ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

INVIRASE 200 mg hard capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains 200 mg of saquinavir as saquinavir mesilate.

Excipient: Contains lactose anhydrous: 63.3 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Light brown and green, opaque hard capsule with the marking "ROCHE" and the code "0245" on each half of the capsule shell.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Invirase is indicated for the treatment of HIV-1 infected adult patients. Invirase should only be given in combination with ritonavir and other antiretroviral medicinal products (see section 4.2).

4.2 Posology and method of administration

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

Adults and adolescents over the age of 16 years:

In combination with ritonavir
The recommended dose of Invirase is 1000 mg (5 x 200 mg capsules) two times daily with ritonavir 100 mg two times daily in combination with other antiretroviral agents.
Invirase capsules should be swallowed whole and taken at the same time as ritonavir with or after food (see section 5.2).

In combination with other protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors
Dose reduction may be required when Invirase/ritonavir is administered with some other HIV protease inhibitors (e.g. nelfinavir, indinavir and delavirdine), since these medicinal products may increase saquinavir plasma levels (see section 4.5).

Renal and hepatic impairment:
No dosage adjustment is necessary for patients with mild to moderate renal or mild hepatic impairment. Caution should be exercised in patients with severe renal or moderate hepatic impairment. Invirase/ritonavir is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 4.4).

Children under the age of 16 and adults over 60 years:
The experience with Invirase in children below the age of 16 and adults over 60 years is limited. In children, as in adults, Invirase should only be given in combination with ritonavir.

4.3 Contraindications

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

Invirase/ritonavir is contraindicated in decompensated liver disease (see section 4.4).

Invirase/ritonavir should not be given together with other medicinal products which may interact and result in potentially life threatening undesirable effects.

Medicinal products which should not be given with Invirase/ritonavir include:

- terfenadine, astemizole, pimozide, cisapride, amiodarone, propafenone and flecainide (potential for life threatening cardiac arrhythmia)
- midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5), triazolam (potential for prolonged or increased sedation, respiratory depression)
- simvastatin, lovastatin (increased risk of myopathy including rhabdomyolysis)
- ergot alkaloids (e.g. ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (potential for acute ergot toxicity)
- rifampicin (risk of severe hepatocellular toxicity) (see sections 4.4, 4.5, and 4.8).

4.4 Special warnings and precautions for use

Considerations when initiating Invirase therapy: Invirase should not be given as the sole protease inhibitor. Invirase should only be given in combination with ritonavir (see section 4.2).

Patients should be informed that saquinavir is not a cure for HIV infection and that they may continue to acquire illnesses associated with advanced HIV infection, including opportunistic infections. Patients should also be advised that they might experience undesirable effects associated with co-administered medications.

Liver disease: The safety and efficacy of saquinavir/ritonavir has not been established in patients with significant underlying liver disorders, therefore saquinavir/ritonavir should be used cautiously in this patient population. Invirase/ritonavir is contraindicated in patients with decompensated liver disease (see section 4.3). Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

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

In cases of mild hepatic impairment no initial dosage adjustment is necessary at the recommended dose. The use of Invirase in combination with ritonavir in patients with moderate hepatic impairment has not been studied. In the absence of such studies, caution should be exercised, as increases in saquinavir levels and/or increases in liver enzymes may occur.
There have been reports of exacerbation of chronic liver dysfunction, including portal hypertension, in patients with underlying hepatitis B or C, cirrhosis and other underlying liver abnormalities.

Renal impairment: Renal clearance is only a minor elimination pathway, the principal route of metabolism and excretion for saquinavir being via the liver. Therefore, no initial dose adjustment is necessary for patients with renal impairment. However, patients with severe renal impairment have not been studied and caution should be exercised when prescribing saquinavir/ritonavir in this population.

Patients with chronic diarrhoea or malabsorption: No information on boosted saquinavir and only limited information on the safety and efficacy of unboosted saquinavir is available for patients

suffering from chronic diarrhoea or malabsorption. It is unknown whether patients with such conditions could receive subtherapeutic saquinavir levels.

Children under the age of 16 and adults over 60 years: The experience with Invirase in children below the age of 16 and adults over 60 years is limited. In children, as in adults, Invirase should only be given in combination with ritonavir.

Lactose intolerance: Invirase 200 mg capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Patients with haemophilia: There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with 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.

Diabetes mellitus and hyperglycaemia: New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving protease inhibitors. In some of these patients, the hyperglycaemia was severe and in some cases was 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 mellitus or hyperglycaemia.

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

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

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

Interaction with ritonavir: The recommended dose of Invirase and ritonavir is 1000 mg Invirase plus 100 mg ritonavir twice daily. Higher doses of ritonavir have been shown to be associated with an increased incidence of adverse events. Co-administration of saquinavir and ritonavir has led to severe adverse events, mainly diabetic ketoacidosis and liver disorders, especially in patients with pre-existing liver disease.

Interaction with tipranavir: Concomitant use of boosted saquinavir and tipranavir, co-administered with low dose ritonavir in a dual-boosted regimen, results in a significant decrease in saquinavir

plasma concentrations (see section 4.5). Therefore, the co-administration of boosted saquinavir and tipranavir, co-administered with low dose ritonavir, is not recommended.

Interaction with HMG-CoA reductase inhibitors: Caution must be exercised if Invirase/ritonavir 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).

Oral contraceptives: Because concentration of ethinyl estradiol may be decreased when co-administered with Invirase/ritonavir, alternative or additional contraceptive measures should be used when oestrogen-based oral contraceptives are co-administered (see section 4.5).

Glucocorticoids: Concomitant use of boosted saquinavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

Interaction with efavirenz: The combination of saquinavir and ritonavir with efavirenz has been shown to be associated with an increased risk of liver toxicity; liver function should be monitored when saquinavir and ritonavir are co-administered with efavirenz. No clinically significant alterations of either saquinavir or efavirenz concentration were noted in studies in healthy volunteers or in HIV-infected patients (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Most drug interaction studies with saquinavir have been completed with unboosted Invirase or unboosted saquinavir soft capsules (Fortovase). A limited number of studies have been completed with ritonavir boosted Invirase or ritonavir boosted saquinavir soft capsules.

Observations from drug interaction studies done with unboosted saquinavir might not be representative of the effects seen with saquinavir/ritonavir therapy. Furthermore, results seen with saquinavir soft capsules may not predict the magnitude of these interactions with Invirase/ritonavir.

The metabolism of saquinavir is mediated by cytochrome P450, with the specific isoenzyme CYP3A4 responsible for 90 % of the hepatic metabolism. Additionally, *in vitro* studies have shown that saquinavir is a substrate and an inhibitor for P-glycoprotein (P-gp). Therefore, medicinal products that either share this metabolic pathway or modify CYP3A4 and/or P-gp activity (see *"Other potential interactions"*) may modify the pharmacokinetics of saquinavir. Similarly, saquinavir might also modify the pharmacokinetics of other medicinal products that are substrates for CYP3A4 or P-gp.

Ritonavir can affect the pharmacokinetics of other medicinal products because it is a potent inhibitor of CYP3A4 and P-gp. Therefore, when saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on other medicinal products (see the Summary of Product Characteristics for Norvir).

Antiretroviral agents

Nucleoside reverse transcriptase inhibitors (NRTIs):

Zalcitabine and/or zidovudine: ***Saquinavir/ritonavir:*** No pharmacokinetic interaction studies have been completed with these agents given in combination with saquinavir/ritonavir. However, for zalcitabine an interaction is unlikely as this medicinal product has differential routes of metabolism and excretion and is unlikely to affect absorption of saquinavir/ritonavir. For zidovudine given 200 mg every 8 hours a 25 % decrease in AUC of zidovudine was reported when combined with ritonavir (300 mg every 6 hours), whereas the pharmacokinetics of ritonavir was not affected by zidovudine. No dose modification of zidovudine is warranted when zidovudine is co-administered with ritonavir. ***Saquinavir:*** Concomitant use of Invirase with zalcitabine and/or zidovudine has been studied in adults.

Absorption, distribution and elimination of each of the medicinal products are unchanged when they are used together.

Didanosine: ***Saquinavir/ritonavir:*** The effects of a single dose of didanosine 400 mg on the pharmacokinetics of saquinavir in eight healthy subjects who received saquinavir soft capsules /ritonavir 1600/100 mg once daily for 2 weeks was investigated. Didanosine decreased saquinavir AUC and C_{max} approximately 30 % and 25 %, respectively, and had essentially no effect on C_{min} of saquinavir. These changes are of doubtful clinical significance.

Tenofovir: ***Saquinavir/ritonavir:*** Concomitant administration of tenofovir disoproxil fumarate with Invirase/ritonavir 1000/100 mg had no clinically significant effect on saquinavir exposure. In 18 HIV-infected patients treated with Invirase/ritonavir 1000/100 mg twice daily and tenofovir disoproxil fumarate 300 mg once daily, saquinavir AUC and C_{max} values were 1 % and 7 % lower than those seen with saquinavir/ritonavir alone. No dose adjustment is required when ritonavir boosted Invirase is combined with tenofovir disoproxil fumarate.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs):

Delavirdine: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and delavirdine has not been evaluated. ***Saquinavir:*** Co-administration of delavirdine with Invirase resulted in a 348 % increase in saquinavir plasma AUC. Currently there are limited safety and no efficacy data available from the use of this combination. In a small, preliminary study, hepatocellular enzyme elevations occurred in 13 % of subjects during the first several weeks of the delavirdine and saquinavir combination (6 % Grade 3 or 4). Hepatocellular changes should be monitored frequently if this combination is prescribed.

Efavirenz: ***Saquinavir/ritonavir:*** No clinically relevant alterations of either saquinavir or efavirenz concentrations were noted in a study in twenty-four healthy subjects who received saquinavir soft capsules /ritonavir/efavirenz 1600/200/600 mg once daily. Two additional studies in HIV patients investigated the effect of concomitant administration of efavirenz with either a twice-daily boosted regimen (Invirase/ritonavir 1000/100 mg twice daily) (n=32) or a once-daily boosted regimen (saquinavir soft capsules /ritonavir 1200/100 mg once daily) (n=35). No clinically significant alterations of either saquinavir or efavirenz concentrations were noted in either study.

Nevirapine: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and nevirapine has not been evaluated. ***Saquinavir:*** Co-administration of nevirapine and Invirase resulted in a 24 % decrease in plasma saquinavir AUC and no change to nevirapine AUC. The decrease is not thought to be clinically relevant and no dose adjustments of Invirase or nevirapine are recommended.

HIV protease inhibitors (PIs):

Atazanavir: ***Saquinavir/ritonavir:*** Concomitant administration of Invirase/ritonavir 1600/100 mg once daily with atazanavir 300 mg once daily to 18 HIV-infected patients resulted in saquinavir AUC and C_{max} values which were 60 % and 42 % respectively, higher than those seen with Invirase/ritonavir (at 1600/100 mg once daily) alone. Ritonavir AUC and Cmax values were increased by 41 % and 34 % respectively, whereas pharmacokinetic parameters of atazanavir remained unchanged. No clinical data exist with the approved dosing regimen of saquinavir/ritonavir and atazanavir.

Fosamprenavir: ***Saquinavir/ritonavir:*** Concomitant administration of fosamprenavir with Invirase/ritonavir 1000/100 mg had no clinically significant effect on saquinavir exposure. In 18 HIV-infected patients treated with Invirase/ritonavir 1000/100 mg and fosamprenavir 700 mg twice daily, saquinavir AUC and C_{max} values were 15 % and 9 % lower than those seen with saquinavir/ritonavir alone. Saquinavir C_{min} remained above the target threshold for effective therapy (decreasing by 24 % from 508 to 386 ng/ml). No dose adjustment is required when ritonavir boosted Invirase is combined with fosamprenavir.

Indinavir: ***Saquinavir/ritonavir:*** The administration of low dose ritonavir increases the concentrations of indinavir, which may result in nephrolithiasis. ***Saquinavir:*** Co-administration of indinavir (800 mg three times daily) and single doses of Invirase (600 mg) or saquinavir soft capsules (800 or 1200 mg) in six healthy volunteers each resulted in 4.6 – 7.2 fold increases in plasma saquinavir AUC_{0-24}. Indinavir plasma levels remained unchanged. Currently, no safety and efficacy data are available from the use of this combination. Appropriate doses of the combination have not been established.

Lopinavir: ***Saquinavir/ritonavir:*** The pharmacokinetic parameters of saquinavir, ritonavir and lopinavir have been investigated in HIV-infected patients treated with either saquinavir soft capsules/ritonavir 1000/100 mg twice daily in combination with 2 or 3 NRTIs (n=32) or saquinavir soft capsules 1000 mg twice daily and the fixed combination of lopinavir/ritonavir 400/100 mg twice daily (n=45). Lopinavir did not alter the pharmacokinetics of boosted saquinavir. The ritonavir exposure was significantly lower in the patients taking lopinavir but its effectiveness as a boosting agent was not modified. Concentrations of lopinavir did not appear to be affected when lopinavir/ritonavir and saquinavir were combined, based on historical comparison with lopinavir/ritonavir alone. No dose adjustment is required when ritonavir boosted Invirase is combined with lopinavir.

Nelfinavir: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and nelfinavir has not been evaluated. ***Saquinavir:*** Concomitant administration of a single 1200 mg dose of saquinavir soft capsules on the fourth day of multiple nelfinavir dosing (750 mg three times daily) to 14 HIV infected patients resulted in saquinavir AUC and C_{max} values which were 392 % and 179 % higher than those seen with saquinavir alone. Concomitant administration of a single 750 mg dose of nelfinavir on the fourth day of multiple saquinavir soft capsules dosing (1200 mg three times daily) to the same patients resulted in nelfinavir AUC values which were 18 % higher than those seen with nelfinavir alone, while C_{max} values remained unchanged. Quadruple therapy, including saquinavir soft capsules and nelfinavir in addition to two nucleoside reverse transcriptase inhibitors gave a more durable response (prolongation of time to virological relapse) than triple therapy with either single protease inhibitor. The regimens were generally well tolerated. However, concomitant administration of nelfinavir and saquinavir soft capsules resulted in a moderate increase in the incidence of diarrhoea.

Ritonavir: Saquinavir has been shown not to alter the pharmacokinetics of ritonavir following single or multiple oral doses in healthy volunteers. Ritonavir extensively inhibits the metabolism of saquinavir resulting in greatly increased saquinavir plasma concentrations. In HIV-infected patients, Invirase or saquinavir soft capsules in combination with ritonavir at doses of 1000/100 mg twice daily provide saquinavir systemic exposure over a 24 hour period similar to or greater than those achieved with saquinavir soft capsules 1200 mg three times daily (see section 5.2).

Tipranavir: ***Saquinavir/ritonavir:*** In a clinical study of dual-boosted protease inhibitor combination therapy in multiple-treatment experienced HIV-positive adults, tipranavir, co-administered with low dose ritonavir, caused a 78% reduction in the Cmin of saquinavir. Therefore the concomitant administration of tipranavir, co-administered with low dose ritonavir, with saquinavir/ritonavir, is not recommended. If the combination is nevertheless considered necessary, a monitoring of the saquinavir plasma levels is strongly encouraged.

HIV fusion inhibitor:

Enfuvirtide: ***Saquinavir/ritonavir:*** No clinically significant interaction was noted from a study in 12 HIV patients who received enfuvirtide concomitantly with saquinavir soft capsules /ritonavir 1000/100 mg twice daily.

Other medicinal products

Antiarrhythmics:

Bepridil, systemic lidocaine, quinidine: Concentrations of these medicinal products may be increased when co-administered with Invirase/ritonavir. Caution is warranted and therapeutic concentration monitoring, if available, is recommended if these antiarrhythmics are given with Invirase/ritonavir.

Amiodarone, flecainide and propafenone: Concentrations of these medicinal products may be increased when co-administered with Invirase/ritonavir. Due to a potential for life threatening cardiac arrhythmia, amiodarone, flecainide and propafenone are contra-indicated with Invirase/ritonavir (see section 4.3).

Anticoagulant:

Warfarin: Concentrations of warfarin may be affected. It is recommended that INR (international normalised ratio) be monitored.

Anticonvulsants:

Carbamazepine, phenobarbital, phenytoin: These medicinal products will induce CYP3A4 and may decrease saquinavir concentrations if Invirase is taken without ritonavir. The interaction between Invirase/ritonavir and these medicinal products has not been evaluated.

Antidepressants:

Tricyclic antidepressants (e.g. amitriptyline, imipramine): Invirase/ritonavir may increase the concentrations of tricyclic antidepressants. Therapeutic concentration monitoring is recommended for tricyclic antidepressants when co-administered with Invirase/ritonavir.

Nefazodone: Will inhibit CYP3A4 and may increase saquinavir concentrations. If nefazodone is taken concomitantly with saquinavir, monitoring for saquinavir toxicity is recommended. The interaction between Invirase/ritonavir and nefazodone has not been evaluated.

Antihistamines:

Terfenadine, astemizole***:*** Co-administration of terfenadine and saquinavir soft capsules leads to an increase in plasma terfenadine exposure (AUC) associated with a prolongation of QTc intervals. Hence, terfenadine is contraindicated in patients receiving saquinavir or saquinavir/ritonavir. As similar interactions are likely, saquinavir or saquinavir/ritonavir should not be administered with astemizole (see section 4.3).

Anti-infectives:

Clarithromycin: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and clarithromycin has not been evaluated. ***Saquinavir:*** Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir soft capsules (1200 mg three times daily) to 12 healthy volunteers resulted in steady-state saquinavir AUC and C_{max} values which were 177 % and 187 % higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} values were approximately 40 % higher than those seen with clarithromycin alone. No dose adjustment is required when the two medicinal products are co-administered for a limited time at the doses studied.

Erythromycin: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and erythromycin has not been evaluated. ***Saquinavir:*** Concomitant administration of erythromycin (250 mg four times daily) and saquinavir soft capsules (1200 mg three times daily) to 22 HIV-infected patients resulted in

steady-state saquinavir AUC and C_{max} values which were 99 % and 106 % higher than those seen with saquinavir alone. No dose adjustment is required when the two medicinal products are co-administered.

Streptogramin antibiotics such as quinupristin/dalfopristin: Will inhibit CYP3A4 and may increase saquinavir concentrations. If these medicinal products are taken concomitantly with saquinavir, monitoring for saquinavir toxicity is recommended. The interaction between Invirase/ritonavir and quinupristin/dalfopristin has not been evaluated.

Antifungals:

Ketoconazole: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and ketoconazole has not been evaluated. ***Saquinavir:*** Concomitant use of ketoconazole (200 mg once daily) and Invirase (600 mg three times daily) to 12 healthy volunteers led to an increase in saquinavir AUC by about 160 % at steady state (day 6 of treatment) with no increase in the elimination half-life or any change in the absorption rate. Ketoconazole pharmacokinetics were not affected by co-administration with saquinavir at a dose of 600 mg three times daily. No dose adjustment for either medicinal product is required when the two medicinal products are co-administered at the doses studied.

Itraconazole: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and itraconazole has not been evaluated. ***Saquinavir:*** Like ketoconazole, itraconazole is a moderately potent inhibitor of the CYP3A4 isoenzyme and an interaction of similar magnitude is possible. If itraconazole is taken concomitantly with saquinavir, monitoring for saquinavir toxicity is recommended.

Fluconazole/miconazole: No specific drug interaction studies with either of these medicinal products have been performed.

Antimycobacterials:

Rifampicin: ***Saquinavir/ritonavir:*** In a study investigating the interaction of rifampicin 600 mg once daily and Invirase 1000 mg/ritonavir 100 mg given twice daily, 11 of 17 (65 %) healthy volunteers developed severe hepatocellular toxicity with transaminase elevations up to > 20-fold the upper limit of normal after 1 to 5 days of co-administration. Therefore, rifampicin is contraindicated in patients taking ritonavir boosted Invirase as part of an ART regimen (see section 4.3).

Rifabutin: ***Saquinavir/ritonavir:*** Concomitant administration of rifabutin with saquinavir/ritonavir 1000/100 mg twice daily has not been evaluated. A dosage reduction to rifabutin 150 mg every 3 days is recommended based on experience with low dose ritonavir boosted protease inhibitors. Patients receiving rifabutin with Invirase/ritonavir should be closely monitored for liver function test elevations and emergence of adverse events associated with rifabutin therapy. Further dosage reduction of rifabutin may be necessary. Therapeutic concentration monitoring for saquinavir is recommended.

Benzodiazepines:

Midazolam: ***Saquinavir/ritonavir:*** Co-administration of a single oral dose of midazolam 7.5 mg after 2 weeks of Invirase/ritonavir 1000/100 mg twice daily to 16 healthy volunteers in a cross-over study, increased midazolam C_{max} by 4.3-fold and AUC by 12.4-fold. Invirase/ritonavir increased the elimination half-life of oral midazolam from 4.7 to 14.9 h. Therefore, the co-administration of Invirase/ritonavir with orally administered midazolam is contraindicated (see section 4.3), whereas caution should be used with co-administration of Invirase and parenteral midazolam. No data are available on concomitant use of ritonavir boosted saquinavir with intravenous midazolam; studies of other CYP3A modulators and i.v. midazolam suggest a possible 3-4 fold increase in midazolam plasma levels. If Invirase is co-administered with parenteral midazolam it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment should be considered, especially if more than a single dose of midazolam is administered.

Alprazolam, clorazepate, diazepam, flurazepam: Concentrations of these medicinal products may be increased when co-administered with Invirase/ritonavir. Careful monitoring of patients with regard to sedative effects is warranted, a decrease in the dose of the benzodiazepine may be required.

Triazolam: Concentrations of triazolam may be increased when co-administered with Invirase/ritonavir. Triazolam is contra-indicated with Invirase/ritonavir, due to the risk of potential for prolonged or increased sedation and respiratory depression (see section 4.3).

Calcium channel blockers:

Felodipine, nifedipine, nicardipine, diltiazem, nimodipine, verapamil, amlodipine, nisoldipine, isradipine: Concentrations of these medicinal products may be increased when co-administered with Invirase/ritonavir. Caution is warranted and clinical monitoring of patients is recommended.

Corticosteroids:

Dexamethasone: Will induce CYP3A4 and may decrease saquinavir concentrations. Use with caution, saquinavir may be less effective in patients taking these medicinal products concomitantly. The interaction between Invirase/ritonavir and dexamethasone has not been evaluated.

Fluticasone propionate (interaction with ritonavir): In a clinical study where ritonavir 100 mg capsules twice daily were co-administered with 50 µg intranasal fluticasone propionate (4 times daily) for 7 days in healthy subjects, the fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86 % (90 % confidence interval 82-89 %). Greater effects may be expected when fluticasone propionate is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolised via the P450 3A pathway e.g. budesonide. Consequently, concomitant administration of boosted saquinavir and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g. beclometasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may have to be performed over a longer period. The effects of high fluticasone systemic exposure on ritonavir plasma levels is yet unknown.

Medicinal products that are substrates of P-glycoprotein:

Digitalis glycosides:

Digoxin: ***Saquinavir/ritonavir:*** Co-administration of a single oral dose of digoxin 0.5 mg after 2 weeks of Invirase/ritonavir 1000/100 mg twice daily to 16 healthy volunteers in a cross-over study, increased digoxin C_{max} by 27% and AUC_{0-72} by 49%. Caution should be exercised when Invirase/ritonavir and digoxin are co-administered. The digoxin levels may differ over time, and large increments of digoxin may be expected when saquinavir/ritonavir is introduced in patients already treated with digoxin. The serum concentration of digoxin should be monitored and a dose reduction of digoxin should be considered if necessary.

Histamine H_2-receptor antagonist:

Ranitidine: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and ranitidine has not been evaluated. ***Saquinavir:*** In a study in 12 healthy male volunteers there was an increase in exposure of saquinavir when Invirase was dosed in the presence of both ranitidine and food, relative to Invirase dosed with food alone. This resulted in AUC values of saquinavir, which were 67 % higher. This increase is not thought to be clinically relevant and no dose adjustment of saquinavir is recommended.

HMG-CoA reductase inhibitors:

Pravastatin, fluvastatin: Are not metabolised by CYP3A4, and interactions are not expected with protease inhibitors including ritonavir. If treatment with a HMG-CoA reductase inhibitor is indicated, either pravastatin or fluvastatin are the products recommended.

Simvastatin, lovastatin: Are highly dependent on CYP3A4 metabolism, and plasma concentrations are markedly increased when co-administered with Invirase/ritonavir. Increased concentrations of these medicinal products have been associated with rhabdomyolysis and these medicinal products are contraindicated for use with Invirase/ritonavir (see section 4.3).

Atorvastatin: Is less dependent on CYP3A4 for metabolism. When used with Invirase/ritonavir, the lowest possible dose of atorvastatin should be administered and the patient carefully monitored for signs/symptoms of myopathy (muscle weakness, muscle pain, rising plasma creatinine kinase levels).

Immunosuppressants:

Ciclosporin, tacrolimus, rapamycin: Concentrations of these medicinal products increase several fold when co-administered with Invirase/ritonavir. Careful therapeutic drug monitoring is necessary for immunosuppressants when co-administered with Invirase/ritonavir.

Narcotic analgesic:

Methadone: Concentration of methadone may be decreased when co-administered with Invirase/ritonavir. Dosage of methadone may need to be increased.

Neuroleptics:

Pimozide: Concentrations of pimozide may be increased when co-administered with Invirase/ritonavir. Due to a potential for life threatening cardiac arrhythmias, Invirase/ritonavir is contra-indicated in combination with pimozide (see section 4.3).

Oral contraceptives:

Ethinyl estradiol: Concentration of ethinyl estradiol may be decreased when co-administered with Invirase/ritonavir. Alternative or additional contraceptive measures should be used when oestrogen-based oral contraceptives are co-administered.

Phosphodiesterase type 5 (PDE5) inhibitors:

Sildenafil: The co-administration of saquinavir soft capsules at steady state (1200 mg three times daily) with sildenafil (100 mg single dose), a substrate of CYP3A4, resulted in a 140 % increase in sildenafil C_{max} and a 210 % increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics. Use sildenafil with caution at reduced doses of no more than 25 mg every 48 hours with increased monitoring of adverse events when administered concomitantly with Invirase/ritonavir.

Vardenafil: Concentrations of vardenafil may be increased when co-administered with Invirase/ritonavir. Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring of adverse events when administered concomitantly with Invirase/ritonavir.

Tadalafil: Concentrations of tadalafil may be increased when co-administered with Invirase/ritonavir. Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring of adverse events when administered concomitantly with Invirase/ritonavir.

Proton pump inhibitors:

Omeprazole: Concomitant administration of omeprazole (40 mg once daily) and Invirase/ritonavir (1000/100 mg twice daily) to 18 healthy volunteers resulted in steady-state saquinavir AUC and C_{max} values which were 82% (90 % confidence interval 44-131 %) and 75% (90 % confidence interval 38-123 %) higher than those seen with Invirase/ritonavir alone. If omeprazole is taken concomitantly with Invirase/ritonavir, monitoring for potential saquinavir toxicities is recommended. The plasma levels of ritonavir did not change significantly after omeprazole use.

Others:

Ergot alkaloids (e.g. ergotamine, dihydroergotamine, ergonovine, and methylergonovine): Invirase/ritonavir may increase ergot alkaloids exposure, and consequently, increase the potential for acute ergot toxicity. Thus, the concomitant use of Invirase/ritonavir and ergot alkaloids is contra-indicated (see section 4.3).

Grapefruit juice: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and grapefruit juice has not been evaluated. ***Saquinavir:*** Co-administration of Invirase and grapefruit juice as single administration in healthy volunteers results in a 50 % and 100 % increase in exposure to saquinavir for normal and double strength grapefruit juice, respectively. This increase is not thought to be clinically relevant and no dose adjustment of Invirase is recommended.

Garlic capsules: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and garlic capsules has not been evaluated. ***Saquinavir:*** Concomitant administration of garlic capsules (dose approx. equivalent to two 4 g cloves of garlic daily) and saquinavir soft capsules 1200 mg three times daily to nine healthy volunteers resulted in a decrease of saquinavir AUC by 51 % and a decrease of the mean trough levels at 8 hours post dose by 49 %. Saquinavir mean C_{max} levels decreased by 54 %. Therefore patients on saquinavir treatment must not take garlic capsules due to the risk of decreased plasma concentrations and loss of virological response and possible resistance to one or more components of the antiretroviral regimen.

St. John's wort *(Hypericum perforatum)*: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and St. John's wort has not been evaluated. ***Saquinavir:*** Plasma levels of saquinavir 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 Invirase. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible saquinavir levels. Saquinavir levels may increase on stopping St. John's wort, and the dose of saquinavir may need adjusting. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment.

Other potential interactions

Medicinal products that are substrates of CYP3A4:

Although specific studies have not been performed, co-administration of Invirase/ritonavir with medicinal products that are mainly metabolised by CYP3A4 pathway (e.g. dapsone, disopyramide, quinine, fentanyl, and alfentanyl) may result in elevated plasma concentrations of these medicinal products. Therefore these combinations should be given with caution.

Medicinal products reducing gastrointestinal transit time:

It is unknown, whether medicinal products which reduce the gastrointestinal transit time (e.g. metoclopramide) could lead to lower saquinavir plasma concentrations.

4.6 Pregnancy and lactation

***Pregnancy*:** Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo or foetus, the course of gestation and peri- and post-natal development. Clinical experience in pregnant women is limited: Congenital malformations, birth defects and other disorders (without a congenital malformation) have been reported rarely in pregnant women who had received saquinavir in combination with other antiretroviral agents. However, so far the available data are insufficient and do not identify specific risks for the unborn child. Saquinavir should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus (see section 5.3).

***Lactation*:** There are no laboratory animal or human data available on secretion of saquinavir in breast milk. The potential for adverse reactions to saquinavir in nursing infants cannot be assessed, and therefore, breast-feeding should be discontinued prior to receiving saquinavir. It is recommended that HIV-infected women do not breast feed their infants under any circumstances in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

Invirase may have a minor influence on the ability to drive and use machines. Dizziness and fatigue have been reported during treatment with Invirase. No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The following adverse events with an at least possible relationship to ritonavir boosted saquinavir (i.e. adverse reactions) were reported most frequently: nausea, diarrhoea, fatigue, vomiting, flatulence, and abdominal pain.

For comprehensive dose adjustment recommendations and drug-associated adverse reactions for ritonavir and other medicinal products used in combination with saquinavir, physicians should refer to the Summary of Product Characteristics for each of these medicinal products.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions from clinical trials where saquinavir was boosted with ritonavir

Limited data is available from two studies where the safety of saquinavir soft capsule (1000 mg twice daily) used in combination with low dose ritonavir (100 mg twice daily) for at least 48 weeks was studied in 311 patients. Adverse reactions in these two pivotal studies are summarised in Table 1. The list also includes marked laboratory abnormalities that have been observed with the saquinavir soft capsule in combination with ritonavir (at 48 weeks).

Table 1: Incidences of Adverse Reactions and marked laboratory abnormalities from the MaxCmin1 and MaxCmin2 study. (Very common (≥ 10 %); common (≥ 1 % and < 10 %))

Body System **Frequency of Reaction**	Adverse Reactions	
	Grades 3&4	All Grades
Blood and the lymphatic system disorders		
Common	Anaemia	Anaemia
Immune system disorders		
Common		Hypersensitivity
Metabolism and nutrition disorders		
Common	Diabetes mellitus	Diabetes mellitus, anorexia, increased appetite
Psychiatric disorders		
Common		Decreased libido, sleep disorder
Nervous System Disorders		
Common		Paraesthesia, peripheral neuropathy, dizziness, dysgeusia, headache
Respiratory, thoracic and mediastinal disorders		
Common		Dyspnoea
Gastrointestinal disorders		
Very common		Diarrhoea, nausea
Common	Diarrhoea, nausea, vomiting	Vomiting, abdominal distension, abdominal pain, upper abdominal pain, constipation, dry mouth, dyspepsia, eructation, flatulence, lip dry, loose stools
Skin and subcutaneous tissue disorders		
Common	Acquired lipodystrophy	Acquired lipodystrophy, alopecia, dry skin, eczema, lipoatrophy, pruritus, rash
Musculoskeletal and connective tissue disorders		
Common		Muscle spasms
General disorders and administration site conditions		
Common	Fatigue	Asthenia, fatigue, increased fat tissue, malaise
Investigations		
Very common		Increased alanine aminotransferase, increased aspartate aminotransferase, increased blood cholesterol, increased blood triglycerides, increased low density lipoprotein, decreased platelet count
Common		Increased blood amylase, increased blood bilirubin, increased blood creatinine, decreased haemoglobin, decreased lymphocyte count, decreased white blood cell count

Post-marketing experience with saquinavir

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

- Immune system disorders: Hypersensitivity.

- Metabolism and nutrition disorders:

  - Diabetes mellitus or hyperglycaemia sometimes associated with ketoacidosis (see section 4.4).
  - Lipodystrophy: Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsicervical fat accumulation (buffalo hump).
  - Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

- Nervous system disorders: Somnolence, convulsions.

- Vascular disorders: There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophilic patients type A and B treated with protease inhibitors (see section 4.4).

- Hepato-biliary disorders: Hepatitis.

- Musculoskeletal, connective tissue and bone disorders: Increased CPK, myalgia, myositis and rarely, rhabdomyolysis have been reported with protease inhibitors, particularly in combination with nucleoside analogues. Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

- Renal and urinary disorders: Renal impairment.

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

4.9 Overdose

There are two reports of patients who had overdoses with unboosted Invirase. One patient exceeded the recommended daily dose of saquinavir and took 8000 mg at once. The patient was treated with induction of emesis within two hours after ingestion of the overdose. The patient did not experience any sequelae. The second patient ingested 2.4 g of Invirase in combination with 600 mg of ritonavir and experienced pain in the throat that lasted for 6 hours and then resolved. In an exploratory small study, oral dosing with saquinavir at 3600 mg per day has not shown increased toxicity through the first 16 weeks of treatment.
Two cases of overdosage with unboosted saquinavir soft capsules have been received (one case with an unknown amount of saquinavir soft capsules, and a second case with 3.6 g to 4 g at once). No adverse events were reported in any of the cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Antiviral agent, ATC code J05A E01

Mechanism of action: The HIV protease carries out specific cleavages of viral precursor proteins as virions bud from infected cells. This is an essential step in the creation of fully formed, infectious virus particles. These viral precursor proteins contain a type of cleavage site which is recognised only

by HIV and closely related viral proteases. Saquinavir is a mimetic of such cleavage sites and fits closely into the HIV-1 and HIV-2 protease active sites, acting as a reversible and selective inhibitor. Saquinavir has approximately 50,000-fold greater affinity for HIV protease than for human proteases. In *in vitro* antiviral assays saquinavir blocks the formation of infectious virus, and hence the spread of infection to naïve cells.

Antiviral activity in vitro: Unlike nucleoside analogues (zidovudine, etc.), saquinavir acts directly on its viral target enzyme. It does not require metabolic activation. This extends its potential effectiveness into resting cells. Saquinavir is active at nanomolar concentrations in lymphoblastoid and monocytic lines and in primary cultures of lymphocytes and monocytes infected with laboratory strains or clinical isolates of HIV-1. Experiments in cell culture show that saquinavir produces an additive to synergistic antiviral effect against HIV-1 in double and triple combination with various reverse transcriptase inhibitors (including zidovudine, zalcitabine, didanosine, lamivudine, stavudine and nevirapine) without enhanced cytotoxicity, and clear synergy in double combination with lopinavir.

Pharmacodynamic effects: Early clinical studies assessed the effects in HIV-1 infected patients of unboosted saquinavir in combination with other antiretroviral agents on clinical endpoints and biological markers. Subsequently, the effects of boosted saquinavir in combination with other antiretroviral agents on biological markers (CD4 cell counts and plasma RNA) were evaluated in HIV-1 infected patients.

Clinical studies performed with boosted saquinavir soft capsules

In the MaxCmin1 study, the safety and efficacy of saquinavir soft capsules/ritonavir 1000/100 mg twice daily plus 2 NRTIs/Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) was compared to indinavir/ritonavir 800/100 mg twice daily plus 2 NRTIs/NNRTIs in over 300 (both protease inhibitor treatment naïve and experienced) subjects. The combination of saquinavir and ritonavir exhibited a superior virological activity compared with the indinavir and ritonavir arm when switch from the assigned treatment was counted as virological failure.

In the MaxCmin2 study, the safety and efficacy of saquinavir soft capsules/ritonavir 1000/100 mg twice daily plus 2 NRTIs/NNRTIs was compared with lopinavir/ritonavir 400/100 mg twice daily plus 2 NRTIs/NNRTIs in 324 (both protease inhibitor treatment naïve and experienced) subjects. None of the subjects in the lopinavir/ritonavir arm had been exposed to lopinavir prior to randomisation whereas 16 of the subjects in the saquinavir/ritonavir arm had previously been exposed to saquinavir.

Demographic characteristics for studies MaxCmin1 and MaxCmin2 are shown in Table 2 and the disposition and efficacy outcomes of studies MaxCmin 1 and MaxCmin 2 are shown in Table 3.

Table 2: Subject Demographics MaxCmin1 and MaxCmin2[†]

[†] data from clinical study report

	MaxCmin1		**MaxCmin2**	
	SQV/r N=148	**IDV/r N=158**	**SQV/r N=161**	**LPV/r N=163**
Sex Male Female	 82% 18%	 74% 26%	 81% 19%	 76% 24%
Race White Black Asian	 86% 9% 1%	 82% 12% 4%	 75% 19% 1%	 74% 19% 2%
Age, median, yrs (IQR)	39 (34-48)	40 (34-46)	40 (35-50)	40 (35-47)
CDC Category C (%)	32%	28%	32%	31%
Antiretroviral naïve (%)	28%	22%	31%	34%
PI naïve (%)	41%	38%	48%	48%
Median Baseline HIV-1 RNA, log_{10} copies/mL (IQR)	4.0 (1.7-5.1)	3.9 (1.7-5.2)	4.4 (3.1-5.1)	4.6 (3.5-5.3)
Baseline VL < 400 copies/mL	38%	39%	22%	21%
Median Baseline $CD4^+$ Cell Count, cells/mm^3 (IQR)	272 (135-420)	280 (139-453)	241 (86-400)	239 (95-420)

Table 3: Outcomes at Week 48 MaxCmin1 and MaxCmin2[†]

Outcomes	**MaxCmin1**		**MaxCmin2**	
Status at week 48	**SQV/r**	**IDV/r**	**SQV/r**	**LPV/r**
Randomized	N=158	N=159	N=172	N=167
Initiated assigned treatment, n (%)	148 (94%)	158 (99%)	161 (94%)	163 (98%)
Discontinued assigned treatment, n (%)	40 (27%)	64 (41%)	48 (30%)	23 (14%)
	P=0.01		P=0.001	
Reason for discontinuation n, (%)				
Virological failure	2 (5%)	3 (5%)	3 (6%)	0
Death	1 (3%)	1 (2%)	3 (6%)	0
Clinical non-fatal adverse event	22 (55%)	45 (70%)	21 (44%)	12 (52%)
Laboratory adverse event	2 (5%)	4 (6%)	1 (2%)	1 (4%)
Patient choice	5 (13%)	3 (5%)	8 (17%)	7 (30%)
Lost to follow-up	3 (8%)	5 (8%)	4 (8%)	2 (9%)
Other	5 (13%)	3 (5%)	8 (17%)	1 (4%)
Completed 48 weeks of assigned treatment	108 (73%)	94 (59%)	113 (70%)	140 (86%)
Patients with outcome at week 48	137 (93%)	148 (94%)	146 (91%)	158 (97%)

[†] data from clinical study report

Table 3 (continued): Outcomes at Week 48 MaxCmin1 and MaxCmin2†

Outcomes **Status at week 48** **Virological and Immunological Outcomes**	**MaxCmin1** **SQV/r**	**IDV/r**	**MaxCmin2** **SQV/r**	**LPV/r**
Virological failure*	36/148 (24%)	41/158 (26%)	53/161 (33%)	29/163 (18%)
	P=0.76		P=0.002	
Virological failure, switch/discontinue = failure	51/148 (34%)	77/158 (49%)	63/161 (39%)	40/161 (25%)
	P=0.01		P=0.005	
Proportion with VL < 50 copies/mL at week 48, ITT/e#	97/144 (67%)	106/154 (69%)	90/158 (57%)	106/162 (65%)
	P >0.05‡		P=0.12	
Proportion with VL < 50 copies/mL at week 48, ITT/e/s##	82/144 (57%)	73/158 (46%)	84/158 (53%)	97/162 (60%)
	P=0.048‡		P=0.23	
Proportion with VL < 50 copies/mL at week 48, On Treatment	82/104 (79%)	73/93 (78%)	84/113 (74%)	97/138 (70%)
	P>0.05‡		P=0.48	
Proportion with VL < 400 copies/mL at week 48, ITT/e#	118/148 (80%)	122/158 (77%)	108/158 (68%)	129/162 (80%)
	P=NA		P=0.02	
Proportion with VL < 400 copies/mL at week 48, ITT/e/s##	102/148 (69%)	84/158 (53%)	98/158 (62%)	120/162 (74%)
	P=NA		P =0.02	
Proportion with VL < 400 copies/mL at week 48, On Treatment	102/108 (94%)	84/93 (90%)	100/113 (88%)	120/138 (87%)
	P=NA		P=0.96	
Median increase in CD4 cell count at week 48 (cells/mm^3)	85	73	110	106

* For both studies: For patients entering study with VL < 200 copies/mL, VF defined as ≥ 200 copies/mL. MaxCmin1: For those entering with VL ≥ 200 copies/mL, VF defined as any increase ≥ 0.5 logs and/or VL ≥ 50,000 copies/mL at week 4, ≥ 5,000 copies/mL at week 12, or ≥ 200 copies/mL at week 24 or thereafter. MaxCmin2: any rise ≥ 0.5 log at a specific visit; ≤ 0.5 log reduction if VL ≥ 200 copies/mL at week 4; ≤ 1.0 log reduction from base line if VL ≥ 200 copies/mL at week 12; and a VL ≥ 200 copies/mL at week 24.

ITT/e = Intent-to-treat/exposed

ITT/e/s = Intent-to-treat/exposed/switch/discontinue = failure

† Data from clinical study report

‡ Data from MaxCmin1 publication

NA= Not available

Potential for resistance and cross-resistance to saquinavir:

Resistance: The objective of antiretroviral therapy is to suppress viral replication to below the limits of quantification. Incomplete viral suppression may lead to the development of drug resistance to one or more components of the regimen. Drug resistance is measured as the change in viral susceptibility to drug in culture (="phenotypic resistance") or in protease amino acid sequence (="genotypic resistance"). Measurements of drug susceptibility in *in vitro* culture are conducted by determination of the IC_{50} of the active moiety, saquinavir, and may not be representative of the incidence or magnitude

of resistance or cross-resistance *in vivo*, during the clinical use of boosted Invirase, where exposure to saquinavir is increased by the co-administration of low-dose ritonavir.

Two primary mutations in the viral protease (L90M and G48V, the former predominating and the combination rare even with saquinavir monotherapy) are found in isolates collected following failure of treatment with unboosted saquinavir regimens. The G48V and L90M mutations give modest (typically less than 10-fold) reductions in susceptibility to saquinavir measured *in vitro*. Secondary mutations (e.g. L10I/V, K20R, M36I/L, A71T, V82X) may accompany or precede the primary resistance mutations and give rise to greater reductions in susceptibility to saquinavir.
In one study, 24 clinical isolates containing G48V and/or L90M after therapy with unboosted Invirase showed a geometric mean reduction of susceptibility (increase in IC_{50}) of 7.3-fold relative to baseline virus (range 1.2 to 97-fold). The overall incidence of protease genotypic resistance to saquinavir observed in a cohort of 51 antiretroviral naïve subjects after a mean of 46 weeks (range 15 to 50 weeks) treatment with unboosted saquinavir soft capsules 1200 mg three times daily in combination with 2 NRTIs was 4 %.

There are limited data on the development of resistance in viral isolates collected following the failure of treatment with boosted Invirase.

Cross-resistance: Resistance mutations selected by one drug can in principle also result in reduced susceptibility to other drugs, particularly those in the same drug class. When this occurs it is termed cross-resistance.

Cross-resistance can result in weakened virological response to drug therapy. The application of data from phenotypic and/or genotypic resistance testing following incomplete viral suppression or virological failure can improve the response to subsequent treatments.

Cross-resistance between saquinavir and reverse transcriptase inhibitors: Cross-resistance between saquinavir and reverse transcriptase inhibitors is unlikely because of their different enzyme targets. HIV isolates resistant to zidovudine are sensitive to saquinavir, and conversely, HIV isolates resistant to saquinavir are sensitive to zidovudine.

Cross-resistance to other protease inhibitors: In a study of virus isolates from four clinical trials with unboosted Invirase, 22 virus isolates were identified as being resistant to saquinavir following treatment for 24 - 147 weeks. Susceptibility *in vitro* of each isolate was assessed to indinavir, ritonavir, nelfinavir and amprenavir. Of the isolates, 6/22 did not show cross-resistance to the other inhibitors, while 4/22 showed broad cross-resistance. The remaining 12/22 retained activity against at least one other protease inhibitor.

Cross-resistance with lopinavir is as yet undetermined in clinical isolates, although laboratory strains with substitutions at residues 10, 84 and 90 or 10, 48, 82 and 90 did not show significant reduction in *in vitro* susceptibility to lopinavir.

Cross-resistance from other protease inhibitors: Viruses with high level resistance to other protease inhibitors do not necessarily show *in vitro* cross-resistance to saquinavir. Studies of molecular clones containing resistance mutations associated with ritonavir, nelfinavir or amprenavir showed significant resistance to these individual protease inhibitors, but not in all cases to saquinavir. In a clinical study of 32 individuals pre-treated with indinavir or ritonavir but naïve to saquinavir, 81 % showed reduced susceptibility to indinavir, 59 % showed reduced susceptibility to ritonavir and 40 % showed reduced susceptibility to saquinavir at baseline. Following 24 weeks of therapy with Invirase 1000 mg in combination with ritonavir 100 mg both two times daily, efavirenz and nucleoside analogues, the median decrease in plasma HIV-RNA was 0.9 $\log_{10}$ copies/ml for patients with phenotypic resistance to saquinavir versus 1.52 $\log_{10}$ copies/ml for those without resistance (p=0.03). HIV RNA levels below 50 copies/ml were achieved at week 24 for 58 % of those patients carrying saquinavir-sensitive virus and for 25 % of those carrying virus with reduced (> 10 fold) sensitivity to saquinavir. The median number of resistance mutations in the protease gene in individuals with phenotypic resistance to saquinavir was 5.5 (range 4 - 8), whereas it was 3 (range 0 - 6) in those sensitive to saquinavir

(p=0.0003). However, extensive treatment of subjects with protease inhibitors after failure can lead to broad cross-resistance in a complex, dynamic process.

Hypersusceptibility to mutant virus: Some virus isolates with reduced susceptibility to other protease inhibitors can have enhanced susceptibility (hypersusceptibility) to inhibition with saquinavir, for example viruses containing the D30N substitution after nelfinavir therapy and viruses, carrying complex substitutions patterns including I50V. Many viruses with substitutions at residue 82, commonly selected by indinavir or ritonavir therapy, either retain, or show enhanced susceptibility to saquinavir. The clinical significance of hypersusceptibility to saquinavir has not been established.

5.2 Pharmacokinetic properties

Saquinavir is essentially completely metabolised by CYP3A4. Ritonavir inhibits the metabolism of saquinavir, thereby increasing ("boosting") the plasma levels of saquinavir.

Absorption and bioavailability in adults: In HIV-infected patients, Invirase in combination with ritonavir at doses of 1000/100 mg twice daily provides saquinavir systemic exposures over a 24-hour period similar to or greater than those achieved with saquinavir soft capsules 1200 mg tid (see Table 4). The pharmacokinetics of saquinavir is stable during long-term treatment.

Table 4: Mean (% CV) AUC, C_{max} and C_{min} of saquinavir in patients following multiple dosing of Invirase, saquinavir soft capsules, Invirase/ritonavir, and saquinavir soft capsules/ritonavir

Treatment	**N**	**AUCτ (ng·h/ml)**	**AUC_{0-24} (ng·h/ml)** †	**C_{max} (ng/ml)**	**C_{min} (ng/ml)**
Invirase (hard capsule) 600 mg tid	10	866 (62)	2,598	197 (75)	75 (82)
saquinavir soft capsule 1200 mg tid	31	7,249 (85)	21,747	2,181 (74)	216 (84)
Invirase (tablet) 1000 mg bid plus ritonavir 100 mg bid* (fasting condition)	22	10,320 (2,530-30,327)	20,640	1509 (355-4,101)	313 (70-1,725) ††
Invirase (tablet) 1000 mg bid plus ritonavir 100 mg bid* (high fat meal)	22	34,926 (11,826-105,992)	69,852	5208 (1,536-14,369)	1,179 (334-5,176) ††

τ = dosing interval, i.e. 8 hour for tid and 12 h for bid dosing
C_{min} = the observed plasma concentration at the end of the dose interval
bid = twice daily
tid = three times daily
* results are geometric mean (min - max)
† derived from tid or bid dosing schedule
†† C_{trough} values

Absolute bioavailability averaged 4 % (CV 73 %, range: 1 % to 9 %) in 8 healthy volunteers who received a single 600 mg dose (3 x 200 mg hard capsule) of Invirase following a heavy breakfast. The low bioavailability is thought to be due to a combination of incomplete absorption and extensive first-pass metabolism. Gastric pH has been shown to be only a minor component in the large increase in bioavailability seen when given with food. The absolute bioavailability of saquinavir co-administered with ritonavir has not been established in humans.

In combination with ritonavir, bioequivalence of Invirase hard capsules and film-coated tablets was demonstrated under fed conditions.

Effective therapy in treatment naïve patients is associated with a C_{min} of approximately 50 ng/ml and an AUC_{0-24} of about 20,000 ng·h/ml. Effective therapy in treatment experienced patients is associated with a C_{min} of approximately 100 ng/ml and an AUC_{0-24} of about 20,000 ng·h/ml.

In vitro studies have shown that saquinavir is a substrate for P-glycoprotein (P-gp).

Effect of food: In a cross-over study in 22 HIV-infected patients treated with Invirase/ritonavir 1000 mg/100 mg twice daily and receiving three consecutive doses under fasting conditions or after a high-fat, high-calorie meal (46 g fat, 1,091 Kcal), the AUC_{0-12}, C_{max} and C_{trough} values of saquinavir under fasting conditions were about 70 per cent lower than with a high-fat meal. All but one of the patients achieved C_{trough} values of saquinavir above the therapeutic threshold (100 ng/ml) in the fasted state. There were no clinically significant differences in the pharmacokinetic profile of ritonavir in fasting and fed conditions but the ritonavir C_{trough} (geometric mean 245 vs. 348 ng/ml) was lower in the fasting state compared to the administration with a meal. Invirase/ritonavir should be administered with or after food.

Distribution in adults: Saquinavir partitions extensively into the tissues. The mean steady-state volume of distribution following intravenous administration of a 12 mg dose of saquinavir was 700 l (CV 39 %). It has been shown that saquinavir is approximately 97 % bound to plasma proteins up to 30 μg/ml. In two patients receiving Invirase 600 mg three times daily, cerebrospinal fluid concentrations of saquinavir were negligible when compared to concentrations from matching plasma samples.

Metabolism and elimination in adults: *In vitro* studies using human liver microsomes have shown that the metabolism of saquinavir is cytochrome P450 mediated with the specific isoenzyme, CYP3A4, responsible for more than 90 % of the hepatic metabolism. Based on *in vitro* studies, saquinavir is rapidly metabolised to a range of mono- and di-hydroxylated inactive compounds. In a mass balance study using 600 mg ^{14}C-saquinavir (n = 8), 88 % and 1 % of the orally administered radioactivity, was recovered in faeces and urine, respectively, within 4 days of dosing. In an additional four subjects administered 10.5 mg ^{14}C-saquinavir intravenously, 81 % and 3 % of the intravenously administered radioactivity was recovered in faeces and urine, respectively, within 4 days of dosing. 13 % of circulating saquinavir in plasma was present as unchanged compound after oral administration and the remainder as metabolites. Following intravenous administration 66 % of circulating saquinavir was present as unchanged compound and the remainder as metabolites, suggesting that saquinavir undergoes extensive first pass metabolism. *In vitro* experiments have shown that the hepatic metabolism of saquinavir becomes saturable at concentrations above 2 μg/ml.
Systemic clearance of saquinavir was high, 1.14 l/h/kg (CV 12 %), slightly above the hepatic plasma flow, and constant after intravenous doses of 6, 36 and 72 mg. The mean residence time of saquinavir was 7 hours (n = 8).

Special populations

Effect of gender following treatment with Invirase/ritonavir: A gender difference was observed with females showing higher saquinavir exposure than males (AUC on average 56 % higher and C_{max} on average 26 % higher) in the bioequivalence study comparing Invirase 500 mg film coated tablets with Invirase 200 mg hard capsules both in combination with ritonavir. There was no evidence that age and body-weight explained the gender difference in this study. Limited data from controlled clinical studies with the approved dosage regimen do not indicate a major difference in the efficacy and safety profile between men and women.

5.3 Preclinical safety data

Acute and chronic toxicity: Saquinavir was well tolerated in oral acute and chronic toxicity studies in mice, rats, dogs and marmosets at dose levels that gave maximum plasma exposures (AUC values) approximately 1.5-, 1.0-, 4 to 9- and 3 fold greater, respectively, than those achieved in humans at the recommended dose.

Mutagenesis: Studies with and without metabolic activation (as appropriate) have shown that saquinavir has no mutagenic or genotoxic activity.

Carcinogenesis: There was no evidence of carcinogenic activity after the administration of saquinavir mesilate for 96 to 104 weeks to rats (maximum dose 1000 mg/kg/day) and mice (maximum dose 2500 mg/kg/day). The plasma exposures (AUC values) in the respective species were up to 60 % of those obtained in humans at the recommended clinical dose of saquinavir soft capsules or equivalent to them.

Reproductive toxicity: (see section 4.6). Fertility and reproductive performance were not affected in rats at plasma exposures (AUC values) approximately 50 % of those achieved in humans at the recommended dose.

Reproduction studies conducted with saquinavir in rats have shown no embryotoxicity or teratogenicity at plasma exposures (AUC values) approximately 50 % of those achieved in humans at the recommended dose or in rabbits at plasma exposures approximately 40 % of those achieved at the recommended clinical dose. Distribution studies in these species showed that placental transfer of saquinavir is low (less than 5 % of maternal plasma concentrations).
Studies in rats indicated that exposure to saquinavir from late pregnancy through lactation at plasma concentrations (AUC values) approximately 50 % of those achieved in humans at the recommended dose had no effect on the survival, growth and development of offspring to weaning.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule filling:
Lactose (anhydrous),
Microcrystalline cellulose,
Povidone,
Sodium starch glycollate,
Talc,
Magnesium stearate.

Capsule shell:
Gelatine,
Iron oxide black, red and yellow (E172),
Indigo carmine (E132),
Titanium dioxide (E171).

Printing ink:
Titanium dioxide (E 171),
Shellac,
Soya lecithin,
Polydimethylsiloxane.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original container.

6.5 Nature and contents of container

Amber glass bottles with plastic screw cap containing 270 capsules of Invirase.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

EU/1/96/026/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 October 1996
Date of last renewal: 04 October 2006

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

INVIRASE 500 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 500 mg of saquinavir as saquinavir mesilate.

Excipient: Contains lactose monohydrate: 38.5 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Light orange to greyish or brownish orange film-coated tablet of oval cylindrical biconvex shape with the marking "SQV 500" on the one side and "ROCHE" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Invirase is indicated for the treatment of HIV-1 infected adult patients. Invirase should only be given in combination with ritonavir and other antiretroviral medicinal products (see section 4.2).

4.2 Posology and method of administration

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

Adults and adolescents over the age of 16 years:

In combination with ritonavir
The recommended dose of Invirase is 1000 mg (2 x 500 mg film-coated tablets) two times daily with ritonavir 100 mg two times daily in combination with other antiretroviral agents.
Invirase film-coated tablets should be swallowed whole and taken at the same time as ritonavir with or after food (see section 5.2).

In combination with other protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors
Dose reduction may be required when Invirase/ritonavir is administered with some other HIV protease inhibitors (e.g. nelfinavir, indinavir and delavirdine), since these medicinal products may increase saquinavir plasma levels (see section 4.5).

Renal and hepatic impairment:
No dosage adjustment is necessary for patients with mild to moderate renal or mild hepatic impairment. Caution should be exercised in patients with severe renal or moderate hepatic impairment. Invirase/ritonavir is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 4.4).

Children under the age of 16 and adults over 60 years:
The experience with Invirase in children below the age of 16 and adults over 60 years is limited. In children, as in adults, Invirase should only be given in combination with ritonavir.

4.3 Contraindications

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

Invirase/ritonavir is contraindicated in decompensated liver disease (see section 4.4).

Invirase/ritonavir should not be given together with other medicinal products which may interact and result in potentially life threatening undesirable effects.

Medicinal products which should not be given with Invirase/ritonavir include:

- terfenadine, astemizole, pimozide, cisapride, amiodarone, propafenone and flecainide (potential for life threatening cardiac arrhythmia)
- midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5), triazolam (potential for prolonged or increased sedation, respiratory depression)
- simvastatin, lovastatin (increased risk of myopathy including rhabdomyolysis)
- ergot alkaloids (e.g. ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (potential for acute ergot toxicity)
- rifampicin (risk of severe hepatocellular toxicity) (see sections 4.4, 4.5, and 4.8).

4.4 Special warnings and precautions for use

Considerations when initiating Invirase therapy: Invirase should not be given as the sole protease inhibitor. Invirase should only be given in combination with ritonavir (see section 4.2).

Patients should be informed that saquinavir is not a cure for HIV infection and that they may continue to acquire illnesses associated with advanced HIV infection, including opportunistic infections. Patients should also be advised that they might experience undesirable effects associated with co-administered medications.

Liver disease: The safety and efficacy of saquinavir/ritonavir has not been established in patients with significant underlying liver disorders, therefore saquinavir/ritonavir should be used cautiously in this patient population. Invirase/ritonavir is contraindicated in patients with decompensated liver disease (see section 4.3). Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

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

In cases of mild hepatic impairment no initial dosage adjustment is necessary at the recommended dose. The use of Invirase in combination with ritonavir in patients with moderate hepatic impairment has not been studied. In the absence of such studies, caution should be exercised, as increases in saquinavir levels and/or increases in liver enzymes may occur.
There have been reports of exacerbation of chronic liver dysfunction, including portal hypertension, in patients with underlying hepatitis B or C, cirrhosis and other underlying liver abnormalities.

Renal impairment: Renal clearance is only a minor elimination pathway, the principal route of metabolism and excretion for saquinavir being via the liver. Therefore, no initial dose adjustment is necessary for patients with renal impairment. However, patients with severe renal impairment have not been studied and caution should be exercised when prescribing saquinavir/ritonavir in this population.

Patients with chronic diarrhoea or malabsorption: No information on boosted saquinavir and only limited information on the safety and efficacy of unboosted saquinavir is available for patients

suffering from chronic diarrhoea or malabsorption. It is unknown whether patients with such conditions could receive subtherapeutic saquinavir levels.

Children under the age of 16 and adults over 60 years: The experience with Invirase in children below the age of 16 and adults over 60 years is limited. In children, as in adults, Invirase should only be given in combination with ritonavir.

Lactose intolerance: Invirase 500 mg film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Patients with haemophilia: There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with 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.

Diabetes mellitus and hyperglycaemia: New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving protease inhibitors. In some of these patients, the hyperglycaemia was severe and in some cases was 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 mellitus or hyperglycaemia.

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

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

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

Interaction with ritonavir: The recommended dose of Invirase and ritonavir is 1000 mg Invirase plus 100 mg ritonavir twice daily. Higher doses of ritonavir have been shown to be associated with an increased incidence of adverse events. Co-administration of saquinavir and ritonavir has led to severe adverse events, mainly diabetic ketoacidosis and liver disorders, especially in patients with pre-existing liver disease.

Interaction with tipranavir: Concomitant use of boosted saquinavir and tipranavir, co-administered with low dose ritonavir in a dual-boosted regimen, results in a significant decrease in saquinavir

plasma concentrations (see section 4.5). Therefore, the co-administration of boosted saquinavir and tipranavir, co-administered with low dose ritonavir, is not recommended.

Interaction with HMG-CoA reductase inhibitors: Caution must be exercised if Invirase/ritonavir 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).

Oral contraceptives: Because concentration of ethinyl estradiol may be decreased when co-administered with Invirase/ritonavir, alternative or additional contraceptive measures should be used when oestrogen-based oral contraceptives are co-administered (see section 4.5).

Glucocorticoids: Concomitant use of boosted saquinavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

Interaction with efavirenz: The combination of saquinavir and ritonavir with efavirenz has been shown to be associated with an increased risk of liver toxicity; liver function should be monitored when saquinavir and ritonavir are co-administered with efavirenz. No clinically significant alterations of either saquinavir or efavirenz concentration were noted in studies in healthy volunteers or in HIV-infected patients (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Most drug interaction studies with saquinavir have been completed with unboosted Invirase or unboosted saquinavir soft capsules (Fortovase). A limited number of studies have been completed with ritonavir boosted Invirase or ritonavir boosted saquinavir soft capsules.

Observations from drug interaction studies done with unboosted saquinavir might not be representative of the effects seen with saquinavir/ritonavir therapy. Furthermore, results seen with saquinavir soft capsules may not predict the magnitude of these interactions with Invirase/ritonavir.

The metabolism of saquinavir is mediated by cytochrome P450, with the specific isoenzyme CYP3A4 responsible for 90 % of the hepatic metabolism. Additionally, *in vitro* studies have shown that saquinavir is a substrate and an inhibitor for P-glycoprotein (P-gp). Therefore, medicinal products that either share this metabolic pathway or modify CYP3A4 and/or P-gp activity (see *"Other potential interactions"*) may modify the pharmacokinetics of saquinavir. Similarly, saquinavir might also modify the pharmacokinetics of other medicinal products that are substrates for CYP3A4 or P-gp.

Ritonavir can affect the pharmacokinetics of other medicinal products because it is a potent inhibitor of CYP3A4 and P-gp. Therefore, when saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on other medicinal products (see the Summary of Product Characteristics for Norvir).

Antiretroviral agents

Nucleoside reverse transcriptase inhibitors (NRTIs):

Zalcitabine and/or zidovudine: ***Saquinavir/ritonavir:*** No pharmacokinetic interaction studies have been completed with these agents given in combination with saquinavir/ritonavir. However, for zalcitabine an interaction is unlikely as this medicinal product has differential routes of metabolism and excretion and is unlikely to affect absorption of saquinavir/ritonavir. For zidovudine given 200 mg every 8 hours a 25 % decrease in AUC of zidovudine was reported when combined with ritonavir (300 mg every 6 hours), whereas the pharmacokinetics of ritonavir was not affected by zidovudine. No dose modification of zidovudine is warranted when zidovudine is co-administered with ritonavir. ***Saquinavir:*** Concomitant use of Invirase with zalcitabine and/or zidovudine has been studied in adults.

Absorption, distribution and elimination of each of the medicinal products are unchanged when they are used together.

Didanosine: ***Saquinavir/ritonavir:*** The effects of a single dose of didanosine 400 mg on the pharmacokinetics of saquinavir in eight healthy subjects who received saquinavir soft capsules /ritonavir 1600/100 mg once daily for 2 weeks was investigated. Didanosine decreased saquinavir AUC and C_{max} approximately 30 % and 25 %, respectively, and had essentially no effect on C_{min} of saquinavir. These changes are of doubtful clinical significance.

Tenofovir: ***Saquinavir/ritonavir:*** Concomitant administration of tenofovir disoproxil fumarate with Invirase/ritonavir 1000/100 mg had no clinically significant effect on saquinavir exposure. In 18 HIV-infected patients treated with Invirase/ritonavir 1000/100 mg twice daily and tenofovir disoproxil fumarate 300 mg once daily, saquinavir AUC and C_{max} values were 1 % and 7 % lower than those seen with saquinavir/ritonavir alone. No dose adjustment is required when ritonavir boosted Invirase is combined with tenofovir disoproxil fumarate.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs):

Delavirdine: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and delavirdine has not been evaluated. ***Saquinavir:*** Co-administration of delavirdine with Invirase resulted in a 348 % increase in saquinavir plasma AUC. Currently there are limited safety and no efficacy data available from the use of this combination. In a small, preliminary study, hepatocellular enzyme elevations occurred in 13 % of subjects during the first several weeks of the delavirdine and saquinavir combination (6 % Grade 3 or 4). Hepatocellular changes should be monitored frequently if this combination is prescribed.

Efavirenz: ***Saquinavir/ritonavir:*** No clinically relevant alterations of either saquinavir or efavirenz concentrations were noted in a study in twenty-four healthy subjects who received saquinavir soft capsules /ritonavir/efavirenz 1600/200/600 mg once daily. Two additional studies in HIV patients investigated the effect of concomitant administration of efavirenz with either a twice-daily boosted regimen (Invirase/ritonavir 1000/100 mg twice daily) (n=32) or a once-daily boosted regimen (saquinavir soft capsules /ritonavir 1200/100 mg once daily) (n=35). No clinically significant alterations of either saquinavir or efavirenz concentrations were noted in either study.

Nevirapine: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and nevirapine has not been evaluated. ***Saquinavir:*** Co-administration of nevirapine and Invirase resulted in a 24 % decrease in plasma saquinavir AUC and no change to nevirapine AUC. The decrease is not thought to be clinically relevant and no dose adjustments of Invirase or nevirapine are recommended.

HIV protease inhibitors (PIs):

Atazanavir: ***Saquinavir/ritonavir:*** Concomitant administration of Invirase/ritonavir 1600/100 mg once daily with atazanavir 300 mg once daily to 18 HIV-infected patients resulted in saquinavir AUC and C_{max} values which were 60 % and 42 % respectively, higher than those seen with Invirase/ritonavir (at 1600/100 mg once daily) alone. Ritonavir AUC and Cmax values were increased by 41 % and 34 % respectively, whereas pharmacokinetic parameters of atazanavir remained unchanged. No clinical data exist with the approved dosing regimen of saquinavir/ritonavir and atazanavir.

Fosamprenavir: ***Saquinavir/ritonavir:*** Concomitant administration of fosamprenavir with Invirase/ritonavir 1000/100 mg had no clinically significant effect on saquinavir exposure. In 18 HIV-infected patients treated with Invirase/ritonavir 1000/100 mg and fosamprenavir 700 mg twice daily, saquinavir AUC and C_{max} values were 15 % and 9 % lower than those seen with saquinavir/ritonavir alone. Saquinavir C_{min} remained above the target threshold for effective therapy (decreasing by 24 % from 508 to 386 ng/ml). No dose adjustment is required when ritonavir boosted Invirase is combined with fosamprenavir.

Indinavir: ***Saquinavir/ritonavir:*** The administration of low dose ritonavir increases the concentrations of indinavir, which may result in nephrolithiasis. ***Saquinavir:*** Co-administration of indinavir (800 mg three times daily) and single doses of Invirase (600 mg) or saquinavir soft capsules (800 or 1200 mg) in six healthy volunteers each resulted in 4.6 – 7.2 fold increases in plasma saquinavir AUC_{0-24}. Indinavir plasma levels remained unchanged. Currently, no safety and efficacy data are available from the use of this combination. Appropriate doses of the combination have not been established.

Lopinavir: ***Saquinavir/ritonavir:*** The pharmacokinetic parameters of saquinavir, ritonavir and lopinavir have been investigated in HIV-infected patients treated with either saquinavir soft capsules/ritonavir 1000/100 mg twice daily in combination with 2 or 3 NRTIs (n=32) or saquinavir soft capsules 1000 mg twice daily and the fixed combination of lopinavir/ritonavir 400/100 mg twice daily (n=45). Lopinavir did not alter the pharmacokinetics of boosted saquinavir. The ritonavir exposure was significantly lower in the patients taking lopinavir but its effectiveness as a boosting agent was not modified. Concentrations of lopinavir did not appear to be affected when lopinavir/ritonavir and saquinavir were combined, based on historical comparison with lopinavir/ritonavir alone. No dose adjustment is required when ritonavir boosted Invirase is combined with lopinavir.

Nelfinavir: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and nelfinavir has not been evaluated. ***Saquinavir:*** Concomitant administration of a single 1200 mg dose of saquinavir soft capsules on the fourth day of multiple nelfinavir dosing (750 mg three times daily) to 14 HIV infected patients resulted in saquinavir AUC and C_{max} values which were 392 % and 179 % higher than those seen with saquinavir alone. Concomitant administration of a single 750 mg dose of nelfinavir on the fourth day of multiple saquinavir soft capsules dosing (1200 mg three times daily) to the same patients resulted in nelfinavir AUC values which were 18 % higher than those seen with nelfinavir alone, while C_{max} values remained unchanged. Quadruple therapy, including saquinavir soft capsules and nelfinavir in addition to two nucleoside reverse transcriptase inhibitors gave a more durable response (prolongation of time to virological relapse) than triple therapy with either single protease inhibitor. The regimens were generally well tolerated. However, concomitant administration of nelfinavir and saquinavir soft capsules resulted in a moderate increase in the incidence of diarrhoea.

Ritonavir: Saquinavir has been shown not to alter the pharmacokinetics of ritonavir following single or multiple oral doses in healthy volunteers. Ritonavir extensively inhibits the metabolism of saquinavir resulting in greatly increased saquinavir plasma concentrations. In HIV-infected patients, Invirase or saquinavir soft capsules in combination with ritonavir at doses of 1000/100 mg twice daily provide saquinavir systemic exposure over a 24 hour period similar to or greater than those achieved with saquinavir soft capsules 1200 mg three times daily (see section 5.2).

Tipranavir: ***Saquinavir/ritonavir:*** In a clinical study of dual-boosted protease inhibitor combination therapy in multiple-treatment experienced HIV-positive adults, tipranavir, co-administered with low dose ritonavir, caused a 78% reduction in the Cmin of saquinavir. Therefore the concomitant administration of tipranavir, co-administered with low dose ritonavir, with saquinavir/ritonavir, is not recommended. If the combination is nevertheless considered necessary, a monitoring of the saquinavir plasma levels is strongly encouraged.

HIV fusion inhibitor:

Enfuvirtide: ***Saquinavir/ritonavir:*** No clinically significant interaction was noted from a study in 12 HIV patients who received enfuvirtide concomitantly with saquinavir soft capsules/ritonavir 1000/100 mg twice daily.

Other medicinal products

Antiarrhythmics:

Bepridil, systemic lidocaine, quinidine: Concentrations of these medicinal products may be increased when co-administered with Invirase/ritonavir. Caution is warranted and therapeutic concentration monitoring, if available, is recommended if these antiarrhythmics are given with Invirase/ritonavir.

Amiodarone, flecainide and propafenone: Concentrations of these medicinal products may be increased when co-administered with Invirase/ritonavir. Due to a potential for life threatening cardiac arrhythmia, amiodarone, flecainide and propafenone are contraindicated with Invirase/ritonavir (see section 4.3).

Anticoagulant:

Warfarin: Concentrations of warfarin may be affected. It is recommended that INR (international normalised ratio) be monitored.

Anticonvulsants:

Carbamazepine, phenobarbital, phenytoin: These medicinal products will induce CYP3A4 and may decrease saquinavir concentrations if Invirase is taken without ritonavir. The interaction between Invirase/ritonavir and these medicinal products has not been evaluated.

Antidepressants:

Tricyclic antidepressants (e.g. amitriptyline, imipramine): Invirase/ritonavir may increase the concentrations of tricyclic antidepressants. Therapeutic concentration monitoring is recommended for tricyclic antidepressants when co-administered with Invirase/ritonavir.

Nefazodone: Will inhibit CYP3A4 and may increase saquinavir concentrations. If nefazodone is taken concomitantly with saquinavir, monitoring for saquinavir toxicity is recommended. The interaction between Invirase/ritonavir and nefazodone has not been evaluated.

Antihistamines:

Terfenadine, astemizole***:*** Co-administration of terfenadine and saquinavir soft capsules leads to an increase in plasma terfenadine exposure (AUC) associated with a prolongation of QTc intervals. Hence, terfenadine is contraindicated in patients receiving saquinavir or saquinavir/ritonavir. As similar interactions are likely, saquinavir or saquinavir/ritonavir should not be administered with astemizole (see section 4.3).

Anti-infectives:

Clarithromycin: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and clarithromycin has not been evaluated. ***Saquinavir:*** Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir soft capsules (1200 mg three times daily) to 12 healthy volunteers resulted in steady-state saquinavir AUC and C_{max} values which were 177 % and 187 % higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} values were approximately 40 % higher than those seen with clarithromycin alone. No dose adjustment is required when the two medicinal products are co-administered for a limited time at the doses studied.

Erythromycin: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and erythromycin has not been evaluated. ***Saquinavir:*** Concomitant administration of erythromycin (250 mg four times daily) and saquinavir soft capsules (1200 mg three times daily) to 22 HIV-infected patients resulted in

steady-state saquinavir AUC and C_{max} values which were 99 % and 106 % higher than those seen with saquinavir alone. No dose adjustment is required when the two medicinal products are co-administered.

Streptogramin antibiotics such as quinupristin/dalfopristin: Will inhibit CYP3A4 and may increase saquinavir concentrations. If these medicinal products are taken concomitantly with saquinavir, monitoring for saquinavir toxicity is recommended. The interaction between Invirase/ritonavir and quinupristin/dalfopristin has not been evaluated.

Antifungals:

Ketoconazole: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and ketoconazole has not been evaluated. ***Saquinavir:*** Concomitant use of ketoconazole (200 mg once daily) and Invirase (600 mg three times daily) to 12 healthy volunteers led to an increase in saquinavir AUC by about 160 % at steady state (day 6 of treatment) with no increase in the elimination half-life or any change in the absorption rate. Ketoconazole pharmacokinetics were not affected by co-administration with saquinavir at a dose of 600 mg three times daily. No dose adjustment for either medicinal product is required when the two medicinal products are co-administered at the doses studied.

Itraconazole: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and itraconazole has not been evaluated. ***Saquinavir:*** Like ketoconazole, itraconazole is a moderately potent inhibitor of the CYP3A4 isoenzyme and an interaction of similar magnitude is possible. If itraconazole is taken concomitantly with saquinavir, monitoring for saquinavir toxicity is recommended.

Fluconazole/miconazole: No specific drug interaction studies with either of these medicinal products have been performed.

Antimycobacterials:

Rifampicin: ***Saquinavir/ritonavir:*** In a study investigating the interaction of rifampicin 600 mg once daily and Invirase 1000 mg/ritonavir 100 mg given twice daily, 11 of 17 (65 %) healthy volunteers developed severe hepatocellular toxicity with transaminase elevations up to > 20-fold the upper limit of normal after 1 to 5 days of co-administration. Therefore, rifampicin is contraindicated in patients taking ritonavir boosted Invirase as part of an ART regimen (see section 4.3).

Rifabutin: ***Saquinavir/ritonavir:*** Concomitant administration of rifabutin with saquinavir/ritonavir 1000/100 mg twice daily has not been evaluated. A dosage reduction to rifabutin 150 mg every 3 days is recommended based on experience with low dose ritonavir boosted protease inhibitors. Patients receiving rifabutin with Invirase/ritonavir should be closely monitored for liver function test elevations and emergence of adverse events associated with rifabutin therapy. Further dosage reduction of rifabutin may be necessary. Therapeutic concentration monitoring for saquinavir is recommended.

Benzodiazepines:

Midazolam: ***Saquinavir/ritonavir:*** Co-administration of a single oral dose of midazolam 7.5 mg after 2 weeks of Invirase/ritonavir 1000/100 mg twice daily to 16 healthy volunteers in a cross-over study, increased midazolam C_{max} by 4.3-fold and AUC by 12.4-fold. Invirase/ritonavir increased the elimination half-life of oral midazolam from 4.7 to 14.9 h. Therefore, the co-administration of Invirase/ritonavir with orally administered midazolam is contraindicated (see section 4.3), whereas caution should be used with co-administration of Invirase and parenteral midazolam. No data are available on concomitant use of ritonavir boosted saquinavir with intravenous midazolam; studies of other CYP3A modulators and i.v. midazolam suggest a possible 3-4 fold increase in midazolam plasma levels. If Invirase is co-administered with parenteral midazolam it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment should be considered, especially if more than a single dose of midazolam is administered.

Alprazolam, clorazepate, diazepam, flurazepam: Concentrations of these medicinal products may be increased when co-administered with Invirase/ritonavir. Careful monitoring of patients with regard to sedative effects is warranted, a decrease in the dose of the benzodiazepine may be required.

Triazolam: Concentrations of triazolam may be increased when co-administered with Invirase/ritonavir. Triazolam is contraindicated with Invirase/ritonavir, due to the risk of potential for prolonged or increased sedation and respiratory depression (see section 4.3).

Calcium channel blockers:

Felodipine, nifedipine, nicardipine, diltiazem, nimodipine, verapamil, amlodipine, nisoldipine, isradipine: Concentrations of these medicinal products may be increased when co-administered with Invirase/ritonavir. Caution is warranted and clinical monitoring of patients is recommended.

Corticosteroids:

Dexamethasone: Will induce CYP3A4 and may decrease saquinavir concentrations. Use with caution, saquinavir may be less effective in patients taking these medicinal products concomitantly. The interaction between Invirase/ritonavir and dexamethasone has not been evaluated.

Fluticasone propionate (interaction with ritonavir): In a clinical study where ritonavir 100 mg capsules twice daily were co-administered with 50 µg intranasal fluticasone propionate (4 times daily) for 7 days in healthy subjects, the fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86 % (90 % confidence interval 82-89 %). Greater effects may be expected when fluticasone propionate is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolised via the P450 3A pathway e.g. budesonide. Consequently, concomitant administration of boosted saquinavir and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g. beclometasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may have to be performed over a longer period. The effects of high fluticasone systemic exposure on ritonavir plasma levels is yet unknown.

Medicinal products that are substrates of P-glycoprotein:

Digitalis glycosides:

Digoxin: ***Saquinavir/ritonavir:*** Co-administration of a single oral dose of digoxin 0.5 mg after 2 weeks of Invirase/ritonavir 1000/100 mg twice daily to 16 healthy volunteers in a cross-over study, increased digoxin C_{max} by 27% and AUC_{0-72} by 49%. Caution should be exercised when Invirase/ritonavir and digoxin are co-administered. The digoxin levels may differ over time, and large increments of digoxin may be expected when saquinavir/ritonavir is introduced in patients already treated with digoxin. The serum concentration of digoxin should be monitored and a dose reduction of digoxin should be considered if necessary.

Histamine H_2-receptor antagonist:

Ranitidine: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and ranitidine has not been evaluated. ***Saquinavir:*** In a study in 12 healthy male volunteers there was an increase in exposure of saquinavir when Invirase was dosed in the presence of both ranitidine and food, relative to Invirase dosed with food alone. This resulted in AUC values of saquinavir, which were 67 % higher. This increase is not thought to be clinically relevant and no dose adjustment of saquinavir is recommended.

HMG-CoA reductase inhibitors:

Pravastatin, fluvastatin: Are not metabolised by CYP3A4, and interactions are not expected with protease inhibitors including ritonavir. If treatment with a HMG-CoA reductase inhibitor is indicated, either pravastatin or fluvastatin are the products recommended.

Simvastatin, lovastatin: Are highly dependent on CYP3A4 metabolism, and plasma concentrations are markedly increased when co-administered with Invirase/ritonavir. Increased concentrations of these medicinal products have been associated with rhabdomyolysis and these medicinal products are contraindicated for use with Invirase/ritonavir (see section 4.3).

Atorvastatin: Is less dependent on CYP3A4 for metabolism. When used with Invirase/ritonavir, the lowest possible dose of atorvastatin should be administered and the patient carefully monitored for signs/symptoms of myopathy (muscle weakness, muscle pain, rising plasma creatinine kinase levels).

Immunosuppressants:

Ciclosporin, tacrolimus, rapamycin: Concentrations of these medicinal products increase several fold when co-administered with Invirase/ritonavir. Careful therapeutic drug monitoring is necessary for immunosuppressants when co-administered with Invirase/ritonavir.

Narcotic analgesic:

Methadone: Concentration of methadone may be decreased when co-administered with Invirase/ritonavir. Dosage of methadone may need to be increased.

Neuroleptics:

Pimozide: Concentrations of pimozide may be increased when co-administered with Invirase/ritonavir. Due to a potential for life threatening cardiac arrhythmias, Invirase/ritonavir is contraindicated in combination with pimozide (see section 4.3).

Oral contraceptives:

Ethinyl estradiol: Concentration of ethinyl estradiol may be decreased when co-administered with Invirase/ritonavir. Alternative or additional contraceptive measures should be used when oestrogen-based oral contraceptives are co-administered.

Phosphodiesterase type 5 (PDE5) inhibitors:

Sildenafil: The co-administration of saquinavir soft capsules at steady state (1200 mg three times daily) with sildenafil (100 mg single dose), a substrate of CYP3A4, resulted in a 140 % increase in sildenafil C_{max} and a 210 % increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics. Use sildenafil with caution at reduced doses of no more than 25 mg every 48 hours with increased monitoring of adverse events when administered concomitantly with Invirase/ritonavir.

Vardenafil: Concentrations of vardenafil may be increased when co-administered with Invirase/ritonavir. Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring of adverse events when administered concomitantly with Invirase/ritonavir.

Tadalafil: Concentrations of tadalafil may be increased when co-administered with Invirase/ritonavir. Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring of adverse events when administered concomitantly with Invirase/ritonavir.

Proton pump inhibitors:

Omeprazole: Concomitant administration of omeprazole (40 mg once daily) and Invirase/ritonavir (1000/100 mg twice daily) to 18 healthy volunteers resulted in steady-state saquinavir AUC and C_{max} values which were 82% (90 % confidence interval 44-131 %) and 75% (90 % confidence interval 38-123 %) higher than those seen with Invirase/ritonavir alone. If omeprazole is taken concomitantly with Invirase/ritonavir, monitoring for potential saquinavir toxicities is recommended. The plasma levels of ritonavir did not change significantly after omeprazole use.

Others:

Ergot alkaloids (e.g. ergotamine, dihydroergotamine, ergonovine, and methylergonovine): Invirase/ritonavir may increase ergot alkaloids exposure, and consequently, increase the potential for acute ergot toxicity. Thus, the concomitant use of Invirase/ritonavir and ergot alkaloids is contra-indicated (see section 4.3).

Grapefruit juice: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and grapefruit juice has not been evaluated. ***Saquinavir:*** Co-administration of Invirase and grapefruit juice as single administration in healthy volunteers results in a 50 % and 100 % increase in exposure to saquinavir for normal and double strength grapefruit juice, respectively. This increase is not thought to be clinically relevant and no dose adjustment of Invirase is recommended.

Garlic capsules: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and garlic capsules has not been evaluated. ***Saquinavir:*** Concomitant administration of garlic capsules (dose approx. equivalent to two 4 g cloves of garlic daily) and saquinavir soft capsules 1200 mg three times daily to nine healthy volunteers resulted in a decrease of saquinavir AUC by 51 % and a decrease of the mean trough levels at 8 hours post dose by 49 %. Saquinavir mean C_{max} levels decreased by 54 %. Therefore patients on saquinavir treatment must not take garlic capsules due to the risk of decreased plasma concentrations and loss of virological response and possible resistance to one or more components of the antiretroviral regimen.

St. John's wort *(Hypericum perforatum)*: ***Saquinavir/ritonavir:*** The interaction between Invirase/ritonavir and St. John's wort has not been evaluated. ***Saquinavir:*** Plasma levels of saquinavir 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 Invirase. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible saquinavir levels. Saquinavir levels may increase on stopping St. John's wort, and the dose of saquinavir may need adjusting. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment.

Other potential interactions

Medicinal products that are substrates of CYP3A4:

Although specific studies have not been performed, co-administration of Invirase/ritonavir with medicinal products that are mainly metabolised by CYP3A4 pathway (e.g. dapsone, disopyramide, quinine, fentanyl, and alfentanyl) may result in elevated plasma concentrations of these medicinal products. Therefore these combinations should be given with caution.

Medicinal products reducing gastrointestinal transit time:

It is unknown, whether medicinal products which reduce the gastrointestinal transit time (e.g. metoclopramide) could lead to lower saquinavir plasma concentrations.

4.6 Pregnancy and lactation

***Pregnancy*:** Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo or foetus, the course of gestation and peri- and post-natal development. Clinical experience in pregnant women is limited: Congenital malformations, birth defects and other disorders (without a congenital malformation) have been reported rarely in pregnant women who had received saquinavir in combination with other antiretroviral agents. However, so far the available data are insufficient and do not identify specific risks for the unborn child. Saquinavir should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus (see section 5.3).

***Lactation*:** There are no laboratory animal or human data available on secretion of saquinavir in breast milk. The potential for adverse reactions to saquinavir in nursing infants cannot be assessed, and therefore, breast-feeding should be discontinued prior to receiving saquinavir. It is recommended that HIV-infected women do not breast feed their infants under any circumstances in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

Invirase may have a minor influence on the ability to drive and use machines. Dizziness and fatigue have been reported during treatment with Invirase. No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The following adverse events with an at least possible relationship to ritonavir boosted saquinavir (i.e. adverse reactions) were reported most frequently: nausea, diarrhoea, fatigue, vomiting, flatulence, and abdominal pain.

For comprehensive dose adjustment recommendations and drug-associated adverse reactions for ritonavir and other medicinal products used in combination with saquinavir, physicians should refer to the Summary of Product Characteristics for each of these medicinal products.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions from clinical trials where saquinavir was boosted with ritonavir

Limited data is available from two studies where the safety of saquinavir soft capsule (1000 mg twice daily) used in combination with low dose ritonavir (100 mg twice daily) for at least 48 weeks was studied in 311 patients. Adverse reactions in these two pivotal studies are summarised in Table 1. The list also includes marked laboratory abnormalities that have been observed with the saquinavir soft capsule in combination with ritonavir (at 48 weeks).

Table 1: Incidences of Adverse Reactions and marked laboratory abnormalities from the MaxCmin1 and MaxCmin2 study. (Very common (≥ 10 %); common (≥ 1 % and < 10 %))

Body System **Frequency of Reaction**	Adverse Reactions	
	Grades 3&4	All Grades
Blood and the lymphatic system disorders		
Common	Anaemia	Anaemia
Immune system disorders		
Common		Hypersensitivity
Metabolism and nutrition disorders		
Common	Diabetes mellitus	Diabetes mellitus, anorexia, increased appetite
Psychiatric disorders		
Common		Decreased libido, sleep disorder
Nervous System Disorders		
Common		Paraesthesia, peripheral neuropathy, dizziness, dysgeusia, headache
Respiratory, thoracic and mediastinal disorders		
Common		Dyspnoea
Gastrointestinal disorders		
Very common		Diarrhoea, nausea
Common	Diarrhoea, nausea, vomiting	Vomiting, abdominal distension, abdominal pain, upper abdominal pain, constipation, dry mouth, dyspepsia, eructation, flatulence, lip dry, loose stools
Skin and subcutaneous tissue disorders		
Common	Acquired lipodystrophy	Acquired lipodystrophy, alopecia, dry skin, eczema, lipoatrophy, pruritus, rash
Musculoskeletal and connective tissue disorders		
Common		Muscle spasms
General disorders and administration site conditions		
Common	Fatigue	Asthenia, fatigue, increased fat tissue, malaise
Investigations		
Very common		Increased alanine aminotransferase, increased aspartate aminotransferase, increased blood cholesterol, increased blood triglycerides, increased low density lipoprotein, decreased platelet count
Common		Increased blood amylase, increased blood bilirubin, increased blood creatinine, decreased haemoglobin, decreased lymphocyte count, decreased white blood cell count

Post-marketing experience with saquinavir

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

- Immune system disorders: Hypersensitivity.

- Metabolism and nutrition disorders:

  - Diabetes mellitus or hyperglycaemia sometimes associated with ketoacidosis (see section 4.4).
  - Lipodystrophy: Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsicervical fat accumulation (buffalo hump).
  - Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

- Nervous system disorders: Somnolence, convulsions.

- Vascular disorders: There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophilic patients type A and B treated with protease inhibitors (see section 4.4).

- Hepato-biliary disorders: Hepatitis.

- Musculoskeletal, connective tissue and bone disorders: Increased CPK, myalgia, myositis and rarely, rhabdomyolysis have been reported with protease inhibitors, particularly in combination with nucleoside analogues. Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

- Renal and urinary disorders: Renal impairment.

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

4.9 Overdose

There are two reports of patients who had overdoses with unboosted Invirase. One patient exceeded the recommended daily dose of saquinavir and took 8000 mg at once. The patient was treated with induction of emesis within two hours after ingestion of the overdose. The patient did not experience any sequelae. The second patient ingested 2.4 g of Invirase in combination with 600 mg of ritonavir and experienced pain in the throat that lasted for 6 hours and then resolved. In an exploratory small study, oral dosing with saquinavir at 3600 mg per day has not shown increased toxicity through the first 16 weeks of treatment.
Two cases of overdosage with unboosted saquinavir soft capsules have been received (one case with an unknown amount of saquinavir soft capsules, and a second case with 3.6 g to 4 g at once). No adverse events were reported in any of the cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Antiviral agent, ATC code J05A E01

Mechanism of action: The HIV protease carries out specific cleavages of viral precursor proteins as virions bud from infected cells. This is an essential step in the creation of fully formed, infectious

virus particles. These viral precursor proteins contain a type of cleavage site which is recognised only by HIV and closely related viral proteases. Saquinavir is a mimetic of such cleavage sites and fits closely into the HIV-1 and HIV-2 protease active sites, acting as a reversible and selective inhibitor. Saquinavir has approximately 50,000-fold greater affinity for HIV protease than for human proteases. In *in vitro* antiviral assays saquinavir blocks the formation of infectious virus, and hence the spread of infection to naïve cells.

Antiviral activity in vitro: Unlike nucleoside analogues (zidovudine, etc.), saquinavir acts directly on its viral target enzyme. It does not require metabolic activation. This extends its potential effectiveness into resting cells. Saquinavir is active at nanomolar concentrations in lymphoblastoid and monocytic lines and in primary cultures of lymphocytes and monocytes infected with laboratory strains or clinical isolates of HIV-1. Experiments in cell culture show that saquinavir produces an additive to synergistic antiviral effect against HIV-1 in double and triple combination with various reverse transcriptase inhibitors (including zidovudine, zalcitabine, didanosine, lamivudine, stavudine and nevirapine) without enhanced cytotoxicity, and clear synergy in double combination with lopinavir.

Pharmacodynamic effects: Early clinical studies assessed the effects in HIV-1 infected patients of unboosted saquinavir in combination with other antiretroviral agents on clinical endpoints and biological markers. Subsequently, the effects of boosted saquinavir in combination with other antiretroviral agents on biological markers (CD4 cell counts and plasma RNA) were evaluated in HIV-1 infected patients.

Clinical studies performed with boosted saquinavir soft capsules

In the MaxCmin1 study, the safety and efficacy of saquinavir soft capsules/ritonavir 1000/100 mg twice daily plus 2 NRTIs/Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) was compared to indinavir/ritonavir 800/100 mg twice daily plus 2 NRTIs/NNRTIs in over 300 (both protease inhibitor treatment naïve and experienced) subjects. The combination of saquinavir and ritonavir exhibited a superior virological activity compared with the indinavir and ritonavir arm when switch from the assigned treatment was counted as virological failure.

In the MaxCmin2 study, the safety and efficacy of saquinavir soft capsules/ritonavir 1000/100 mg twice daily plus 2 NRTIs/NNRTIs was compared with lopinavir/ritonavir 400/100 mg twice daily plus 2 NRTIs/NNRTIs in 324 (both protease inhibitor treatment naïve and experienced) subjects. None of the subjects in the lopinavir/ritonavir arm had been exposed to lopinavir prior to randomisation whereas 16 of the subjects in the saquinavir/ritonavir arm had previously been exposed to saquinavir.

Demographic characteristics for studies MaxCmin1 and MaxCmin2 are shown in Table 2 and the disposition and efficacy outcomes of studies MaxCmin 1 and MaxCmin 2 are shown in Table 3.

Table 2: Subject Demographics MaxCmin1 and MaxCmin2[†]

	MaxCmin1		**MaxCmin2**	
	SQV/r N=148	**IDV/r N=158**	**SQV/r N=161**	**LPV/r N=163**
Sex Male Female	 82% 18%	 74% 26%	 81% 19%	 76% 24%
Race White Black Asian	 86% 9% 1%	 82% 12% 4%	 75% 19% 1%	 74% 19% 2%
Age, median, yrs (IQR)	39 (34-48)	40 (34-46)	40 (35-50)	40 (35-47)
CDC Category C (%)	32%	28%	32%	31%
Antiretroviral naïve (%)	28%	22%	31%	34%
PI naïve (%)	41%	38%	48%	48%
Median Baseline HIV-1 RNA, log_{10} copies/mL (IQR)	4.0 (1.7-5.1)	3.9 (1.7-5.2)	4.4 (3.1-5.1)	4.6 (3.5-5.3)
Baseline VL < 400 copies/mL	38%	39%	22%	21%
Median Baseline $CD4^+$ Cell Count, cells/mm^3 (IQR)	272 (135-420)	280 (139-453)	241 (86-400)	239 (95-420)

[†] data from clinical study report

Table 3: Outcomes at Week 48 MaxCmin1 and MaxCmin2[†]

Outcomes **Status at week 48**	**MaxCmin1** **SQV/r**	**IDV/r**	**MaxCmin2** **SQV/r**	**LPV/r**
Randomized	N=158	N=159	N=172	N=167
Initiated assigned treatment, n (%)	148 (94%)	158 (99%)	161 (94%)	163 (98%)
Discontinued assigned treatment, n (%)	40 (27%)	64 (41%)	48 (30%)	23 (14%)
	P=0.01		P=0.001	
Reason for discontinuation n, (%)				
Virological failure	2 (5%)	3 (5%)	3 (6%)	0
Death	1 (3%)	1 (2%)	3 (6%)	0
Clinical non-fatal adverse event	22 (55%)	45 (70%)	21 (44%)	12 (52%)
Laboratory adverse event	2 (5%)	4 (6%)	1 (2%)	1 (4%)
Patient choice	5 (13%)	3 (5%)	8 (17%)	7 (30%)
Lost to follow-up	3 (8%)	5 (8%)	4 (8%)	2 (9%)
Other	5 (13%)	3 (5%)	8 (17%)	1 (4%)
Completed 48 weeks of assigned treatment	108 (73%)	94 (59%)	113 (70%)	140 (86%)
Patients with outcome at week 48	137 (93%)	148 (94%)	146 (91%)	158 (97%)

[†] data from clinical study report

Table 3 (continued): Outcomes at Week 48 MaxCmin1 and MaxCmin2[†]

Outcomes **Status at week 48** **Virological and Immunological Outcomes**	**MaxCmin1** **SQV/r**	**IDV/r**	**MaxCmin2** **SQV/r**	**LPV/r**
Virological failure*	36/148 (24%)	41/158 (26%)	53/161 (33%)	29/163 (18%)
	P=0.76		P=0.002	
Virological failure, switch/discontinue = failure	51/148 (34%)	77/158 (49%)	63/161 (39%)	40/161 (25%)
	P=0.01		P=0.005	
Proportion with VL < 50 copies/mL at week 48, ITT/e[#]	97/144 (67%)	106/154 (69%)	90/158 (57%)	106/162 (65%)
	P >0.05[‡]		P=0.12	
Proportion with VL < 50 copies/mL at week 48, ITT/e/s[##]	82/144 (57%)	73/158 (46%)	84/158 (53%)	97/162 (60%)
	P=0.048[‡]		P=0.23	
Proportion with VL < 50 copies/mL at week 48, On Treatment	82/104 (79%)	73/93 (78%)	84/113 (74%)	97/138 (70%)
	P>0.05[‡]		P=0.48	
Proportion with VL < 400 copies/mL at week 48, ITT/e[#]	118/148 (80%)	122/158 (77%)	108/158 (68%)	129/162 (80%)
	P=NA		P=0.02	
Proportion with VL < 400 copies/mL at week 48, ITT/e/s[##]	102/148 (69%)	84/158 (53%)	98/158 (62%)	120/162 (74%)
	P=NA		P =0.02	
Proportion with VL < 400 copies/mL at week 48, On Treatment	102/108 (94%)	84/93 (90%)	100/113 (88%)	120/138 (87%)
	P=NA		P=0.96	
Median increase in CD4 cell count at week 48 (cells/mm^3)	85	73	110	106

* For both studies: For patients entering study with VL < 200 copies/mL, VF defined as ≥ 200 copies/mL. MaxCmin1: For those entering with VL ≥ 200 copies/mL, VF defined as any increase ≥ 0.5 logs and/or VL ≥ 50,000 copies/mL at week 4, ≥ 5,000 copies/mL at week 12, or ≥ 200 copies/mL at week 24 or thereafter. MaxCmin2: any rise ≥ 0.5 log at a specific visit; ≤ 0.5 log reduction if VL ≥ 200 copies/mL at week 4; ≤ 1.0 log reduction from base line if VL ≥ 200 copies/mL at week 12; and a VL ≥ 200 copies/mL at week 24.

[#] ITT/e = Intent-to-treat/exposed

[##] ITT/e/s = Intent-to-treat/exposed/switch/discontinue = failure

[†] Data from clinical study report

[‡] Data from MaxCmin1 publication

NA= Not available

Potential for resistance and cross-resistance to saquinavir:

Resistance: The objective of antiretroviral therapy is to suppress viral replication to below the limits of quantification. Incomplete viral suppression may lead to the development of drug resistance to one or more components of the regimen. Drug resistance is measured as the change in viral susceptibility to drug in culture (=”phenotypic resistance”) or in protease amino acid sequence (=”genotypic resistance”). Measurements of drug susceptibility in *in vitro* culture are conducted by determination of the IC_{50} of the active moiety, saquinavir, and may not be representative of the incidence or magnitude

of resistance or cross-resistance *in vivo*, during the clinical use of boosted Invirase, where exposure to saquinavir is increased by the co-administration of low-dose ritonavir.

Two primary mutations in the viral protease (L90M and G48V, the former predominating and the combination rare even with saquinavir monotherapy) are found in isolates collected following failure of treatment with unboosted saquinavir regimens. The G48V and L90M mutations give modest (typically less than 10-fold) reductions in susceptibility to saquinavir measured *in vitro*. Secondary mutations (e.g. L10I/V, K20R, M36I/L, A71T, V82X) may accompany or precede the primary resistance mutations and give rise to greater reductions in susceptibility to saquinavir.
In one study, 24 clinical isolates containing G48V and/or L90M after therapy with unboosted Invirase showed a geometric mean reduction of susceptibility (increase in IC_{50}) of 7.3-fold relative to baseline virus (range 1.2 to 97-fold). The overall incidence of protease genotypic resistance to saquinavir observed in a cohort of 51 antiretroviral naïve subjects after a mean of 46 weeks (range 15 to 50 weeks) treatment with unboosted saquinavir soft capsules 1200 mg three times daily in combination with 2 NRTIs was 4 %.

There are limited data on the development of resistance in viral isolates collected following the failure of treatment with boosted Invirase.

Cross-resistance: Resistance mutations selected by one drug can in principle also result in reduced susceptibility to other drugs, particularly those in the same drug class. When this occurs it is termed cross-resistance.

Cross-resistance can result in weakened virological response to drug therapy. The application of data from phenotypic and/or genotypic resistance testing following incomplete viral suppression or virological failure can improve the response to subsequent treatments.

Cross-resistance between saquinavir and reverse transcriptase inhibitors: Cross-resistance between saquinavir and reverse transcriptase inhibitors is unlikely because of their different enzyme targets. HIV isolates resistant to zidovudine are sensitive to saquinavir, and conversely, HIV isolates resistant to saquinavir are sensitive to zidovudine.

Cross-resistance to other protease inhibitors: In a study of virus isolates from four clinical trials with unboosted Invirase, 22 virus isolates were identified as being resistant to saquinavir following treatment for 24 - 147 weeks. Susceptibility *in vitro* of each isolate was assessed to indinavir, ritonavir, nelfinavir and amprenavir. Of the isolates, 6/22 did not show cross-resistance to the other inhibitors, while 4/22 showed broad cross-resistance. The remaining 12/22 retained activity against at least one other protease inhibitor.

Cross-resistance with lopinavir is as yet undetermined in clinical isolates, although laboratory strains with substitutions at residues 10, 84 and 90 or 10, 48, 82 and 90 did not show significant reduction in *in vitro* susceptibility to lopinavir.

Cross-resistance from other protease inhibitors: Viruses with high level resistance to other protease inhibitors do not necessarily show *in vitro* cross-resistance to saquinavir. Studies of molecular clones containing resistance mutations associated with ritonavir, nelfinavir or amprenavir showed significant resistance to these individual protease inhibitors, but not in all cases to saquinavir. In a clinical study of 32 individuals pre-treated with indinavir or ritonavir but naïve to saquinavir, 81 % showed reduced susceptibility to indinavir, 59 % showed reduced susceptibility to ritonavir and 40 % showed reduced susceptibility to saquinavir at baseline. Following 24 weeks of therapy with Invirase 1000 mg in combination with ritonavir 100 mg both two times daily, efavirenz and nucleoside analogues, the median decrease in plasma HIV-RNA was 0.9 $\log_{10}$ copies/ml for patients with phenotypic resistance to saquinavir versus 1.52 $\log_{10}$ copies/ml for those without resistance (p=0.03). HIV RNA levels below 50 copies/ml were achieved at week 24 for 58 % of those patients carrying saquinavir-sensitive virus and for 25 % of those carrying virus with reduced (> 10 fold) sensitivity to saquinavir. The median number of resistance mutations in the protease gene in individuals with phenotypic resistance to saquinavir was 5.5 (range 4 - 8), whereas it was 3 (range 0 - 6) in those sensitive to saquinavir

(p=0.0003). However, extensive treatment of subjects with protease inhibitors after failure can lead to broad cross-resistance in a complex, dynamic process.

Hypersusceptibility to mutant virus: Some virus isolates with reduced susceptibility to other protease inhibitors can have enhanced susceptibility (hypersusceptibility) to inhibition with saquinavir, for example viruses containing the D30N substitution after nelfinavir therapy and viruses, carrying complex substitutions patterns including I50V. Many viruses with substitutions at residue 82, commonly selected by indinavir or ritonavir therapy, either retain, or show enhanced susceptibility to saquinavir. The clinical significance of hypersusceptibility to saquinavir has not been established.

5.2 Pharmacokinetic properties

Saquinavir is essentially completely metabolised by CYP3A4. Ritonavir inhibits the metabolism of saquinavir, thereby increasing ("boosting") the plasma levels of saquinavir.

Absorption and bioavailability in adults: In HIV-infected patients, Invirase in combination with ritonavir at doses of 1000/100 mg twice daily provides saquinavir systemic exposures over a 24-hour period similar to or greater than those achieved with saquinavir soft capsules 1200 mg tid (see Table 4). The pharmacokinetics of saquinavir is stable during long-term treatment.

Table 4: Mean (% CV) AUC, C_{max} and C_{min} of saquinavir in patients following multiple dosing of Invirase, saquinavir soft capsules, Invirase/ritonavir, and saquinavir soft capsules/ritonavir

Treatment	**N**	**AUCτ (ng·h/ml)**	**AUC_{0-24} (ng·h/ml)** †	**C_{max} (ng/ml)**	**C_{min} (ng/ml)**
Invirase (hard capsule) 600 mg tid	10	866 (62)	2,598	197 (75)	75 (82)
saquinavir soft capsule 1200 mg tid	31	7,249 (85)	21,747	2,181 (74)	216 (84)
Invirase (tablet) 1000 mg bid plus ritonavir 100 mg bid* (fasting condition)	22	10,320 (2,530-30,327)	20,640	1509 (355-4,101)	313 (70-1,725) ††
Invirase (tablet) 1000 mg bid plus ritonavir 100 mg bid* (high fat meal)	22	34,926 (11,826-105,992)	69,852	5208 (1,536-14,369)	1,179 (334-5,176) ††

τ = dosing interval, i.e. 8 hour for tid and 12 h for bid dosing.
C_{min} = the observed plasma concentration at the end of the dose interval.
bid = twice daily
tid = three times daily
* results are geometric mean (min - max)
† derived from tid or bid dosing schedule
†† C_{trough} values

Absolute bioavailability averaged 4 % (CV 73 %, range: 1 % to 9 %) in 8 healthy volunteers who received a single 600 mg dose (3 x 200 mg hard capsule) of Invirase following a heavy breakfast. The low bioavailability is thought to be due to a combination of incomplete absorption and extensive first-pass metabolism. Gastric pH has been shown to be only a minor component in the large increase in bioavailability seen when given with food. The absolute bioavailability of saquinavir co-administered with ritonavir has not been established in humans.

In combination with ritonavir, bioequivalence of Invirase hard capsules and film-coated tablets was demonstrated under fed conditions.

Effective therapy in treatment naïve patients is associated with a C_{min} of approximately 50 ng/ml and an AUC_{0-24} of about 20,000 ng·h/ml. Effective therapy in treatment experienced patients is associated with a C_{min} of approximately 100 ng/ml and an AUC_{0-24} of about 20,000 ng·h/ml.

In vitro studies have shown that saquinavir is a substrate for P-glycoprotein (P-gp).

Effect of food: In a cross-over study in 22 HIV-infected patients treated with Invirase/ritonavir 1000 mg/100 mg twice daily and receiving three consecutive doses under fasting conditions or after a high-fat, high-calorie meal (46 g fat, 1,091 Kcal), the AUC_{0-12}, C_{max} and C_{trough} values of saquinavir under fasting conditions were about 70 per cent lower than with a high-fat meal. All but one of the patients achieved C_{trough} values of saquinavir above the therapeutic threshold (100 ng/ml) in the fasted state. There were no clinically significant differences in the pharmacokinetic profile of ritonavir in fasting and fed conditions but the ritonavir C_{trough} (geometric mean 245 vs. 348 ng/ml) was lower in the fasting state compared to the administration with a meal. Invirase/ritonavir should be administered with or after food.

Distribution in adults: Saquinavir partitions extensively into the tissues. The mean steady-state volume of distribution following intravenous administration of a 12 mg dose of saquinavir was 700 l (CV 39 %). It has been shown that saquinavir is approximately 97 % bound to plasma proteins up to 30 μg/ml. In two patients receiving Invirase 600 mg three times daily, cerebrospinal fluid concentrations of saquinavir were negligible when compared to concentrations from matching plasma samples.

Metabolism and elimination in adults: *In vitro* studies using human liver microsomes have shown that the metabolism of saquinavir is cytochrome P450 mediated with the specific isoenzyme, CYP3A4, responsible for more than 90 % of the hepatic metabolism. Based on *in vitro* studies, saquinavir is rapidly metabolised to a range of mono- and di-hydroxylated inactive compounds. In a mass balance study using 600 mg 14C-saquinavir (n = 8), 88 % and 1 % of the orally administered radioactivity, was recovered in faeces and urine, respectively, within 4 days of dosing. In an additional four subjects administered 10.5 mg 14C-saquinavir intravenously, 81 % and 3 % of the intravenously administered radioactivity was recovered in faeces and urine, respectively, within 4 days of dosing. 13 % of circulating saquinavir in plasma was present as unchanged compound after oral administration and the remainder as metabolites. Following intravenous administration 66 % of circulating saquinavir was present as unchanged compound and the remainder as metabolites, suggesting that saquinavir undergoes extensive first pass metabolism. *In vitro* experiments have shown that the hepatic metabolism of saquinavir becomes saturable at concentrations above 2 μg/ml.
Systemic clearance of saquinavir was high, 1.14 l/h/kg (CV 12 %), slightly above the hepatic plasma flow, and constant after intravenous doses of 6, 36 and 72 mg. The mean residence time of saquinavir was 7 hours (n = 8).

Special populations

Effect of gender following treatment with Invirase/ritonavir: A gender difference was observed with females showing higher saquinavir exposure than males (AUC on average 56 % higher and C_{max} on average 26 % higher) in the bioequivalence study comparing Invirase 500 mg film coated tablets with Invirase 200 mg hard capsules both in combination with ritonavir. There was no evidence that age and body-weight explained the gender difference in this study. Limited data from controlled clinical studies with the approved dosage regimen do not indicate a major difference in the efficacy and safety profile between men and women.

5.3 Preclinical safety data

Acute and chronic toxicity: Saquinavir was well tolerated in oral acute and chronic toxicity studies in mice, rats, dogs and marmosets at dose levels that gave maximum plasma exposures (AUC values) approximately 1.5-, 1.0-, 4 to 9- and 3 fold greater, respectively, than those achieved in humans at the recommended dose.

Mutagenesis: Studies, with and without metabolic activation (as appropriate) have shown that saquinavir has no mutagenic or genotoxic activity.

Carcinogenesis: There was no evidence of carcinogenic activity after the administration of saquinavir mesilate for 96 to 104 weeks to rats (maximum dose 1000 mg/kg/day) and mice (maximum dose 2500 mg/kg/day). The plasma exposures (AUC values) in the respective species were up to 60 % of those obtained in humans at the recommended clinical dose of saquinavir soft capsules or equivalent to them.

Reproductive toxicity: (see section 4.6). Fertility and reproductive performance were not affected in rats at plasma exposures (AUC values) approximately 50 % of those achieved in humans at the recommended dose.

Reproduction studies conducted with saquinavir in rats have shown no embryotoxicity or teratogenicity at plasma exposures (AUC values) approximately 50 % of those achieved in humans at the recommended dose or in rabbits at plasma exposures approximately 40 % of those achieved at the recommended clinical dose. Distribution studies in these species showed that placental transfer of saquinavir is low (less than 5 % of maternal plasma concentrations).
Studies in rats indicated that exposure to saquinavir from late pregnancy through lactation at plasma concentrations (AUC values) approximately 50 % of those achieved in humans at the recommended dose had no effect on the survival, growth and development of offspring to weaning.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose,
Croscarmellose sodium,
Povidone,
Lactose (monohydrate),
Magnesium stearate.

Tablet coat:
Hypromellose,
Titanium dioxide (E 171),
Talc,
Glycerol triacetate,
Iron oxide yellow and red (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Plastic bottles (HDPE) containing 120 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

EU/1/96/026/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 October 1996
Date of last renewal: 04 October 2006

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Invirase 200 mg hard capsules
Name and address of the manufacturer responsible for batch release

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

Invirase 500 mg film-coated tablets
Name and address of the manufacturer responsible for batch release

ROCHE FARMA, S.A.
c/ Severo Ochoa, 13
Polígono Industrial de Leganés
Madrid
Spain

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

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

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

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

Not applicable.

- **OTHER CONDITIONS**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

TEXT FOR THE BOTTLE LABEL AND THE OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Invirase 200 mg hard capsules
Saquinavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains saquinavir mesilate corresponding to 200 mg saquinavir.

3. LIST OF EXCIPIENTS

Also contains lactose (anhydrous) 63.3 mg, colourants (titanium dioxide E 171, iron oxide E 172, indigocarmine E 132) and other constituents. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

270 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
The capsules should be swallowed whole
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original container

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/026/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

invirase 200 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

TEXT FOR THE BOTTLE LABEL AND THE OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Invirase 500 mg film-coated tablets
Saquinavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg of saquinavir as saquinavir mesilate.

3. LIST OF EXCIPIENTS

Also contains lactose (monohydrate) 38.5 mg, colourants (titanium dioxide E 171, iron oxide E 172) and other constituents. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

120 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/026/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

invirase 500 mg

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Invirase 200 mg hard capsules
Saquinavir

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT INVIRASE IS AND WHAT IT IS USED FOR

Invirase is an antiviral agent. It is a member of a class of medicines called protease inhibitors. It is for the treatment of infection with the human immunodeficiency virus (HIV).

Invirase is used by HIV-infected individuals over 16 years of age. Invirase is prescribed for use in combination with ritonavir and other antiretroviral medicines.

2. BEFORE YOU TAKE INVIRASE

Do not take Invirase
- if you are allergic (hypersensitive) to saquinavir, ritonavir or any of the other ingredients.
- if you have decompensated liver disease (e.g. jaundice or hepatitis with ascites, mental confusion and/or bleeding from veins of the oesophagus).
- if you are currently taking any of the following medicines:

- terfenadine and astemizole (commonly used to treat allergy symptoms),
- pimozide (for psychiatric problems),
- cisapride (for heart burn or problems with the digestive system),
- ergot alkaloids (used to treat migraine attacks),
- triazolam and oral (taken by mouth) midazolam (used to help you sleep and/or relieve anxiety),
- amiodarone (used to treat abnormal heart beat),
- flecainide and propafenone (heart medicines),
- rifampicin (used to prevent or treat tuberculosis),
- simvastatin and lovastatin (used to lower blood cholesterol).

Take special care with Invirase
You should know that Invirase/ritonavir 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 Invirase/ritonavir.

Treatment with Invirase/ritonavir has not been shown to reduce the risk of transmission of HIV to others through sexual contacts or contamination with blood. Therefore, you must continue to take appropriate precautions to avoid giving the virus to others.

At present, there is only limited information on the use of Invirase/ritonavir in children under the age of 16 years and in adults over 60 years.

Consult your doctor if you have a history of kidney disease.

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

There are certain conditions, which you may have, or have had, which require special care before or while taking Invirase/ritonavir. Therefore, before using this medicine, you should have told your doctor if you suffer from diabetes mellitus, diarrhoea, or if you have allergies (see section 4).

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately (see section 4).

Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat (see section 4).

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

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Invirase/ritonavir *may be taken* with a number of other medications that are commonly used in HIV infection.

There are some medications that *must not be taken* with Invirase/ritonavir *(see section "Do not take Invirase")* or that *require dosage reduction* of that medicine or Invirase or ritonavir. Ask your doctor or pharmacist for more information about taking Invirase/ritonavir with other medicines.

Medicines that can interact with saquinavir and/or ritonavir include:
- other HIV antiviral agents (e.g. nelfinavir, indinavir, nevirapine, delavirdine, efavirenz),
- some medicines affecting the immune system (e.g. ciclosporin, sirolimus (rapamycin), tacrolimus),
- various steroids (e.g. dexamethasone, ethinyl estradiol, fluticasone),
- certain heart medicines (e.g. calcium channel blockers, quinidine, digoxin),
- medicines used to lower blood cholesterol (e.g. statins),
- antifungals (ketoconazole, itraconazole),
- morphine-like medicines (e.g. methadone),
- anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine),
- sedative agents (e.g. midazolam administered by injection),
- certain antibiotics (e.g. clarithromycin, erythromycin, quinupristin/dalfopristin, dapsone, rifabutin),
- medicines used to treat erectile dysfunction (sildenafil, vardenafil, tadalafil),
- medicines to treat depression (e.g. nefazodone, tricyclic antidepressants),

- medicines for anticoagulation (warfarin),
- herbal preparations containing St. John's wort or garlic capsules.
- some medicines that treat diseases related to the acid in the stomach (e.g. omeprazole).

Therefore you should not take Invirase/ritonavir with other medicines without your doctor's consent.

If you are taking sildenafil, vardenafil, or tadalafil with Invirase/ritonavir talk to your doctor about possible interactions between these medicines and the possible side effects. If you take sildenafil, vardenafil, or tadalafil together with Invirase/ritonavir, you may be at a risk of side effects such as low blood pressure, passing out, visual changes and penile erection lasting for more than 4 hours. If an erection lasts longer than 4 hours, you should get medical help immediately to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

If you are taking an oral contraceptive to prevent pregnancy, you should use an additional or different type of contraception since ritonavir may reduce the effectiveness of oral contraceptives.

Taking Invirase with food and drink
Invirase must be taken together with ritonavir and with or after food.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. Inform your doctor if you are pregnant or planning to become pregnant. This medicine should be taken during pregnancy only after consultation with your doctor.

You should not breast-feed your baby if you are taking Invirase/ritonavir.

Driving and using machines
Invirase has not been tested for its effect on your ability to drive a car or operate machinery. However, dizziness and fatigue have been reported during treatment with Invirase. Do not drive or operate machines if you experience these symptoms.

Important information about an ingredient of Invirase
Each capsule contains lactose (anhydrous) 63.3 mg. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE INVIRASE

Always take Invirase/ritonavir exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Invirase is provided as 200 mg capsules. Your doctor will prescribe Invirase in combination with Norvir (ritonavir) and other HIV medicines. The dosage of Invirase is five 200 mg capsules with one 100 mg capsule of Norvir (ritonavir) two times daily. Invirase should be taken at the same time as Norvir (ritonavir) and with or after food.

The capsules should be swallowed unchewed together with water.

If you take more Invirase than you should
If you have taken more than the prescribed dose of Invirase/ritonavir you must contact your doctor or pharmacist.

If you forget to take Invirase
Do not take a double dose to make up for a forgotten individual dose. If you forget to take one dose, take this dose as soon as you remember together with some food. Then go on with the regular schedule as prescribed. Do not change the prescribed dose yourself.

If you stop taking Invirase
Continue to take this medicine until your doctor tells you otherwise.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Invirase/ritonavir can cause side effects, although not everybody gets them.

When treating HIV infection it is not always possible to differentiate between unwanted effects caused by Invirase or by any other medicines you take at the same time or by the complications of the infection. For these reasons it is very important to inform your doctor of any change in your condition.

The most frequently *(in more than ten in a hundred)* reported side effects of saquinavir taken with ritonavir concern the gastrointestinal tract, with feeling sick, diarrhoea, tiredness, vomiting, wind and abdominal pain being the most common. Also, changes in laboratory markers have been reported very commonly.

Other, less frequently reported side effects (*in more than one in a hundred but less than one in ten persons)*, which may occur are: rash, itching, eczema and dry skin, hair loss, dry mouth, headache, peripheral neuropathy (a disturbance of the nerves in the feet and hands that may take the form of numbness, pins and needles, shooting or burning pain), co-ordination problems, fainting, confusion, weakness, dizziness, depression, anxiety, moodswings, night sweats and hot flushes, inability to sleep, libido problems, taste alteration, warts, mouth ulcers, dehydration, abdominal discomfort, indigestion, fever, pain, constipation, decreased as well as increased appetite, inflammation of gastrointestinal tract, piles, discoloured faeces, visual disturbance, eye pain, raised blood pressure, infections of the respiratory tract, muscle spasms, joint pain, blood collection in the joint, painful micturition and infections of the urinary tract, fever and shivering, shortness of breath and chest pain.

Furthermore, inflammation of the liver, fits, allergic reactions, sleepiness and abnormal renal function have been reported.

Your doctor will test your blood regularly to detect possible abnormalities.

Cases of diabetes mellitus or increased blood sugar levels have been reported in patients receiving this treatment or another protease inhibitor.

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.

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

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

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

5. HOW TO STORE INVIRASE

Keep out of the reach and sight of children.

Store in the original container.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Invirase contains

- The active substance is saquinavir. One capsule of Invirase contains 228.7 mg of saquinavir mesilate corresponding to 200 mg saquinavir.
- The other ingredients are lactose (anhydrous) 63.3 mg, microcrystalline cellulose, povidone, sodium starch glycollate, talc and magnesium stearate. The capsule shell consists of gelatine, iron oxide black, red and yellow (E172), indigocarmine (E132), titanium dioxide (E171), and the printing ink contains titanium dioxide (E 171), shellac, soya lecithin, polydimethylsiloxane.

What Invirase looks like and contents of the pack

Invirase 200 mg hard capsules are light brown and green. Each half of the capsule shell is marked with the printing “ROCHE” and the code “0245”. Invirase is available in an amber glass bottle containing 270 capsules.

Marketing Authorisation Holder and Manufacturer

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

Manufacturer
Roche Pharma AG,
Emil-Barell-Strasse 1,
79639 Grenzach-Wyhlen,
Germany.

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

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

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Slovenská republika
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Sverige
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United Kingdom
Roche Products Ltd.
Tel: +44 (0) 1707 366000

This leaflet was last approved in

PACKAGE LEAFLET: INFORMATION FOR THE USER

Invirase 500 mg film-coated tablets
Saquinavir

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT INVIRASE IS AND WHAT IT IS USED FOR

Invirase is an antiviral agent. It is a member of a class of medicines called protease inhibitors. It is for the treatment of infection with the human immunodeficiency virus (HIV).

Invirase is used by HIV-infected individuals over 16 years of age. Invirase is prescribed for use in combination with ritonavir and other antiretroviral medicines.

2. BEFORE YOU TAKE INVIRASE

Do not take Invirase
- if you are allergic (hypersensitive) to saquinavir, ritonavir or any of the other ingredients.
- if you have decompensated liver disease (e.g. jaundice or hepatitis with ascites, mental confusion and/or bleeding from veins of the oesophagus).
- if you are currently taking any of the following medicines:

- terfenadine and astemizole (commonly used to treat allergy symptoms),
- pimozide (for psychiatric problems),
- cisapride (for heart burn or problems with the digestive system),
- ergot alkaloids (used to treat migraine attacks),
- triazolam and oral (taken by mouth) midazolam (used to help you sleep and/or relieve anxiety),
- amiodarone (used to treat abnormal heart beat),
- flecainide and propafenone (heart medicines),
- rifampicin (used to prevent or treat tuberculosis),
- simvastatin and lovastatin (used to lower blood cholesterol).

Take special care with Invirase
You should know that Invirase/ritonavir 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 Invirase/ritonavir.

Treatment with Invirase/ritonavir has not been shown to reduce the risk of transmission of HIV to others through sexual contacts or contamination with blood. Therefore, you must continue to take appropriate precautions to avoid giving the virus to others.

At present, there is only limited information on the use of Invirase/ritonavir in children under the age of 16 years and in adults over 60 years.

Consult your doctor if you have a history of kidney disease.

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

There are certain conditions, which you may have, or have had, which require special care before or while taking Invirase/ritonavir. Therefore, before using this medicine, you should have told your doctor if you suffer from diabetes mellitus, diarrhoea, or if you have allergies (see section 4).

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately (see section 4).

Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat (see section 4).

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

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Invirase/ritonavir *may be taken* with a number of other medications that are commonly used in HIV infection.

There are some medications that *must not be taken* with Invirase/ritonavir *(see section "Do not take Invirase")* or that *require dosage reduction* of that medicine or Invirase or ritonavir. Ask your doctor or pharmacist for more information about taking Invirase/ritonavir with other medicines.

Medicines that can interact with saquinavir and/or ritonavir include:
- other HIV antiviral agents (e.g. nelfinavir, indinavir, nevirapine, delavirdine, efavirenz),
- some medicines affecting the immune system (e.g. ciclosporin, sirolimus (rapamycin), tacrolimus),
- various steroids (e.g. dexamethasone, ethinyl estradiol, fluticasone),
- certain heart medicines (e.g. calcium channel blockers, quinidine, digoxin),
- medicines used to lower blood cholesterol (e.g. statins),
- antifungals (ketoconazole, itraconazole),
- morphine-like medicines (e.g. methadone),
- anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine),
- sedative agents (e.g. midazolam administered by injection),
- certain antibiotics (e.g. clarithromycin, erythromycin, quinupristin/dalfopristin, dapsone, rifabutin),
- medicines used to treat erectile dysfunction (sildenafil, vardenafil, tadalafil),
- medicines to treat depression (e.g. nefazodone, tricyclic antidepressants),

- medicines for anticoagulation (warfarin),
- herbal preparations containing St. John's wort or garlic capsules.
- some medicines that treat diseases related to the acid in the stomach (e.g. omeprazole).

Therefore you should not take Invirase/ritonavir with other medicines without your doctor's consent.

If you are taking sildenafil, vardenafil, or tadalafil with Invirase/ritonavir talk to your doctor about possible interactions between these medicines and the possible side effects. If you take sildenafil, vardenafil, or tadalafil together with Invirase/ritonavir, you may be at a risk of side effects such as low blood pressure, passing out, visual changes and penile erection lasting for more than 4 hours. If an erection lasts longer than 4 hours, you should get medical help immediately to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

If you are taking an oral contraceptive to prevent pregnancy, you should use an additional or different type of contraception since ritonavir may reduce the effectiveness of oral contraceptives.

Taking Invirase with food and drink
Invirase must be taken together with ritonavir and with or after food.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. Inform your doctor if you are pregnant or planning to become pregnant. This medicine should be taken during pregnancy only after consultation with your doctor.

You should not breast-feed your baby if you are taking Invirase/ritonavir.

Driving and using machines
Invirase has not been tested for its effect on your ability to drive a car or operate machinery. However, dizziness and fatigue have been reported during treatment with Invirase. Do not drive or operate machines if you experience these symptoms.

Important information about an ingredient of Invirase
Each film-coated tablet contains lactose (monohydrate) 38.5 mg. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE INVIRASE

Always take Invirase/ritonavir exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Invirase is provided as 500 mg film-coated tablet. For patients in whom the 500 mg film-coated tablet is not suitable, Invirase is also available in the form of 200 mg hard capsules. Your doctor will prescribe Invirase in combination with Norvir (ritonavir) and other HIV medicines. The dosage of Invirase is two 500 mg film-coated tablets with one 100 mg capsule of Norvir (ritonavir) two times daily. Invirase should be taken at the same time as Norvir (ritonavir) and with or after food.

The film-coated tablets should be swallowed together with water.

If you take more Invirase than you should
If you have taken more than the prescribed dose of Invirase/ritonavir you must contact your doctor or pharmacist.

If you forget to take Invirase
Do not take a double dose to make up for a forgotten individual dose. If you forget to take one dose, take this dose as soon as you remember together with some food. Then go on with the regular schedule as prescribed. Do not change the prescribed dose yourself.

If you stop taking Invirase
Continue to take this medicine until your doctor tells you otherwise.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Invirase/ritonavir can cause side effects, although not everybody gets them.

When treating HIV infection it is not always possible to differentiate between unwanted effects caused by Invirase or by any other medicines you take at the same time or by the complications of the infection. For these reasons it is very important to inform your doctor of any change in your condition.

The most frequently *(in more than ten in a hundred)* reported side effects of saquinavir taken with ritonavir concern the gastrointestinal tract, with feeling sick, diarrhoea, tiredness, vomiting, wind and abdominal pain being the most common. Also, changes in laboratory markers have been reported very commonly.

Other, less frequently reported side effects (*in more than one in a hundred but less than one in ten persons)*, which may occur are: rash, itching, eczema and dry skin, hair loss, dry mouth, headache, peripheral neuropathy (a disturbance of the nerves in the feet and hands that may take the form of numbness, pins and needles, shooting or burning pain), co-ordination problems, fainting, confusion, weakness, dizziness, depression, anxiety, moodswings, night sweats and hot flushes, inability to sleep, libido problems, taste alteration, warts, mouth ulcers, dehydration, abdominal discomfort, indigestion, fever, pain, constipation, decreased as well as increased appetite, inflammation of gastrointestinal tract, piles, discoloured faeces, visual disturbance, eye pain, raised blood pressure, infections of the respiratory tract, muscle spasms, joint pain, blood collection in the joint, painful micturition and infections of the urinary tract, fever and shivering, shortness of breath and chest pain.

Furthermore, inflammation of the liver, fits, allergic reactions, sleepiness and abnormal renal function have been reported.

Your doctor will test your blood regularly to detect possible abnormalities.

Cases of diabetes mellitus or increased blood sugar levels have been reported in patients receiving this treatment or another protease inhibitor.

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.

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

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

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

5. HOW TO STORE INVIRASE

Keep out of the reach and sight of children.

Invirase does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Invirase contains

- The active substance is saquinavir. One film-coated tablet of Invirase contains 500 mg of saquinavir as saquinavir mesilate.
- The other ingredients are microcrystalline cellulose, croscarmellose sodium, povidone, lactose (monohydrate) 38.5 mg, magnesium stearate, hypromellose, titanium dioxide (E 171), talc, glycerol triacetate, iron oxide yellow (E172) and iron oxide red (E172).

What Invirase looks like and contents of the pack

Invirase 500 mg film-coated tablets are light orange to greyish or brownish orange tablets of oval shape with the marking "SQV 500" on the one side and "ROCHE" on the other side. One plastic (HDPE) bottle contains 120 tablets.

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