken in combination with antiretroviral nucleoside analogues. This combination has been shown to reduce the number of HIV particles in the blood and to increase circulating CD4 cells.

7. LIST OF INFORMATION NECESSARY BEFORE TAKING THE MEDICINAL PRODUCT
When should you not take or use VIRACEPT?
Do not take VIRACEPT if you experience an allergic reaction to nelfinavir or to any of the other ingredients. VIRACEPT should not be taken with certain medications which are listed below.
What are the appropriate precautions before use?
VIRACEPT 50 mg/g Oral Powder contains aspartame as a sweetening agent. Aspartame provides a source of phenylalanine and, therefore, may not be suitable for persons with phenylketonuria.

You should know that VIRACEPT is not a cure for HIV infection and that you may continue to develop infections or other illnesses associated with HIV disease. You should, therefore, remain under the care of your doctor while taking VIRACEPT.

Treatment with VIRACEPT has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

VIRACEPT has been shown to greatly lower the number of HIV particles in the blood. The clinical benefits of this effect are presently being studied.

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

Can VIRACEPT be taken by children?
The safety and activity of VIRACEPT in children below the age of 2 years is not yet known.

Can VIRACEPT be taken by patients with kidney or liver impairment?
There is no data available on patients with these conditions taking VIRACEPT. Consult your doctor if you have kidney or liver impairment.

Can VIRACEPT be taken with other medications?
VIRACEPT may be taken with a number of medications that are commonly used in HIV infection. Clinically important drug interactions have not been observed with zidovudine plus lamivudine, didanosine plus stavudine, stavudine, and ketoconazole. There is no evidence of inadequate effect of zidovudine in the brain when zidovudine is co-administered with VIRACEPT. Clinically important drug interactions would not be expected with itraconazole, fluconazole, erythromycin, and clarithromycin; however, the possibility cannot be excluded.

There are some medications that may not be taken with VIRACEPT or that require dosage reduction of that medicine or VIRACEPT.

Drugs that cannot be taken with VIRACEPT include rifampicin, terfenadine, astemizole, cisapride, amiodarone, quinidine, triazolam, midazolam, ergot derivatives (migraine medicinal products), phenobarbital, phenytoin, and carbamazepine.

Also consult your doctor if you are taking ritonavir, indinavir, saquinavir, rifabutin, birth control pills, calcium channel blockers or any other medications.

You should always inform your doctor about all drugs you are taking or plan to take, including those obtained without a prescription.

What do you have to consider while breast-feeding?
Breast-feeding is not recommended while taking VIRACEPT because of the potential for the drug to be excreted in breast milk. Inform your doctor if you are breast-feeding or intend to breast-feed. It is recommended that HIV-infected women should not breast feed their infants to avoid transmission of HIV.

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

What has to be observed if driving or operating machines?
There is no indication that VIRACEPT affects the ability to drive or use machines.
8. INSTRUCTIONS FOR PROPER USE

How and when should VIRACEPT be taken?

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

The powder form of VIRACEPT must be taken by mouth, with a meal or light snack.

For adults and children older than 13 years who are unable to take tablets, the recommended dose of VIRACEPT 50 mg/g Oral Powder is 750 mg three times a day.

For children, aged 2 to 13 years, the usual dose of VIRACEPT Oral Powder is 25-30 mg per kg of body weight given three times daily as follows:

<table>
<thead>
<tr>
<th>Body Weight kg</th>
<th>Number of Level 1 g Scoops three times daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5 to &lt; 8.5</td>
<td>4</td>
</tr>
<tr>
<td>8.5 to &lt; 10.5</td>
<td>5</td>
</tr>
<tr>
<td>10.5 to &lt; 12</td>
<td>6</td>
</tr>
<tr>
<td>12 to &lt; 14</td>
<td>7</td>
</tr>
<tr>
<td>14 to &lt; 16</td>
<td>8</td>
</tr>
<tr>
<td>16 to &lt; 18</td>
<td>9</td>
</tr>
<tr>
<td>18 to &lt; 23</td>
<td>10</td>
</tr>
<tr>
<td>≥ 23</td>
<td>15</td>
</tr>
</tbody>
</table>

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

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

What if I take too much? (Overdose)

If you realize you have taken more VIRACEPT than you were prescribed, contact your doctor right away. If you cannot reach your doctor, go to the emergency room.

9. DESCRIPTION OF UNDESIRABLE EFFECTS UNDER NORMAL USE

What undesirable effects may VIRACEPT cause?

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

Any medicinal product may have unintended or undesirable effects. Unwanted effects of moderate to severe intensity reported in greater than or equal to two percent of patients receiving VIRACEPT 750 mg three times daily include diarrhoea, flatulence, nausea, rash, decreased white blood cell counts and increased values for liver enzyme and kidney function tests.

Other unwanted effects may occur with VIRACEPT. Ask your doctor or pharmacist for more information about unwanted effects. Both have a more complete list of unwanted effects. Inform your doctor promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

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

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

What measures are to be taken if unwanted effects occur?
Most unwanted effects stop by themselves without treatment. If these unwanted effects do not stop, you should consult your doctor since he may wish to prescribe a medication to help relieve or stop the symptoms.

10. REFERENCE TO THE EXPIRY DATE INDICATED ON THE LABEL
Use before the expiry date indicated on the label.

How is VIRACEPT to be stored?
Store VIRACEPT in its original container at temperatures between 15-30°C and out of reach of children.

11. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST REVISED
If you have any further questions please consult your doctor or pharmacist.
Belgique/België:
N.V. Roche S.A.
Rue Dantestraat 75
1070 Bruxelles - Brussels
Tel: 02 525 82 11

Italia:
Roche S.p.A.
Piazza Durante 11
20131 Milano
Tel: 02 2884

Luxembourg:
Refer to Belgique/België

Danmark:
Roche a/s
Industriholmen 59
2650 Hvidovre
Tel: 36 39 99 99

Nederland:
Roche Nederland B.V.
Postbus 42
3640 AA Mijdrecht
Tel: 0297 291222

Deutschland:
Hoffmann-La Roche AG
Postfach 1270
79630 Grenzach-Wyhlen
Tel: 07624 140

Österreich:
Hoffmann-La Roche Wien Ges.m.b.H.
Jacquingasse 16-18
1030 Wien
Tel: 01 79521

? ???da:
Roche (Hellas) A.E.
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151 25 ???s? ??t???
???: 68 06 600

Portugal:
Roche Farmacêutica Química Lda
Estrada Nacional 249-1
2720 Amadora
Tel: 418 45 65

España:
Productos Roche S.A.
Cª de Carabanchel
a la de Andalucía s/n
28025 Madrid
Tel: 34 1 508 62 40

Suomi/Finland:
Roche Oy
PL 12
02631 Espoo/Esbo
Puh/Tel: 09 525 331

France:
Produits Roche
52 Boulevard du Parc
92521 Neuilly-Sur-Seine
Tel: 1 46 40 50 00

Sverige:
Roche AB
Box 47327
100 74 Stockholm
Tel: 08 726 12 00

Ireland:
Roche Pharmaceuticals
3 Richview
Clonskeagh, Dublin 14
Tel: 128 37977

United Kingdom:
Roche Products Ltd
PO Box 8, Welwyn Garden City, Hertfordshire
AL7 3AY
Tel: 01 707 366000
1. NAME OF THE MEDICINAL PRODUCT
VIRACEPT (nelfinavir) 250 mg Tablets

2. FULL STATEMENT OF THE ACTIVE SUBSTANCE AND EXCIPIENTS
What is the active substance?
VIRACEPT 250 mg Tablets contain 292.25 mg of nelfinavir mesylate corresponding to 250 mg of nelfinavir (as free base).

What else does VIRACEPT contain?
Each tablet contains calcium silicate, crospovidone, magnesium stearate, indigocarmine (E132), as powder, and aluminum lake.

3. PHARMACEUTICAL FORM AND CONTENTS
250 mg Tablets

How is VIRACEPT supplied?
VIRACEPT 250 mg Tablets are provided in plastic bottles containing 180 or 270 tablets.

4. PHARMACOTHERAPEUTIC GROUP
VIRACEPT is an antiviral agent. It is a member of a class of medicinal products called protease inhibitors. It is active against the Human Immunodeficiency Virus (HIV) helping to reduce the number of HIV particles in blood.

5. NAME AND ADDRESS OF THE MARKETING AUTHOURISATION HOLDER AND MANUFACTURING AUTHOURISATION HOLDER RESPONSIBLE FOR BATCH RELEASE
Who holds the marketing authorisation for VIRACEPT?
Roche Registration Limited
40 Broadwater Road
Welwyn Garden City
Hertfordshire AL7 3AY
United Kingdom

Who is responsible for the manufacture of VIRACEPT?
Galen Limited
Seagoe Industrial Estate
Craigavon, Armagh
Northern Ireland BT63 5UA
United Kingdom

6. THERAPEUTIC INDICATIONS
Why has your doctor prescribed VIRACEPT?
Your doctor has prescribed VIRACEPT for you because you have HIV infection. HIV infection is a disease spread by contact with blood or sexual contact with an infected individual.

VIRACEPT should be taken in combination with antiretroviral nucleoside analogues. This combination has been shown to reduce the number of HIV particles in the blood and to increase circulating CD4 cells.

7. LIST OF INFORMATION NECESSARY BEFORE TAKING THE MEDICINAL PRODUCT
When should you not take or use VIRACEPT?
Do not take VIRACEPT if you experience an allergic reaction to nelfinavir or to any of the other ingredients. VIRACEPT should not be taken with certain medications which are listed below.

What are the appropriate precautions before use?
You should know that VIRACEPT is not a cure for HIV infection and that you may continue to develop infections or other illnesses associated with HIV disease. You should, therefore, remain under the care of your doctor while taking VIRACEPT.

Treatment with VIRACEPT has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. VIRACEPT has been shown to greatly lower the number of HIV particles in the blood. The clinical benefits of this effect are presently being studied.

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

**Can VIRACEPT be taken by children?**
The safety and activity of VIRACEPT in children below the age of 2 years is not yet known.

**Can VIRACEPT be taken by patients with kidney or liver impairment?**
There is no data available on patients with these conditions taking VIRACEPT. Consult your doctor if you have kidney or liver impairment.

**Can VIRACEPT be taken with other medications?**
VIRACEPT may be taken with a number of medications that are commonly used in HIV infection. Clinically important drug interactions have not been observed with zidovudine plus lamivudine, didanosine plus stavudine, stavudine, and ketoconazole. There is no evidence of inadequate effect of zidovudine in the brain when zidovudine is co-administered with VIRACEPT. Clinically important drug interactions would not be expected with itraconazole, fluconazole, erythromycin, and clarithromycin; however, the possibility cannot be excluded.

There are some medications that may not be taken with VIRACEPT or that require dosage reduction of that medicine or VIRACEPT.

Drugs that cannot be taken with VIRACEPT include rifampicin, terfenadine, astemizole, cisapride, amiodarone, quinidine, triazolam, midazolam, ergot derivatives (migraine medicinal products), phenobarbital, phenytoin, and carbamazapine.

Also consult your doctor if you are taking ritonavir, indinavir, saquinavir, rifabutin, birth control pills, calcium channel blockers or any other medications. You should always inform your doctor about all drugs you are taking or plan to take, including those obtained without a prescription.

**What do you have to consider while breast-feeding?**
Breast-feeding is not recommended while taking VIRACEPT because of the potential for the drug to be excreted in breast milk. Inform your doctor if you are breast-feeding or intend to breast-feed. It is recommended that HIV-infected women should not breast feed their infants to avoid transmission of HIV.

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

**What has to be observed if driving or operating machines?**
There is no indication that VIRACEPT affects the ability to drive or use machines.

**8. INSTRUCTIONS FOR PROPER USE**

**How and when should VIRACEPT be taken?**
The following statements apply to VIRACEPT unless otherwise prescribed by your doctor. Please observe these instructions for use, otherwise you will not fully benefit from VIRACEPT.

The tablet form of VIRACEPT must be taken by mouth. VIRACEPT tablets should be swallowed whole and should be taken with a meal or light snack.
The usual dose of VIRACEPT 250 mg Tablets for individuals 13 years of age or older is 750 mg given as three 250 mg tablets three times daily.
The usual dose for children, aged 2 to 13 years, is 25-30 mg per kg of body weight three times daily as follows:

<table>
<thead>
<tr>
<th>Body Weight kg</th>
<th>Number of Tablets* three times daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 to &lt; 23</td>
<td>2</td>
</tr>
<tr>
<td>≥ 23</td>
<td>3</td>
</tr>
</tbody>
</table>

* see Package Leaflet for VIRACEPT Oral Powder for patients less than 18 kg body weight.

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

**What if I take too much? (Overdose)**
If you realize you have taken more VIRACEPT than you were prescribed, contact your doctor right away. If you cannot reach your doctor, go to the emergency room.

9. **DESCRIPTION OF UNDESIRABLE EFFECTS UNDER NORMAL USE**

What undesirable effects may VIRACEPT cause?
If you notice any unwanted effects not mentioned in this leaflet or if you are unsure about the effect of this product, please inform your doctor or pharmacist.

Any medicinal product may have unintended or undesirable effects. Unwanted effects of moderate to severe intensity reported in greater than or equal to two percent of patients receiving VIRACEPT 750 mg three times daily include diarrhoea, flatulence, nausea, rash, decreased white blood cell counts and increased values for liver enzyme and kidney function tests.

Other unwanted effects may occur with VIRACEPT. Ask your doctor or pharmacist for more information about unwanted effects. Both have a more complete list of unwanted effects. Inform your doctor promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

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

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

**What measures are to be taken if unwanted effects occur?**
Most unwanted effects stop by themselves without treatment. If these unwanted effects do not stop, you should consult your doctor since he may wish to prescribe a medication to help relieve or stop the symptoms.

10. **REFERENCE TO THE EXPIRY DATE INDICATED ON THE LABEL**
Use before the expiry date indicated on the label.

11. **DATE ON WHICH THE PACKAGE LEAFLET WAS LAST REVISED**
If you have any further questions please consult your doctor or pharmacist.
12. OTHER INFORMATION

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