ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 with known effect: Lactose monohydrate: 38.5 mg.

For the 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

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

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. For treatment-naive patients initiating treatment with Invirase/ritonavir, the starting recommended dose of Invirase is 500 mg (1 x 500 mg film-coated tablet) two times daily with ritonavir 100 mg two times daily in combination with other antiretroviral agents for the first 7 days of treatment. After 7 days, the recommended dose of Invirase is 1000 mg two times daily with ritonavir 100 mg two times daily in combination with other antiretroviral agents. Patients switching immediately from treatment with another protease inhibitor taken with ritonavir or from a non-nucleoside reverse transcriptase inhibitor based regimen, except rilpivirine (see section 4.5), without a wash-out period, should however initiate and continue Invirase at the standard recommended dose of 1000 mg two times daily with ritonavir 100 mg two times daily.

Renal impairment:
No dosage adjustment is necessary for patients with mild to moderate renal impairment. Caution should be exercised in patients with severe renal impairment (see section 4.4).

Hepatic impairment:
No dosage adjustment is necessary for HIV-infected patients with mild hepatic impairment. No dosage adjustment seems warranted for patients with moderate hepatic impairment based on limited data. Close monitoring of safety (including signs of cardiac arrhythmia) and of virologic response is

recommended due to increased variability of the exposure in this population. Invirase/ritonavir is contraindicated in patients with decompensated hepatic impairment (see sections 4.3 and 4.4).

Paediatric population:
The safety and activity of saquinavir boosted with ritonavir in HIV-infected patients less than 2 years have not been established. No dose recommendations for paediatric patients ≥2 years of age could be established that are both effective and below thresholds of concern for QT and PR interval prolongation.

Adults over 60 years:
The experience with Invirase in adults over 60 years is limited.

Method of administration
Invirase film-coated tablets should be swallowed whole and taken at the same time as ritonavir with or after food (see section 5.2).

4.3 Contraindications

Invirase is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- decompensated liver disease (see section 4.4)
- **congenital or documented acquired QT prolongation**
- **electrolyte disturbances, particularly uncorrected hypokalaemia**
- **clinically relevant bradycardia**
- **clinically relevant heart failure with reduced left-ventricular ejection fraction**
- **previous history of symptomatic arrhythmias**
- concurrent therapy with any of the following drugs, which may interact and result in potentially life-threatening undesirable effects (see sections 4.4, 4.5 and 4.8):
  - **drugs that prolong the QT and/or PR interval (see sections 4.4 and 4.5)**
  - 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)
  - quetiapine (risk of coma, see section 4.5).
  - lurasidone (potential for serious and/or life-threatening reactions, see section 4.5)

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). Invirase is not recommended for use in combination with cobicistat as dosing recommendations for this combination have not been established.

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.

Cardiac conduction and repolarisation abnormalities:
Dose-dependent prolongations of QT and PR intervals have been observed in healthy volunteers receiving ritonavir-boosted Invirase (see section 5.1). **Concomitant use of ritonavir-boosted Invirase with other medicinal products that prolong the QT and/or PR interval is therefore contraindicated (see section 4.3).**

Since the magnitude of QT and PR prolongation increases with increasing concentrations of saquinavir, the recommended dose of ritonavir-boosted Invirase should not be exceeded. Ritonavir-boosted Invirase at a dose of 2000 mg once daily with ritonavir 100 mg once daily has not been studied with regard to the risk of QT prolongation and is not recommended. Other medicinal products known to increase the plasma concentration of ritonavir-boosted Invirase should be used with caution.

Women and elderly patients may be more susceptible to drug-associated effects on the QT and/or PR interval.

- **Clinical Management:**

Consideration should be given for performing baseline and follow-up electrocardiograms after initiation of treatment, e.g. in patients taking concomitant medication known to increase the exposure of saquinavir (see section 4.5). If signs or symptoms suggesting cardiac arrhythmia occur, continuous monitoring of ECG should be performed. Ritonavir-boosted Invirase should be discontinued if arrhythmias are demonstrated, or if prolongation occurs in the QT or PR interval.

Patients initiating therapy with ritonavir-boosted Invirase:

- An ECG should be performed on all patients prior to initiation of treatment: patients with a QT interval > 450 msec should not use ritonavir-boosted Invirase. For patients with a QT interval < 450 msec, an on treatment ECG is recommended.
- For treatment-naïve patients initiating treatment with Invirase/ritonavir 500/100 mg two times daily for the first 7 days of treatment followed by Invirase 1000 mg two times daily with ritonavir 100 mg two times daily after 7 days and with a baseline QT interval < 450 msec, an on-treatment ECG is suggested after approximately 10 days of therapy.
- Patients demonstrating a subsequent increase in QT-interval to > 480 msec or prolongation over pre-treatment by > 20 msec should discontinue ritonavir-boosted Invirase.

Patients stable on ritonavir-boosted Invirase and requiring concomitant medication with potential to increase the exposure of saquinavir or patients on medication with potential to increase the exposure of saquinavir and requiring concomitant ritonavir-boosted Invirase where no alternative therapy is available and the benefits outweigh the risks:

- An ECG should be performed prior to initiation of the concomitant therapy: patients with a QT interval > 450 msec should not initiate the concomitant therapy (see section 4.5).
- For patients with a baseline QT interval < 450 msec, an on-treatment ECG should be performed. For patients demonstrating a subsequent increase in QT-interval to > 480 msec or increase by > 20 msec after commencing concomitant therapy, the physician should use best clinical judgment to discontinue either ritonavir-boosted Invirase or the concomitant therapy or both.

- **Essential Patient Information:**

Prescribers must ensure that patients are fully informed regarding the following information on cardiac conduction and repolarisation abnormalities:

- Patients initiating therapy with ritonavir boosted Invirase should be warned of the arrhythmogenic risk associated with QT and PR prolongation and told to report any sign or symptom suspicious of cardiac arrhythmia (e.g., chest palpitations, syncope, presyncope) to their physician.
- Physicians should enquire about any known familial history of sudden death at a young age as this may be suggestive of congenital QT prolongation.
- Patients should be advised of the importance not to exceed the recommended dose.
- Each patient (or patient's caregiver) should be reminded to read the Package Leaflet included in the Invirase Package.

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.

No dosage adjustment seems warranted for patients with moderate hepatic impairment based on limited data. Close monitoring of safety (including signs of cardiac arrhythmia) and of virologic response is recommended due to increased variability of the exposure in this population (see sections 4.2 and 5.2). 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.

Paediatric population: The safety and activity of saquinavir boosted with ritonavir in HIV-infected patients less than 2 years have not been established. No dose recommendations for paediatric patients ≥2 years of age could be established that are both effective and below thresholds of concern for QT and PR interval prolongation. Therefore, use in this population is not recommended.

Adults over 60 years: The experience with Invirase in adults over 60 years is limited. Elderly patients may be more susceptible to drug-associated effects on the QT and/or PR interval.

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.

Weight and metabolic parameters: An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

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.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

CYP3A4 Interactions: Saquinavir could interact and modify the pharmacokinetics of other drugs that are substrates for CYP3A4 and/or P-gp and should be used with caution. Conversely, other drugs that induce CYP3A4 may also reduce saquinavir plasma concentrations. Monitoring of saquinavir plasma concentration might be indicated. See table 1, section 4.5, for drugs known and/or having the potential to interact with saquinavir and specific recommendations.

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 with careful monitoring (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. 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).

Based on the finding of dose-dependent prolongations of QT and PR intervals in healthy volunteers receiving Invirase/ritonavir (see sections 4.3, 4.4 and 5.1), additive effects on QT and PR interval prolongation may occur. Therefore, concomitant use of ritonavir-boosted Invirase with other medicinal products that prolong the QT and/or PR interval is contraindicated. The combination of Invirase/ritonavir with drugs known to increase the exposure of saquinavir is not recommended and should be avoided when alternative treatment options are available. If concomitant use is deemed necessary because the potential benefit to the patient outweighs the risk, particular caution is warranted (see section 4.4; for information on individual drugs, see Table 1).

Table 1: Interactions and dose recommendations with other medicinal products

Medicinal product by therapeutic area (dose of Invirase used in study)	**Interaction**	**Recommendations concerning co-administration**
<u>Antiretroviral agents</u> ***Nucleoside reverse transcriptase inhibitors (NRTIs)***		
- Zalcitabine and/or Zidovudine	No pharmacokinetic interaction studies have been completed. Use of unboosted saquinavir with zalcitabine and/or zidovudine has been studied in adults. Absorption, distribution and elimination of each of the drugs are unchanged when they are used together. Interaction with zalcitabine is unlikely due to different routes of metabolism and excretion. For zidovudine (200 mg every 8 hours) a 25 % decrease in AUC was reported when combined with ritonavir (300 mg every 6 hours). The pharmacokinetics of ritonavir remained unchanged.	No dose adjustment required.
Didanosine 400 mg single dose (saquinavir/ritonavir 1600/100 mg qd)	Saquinavir AUC ↓ 30% Saquinavir C_{max} ↓ 25% Saquinavir C_{min} ↔	No dose adjustment required.
Tenofovir disoproxil fumarate 300 mg qd (saquinavir/ritonavir 1000/100 mg bid)	Saquinavir AUC ↓ 1% Saquinavir C_{max} ↓ 7% Saquinavir C_{min} ↔	No dose adjustment required.

Medicinal product by therapeutic area (dose of Invirase used in study)	**Interaction**	**Recommendations concerning co-administration**
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
- Delavirdine (saquinavir/ritonavir)	Interaction with Invirase/ritonavir not studied.	
- Delavirdine (unboosted saquinavir)	Saquinavir AUC ↑ 348%. 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 600 mg qd (saquinavir/ritonavir 1600/200 mg qd, *or* saquinavir/ritonavir 1000/100 mg bid, *or* saquinavir/ritonavir 1200/100 mg qd)	Saquinavir ↔ Efavirenz ↔	No dose adjustment required. Liver function should be monitored (see section 4.4).
Rilpivirine		Switching directly from a rilpivirine containing regimen to Invirase/ritonavir is contraindicated as is concomitant use due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
- Nevirapine (saquinavir/ritonavir)	Interaction with Invirase/ritonavir not studied.	
- Nevirapine (unboosted saquinavir)	Saquinavir AUC ↓ 24% Nevirapine AUC ↔	No dose adjustment required.

Medicinal product by therapeutic area (dose of Invirase used in study)	**Interaction**	**Recommendations concerning co-administration**
HIV protease inhibitors (PIs)		
Atazanavir 300 mg qd (saquinavir/ritonavir 1600/100 mg qd)	Saquinavir AUC ↑ 60% Saquinavir C_{max} ↑ 42% Ritonavir AUC ↑ 41% Ritonavir C_{max} ↑ 34% Atazanavir ↔ No clinical data available for the combination of saquinavir/ritonavir 1000/100 mg bid and atazanavir.	Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Fosamprenavir 700 mg bid (saquinavir/ritonavir 1000/100 mg bid)	Saquinavir AUC ↓ 15% Saquinavir C_{max} ↓ 9% Saquinavir C_{min} ↓ 24% (remained above the target threshold for effective therapy.)	No dose adjustment required for Invirase/ritonavir.
- Indinavir (saquinavir/ritonavir)	Low dose ritonavir increases the concentration of indinavir.	Increased concentrations of indinavir may result in nephrolithiasis.
- Indinavir 800 mg tid (saquinavir 600-1200 mg single dose)	Saquinavir AUC ↑ 4.6-7.2 fold Indinavir ↔ No safety and efficacy data available for this combination. Appropriate doses of combination not established.	
Lopinavir/ritonavir 400/100 mg bid (saquinavir 1000 mg bid in combination with 2 or 3 NRTIs)	Saquinavir ↔ Ritonavir ↓ (effectiveness as boosting agent not modified). Lopinavir ↔ (based on historical comparison with unboosted lopinavir)	Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
- Nelfinavir 1250 mg bid (saquinavir/ritonavir 1000/100 mg bid)	Saquinavir AUC ↑ 13% (90% CI: 27↓ - 74↑) Saquinavir Cmax ↑ 9% (90% CI: 27↓ - 61↑) Nelfinavir AUC ↓ 6% (90% CI: 28↓ - 22↑) Nelfinavir Cmax ↓ 5% (90% CI: 23↓ - 16↑)	Combination not recommended.
Ritonavir 100 mg bid (saquinavir 1000 mg bid)	Saquinavir ↑ Ritonavir ↔ In HIV-infected patients, Invirase or saquinavir soft capsules in combination with ritonavir at doses of 1000/100 mg twice daily provide a systemic exposure of saquinavir over a 24 hour period similar to or greater than that achieved with saquinavir soft capsules 1200 mg three times daily (see section 5.2).	This is the approved combination regimen. No dose adjustment is recommended.

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
Tipranavir/ritonavir (saquinavir/ritonavir)	Saquinavir C_{min} ↓ 78% Dual-boosted protease inhibitor combination therapy in multiple-treatment experienced HIV-positive adults.	Concomitant administration of tipranavir, co-administered with low dose ritonavir, with saquinavir/ritonavir, is not recommended. If the combination is considered necessary, monitoring of the saquinavir plasma levels is strongly encouraged (see section 4.4).
HIV fusion inhibitor		
Enfuvirtide (saquinavir/ritonavir 1000/100 mg bid)	Saquinavir ↔ Enfuvirtide ↔ No clinically significant interaction was noted.	No dose adjustment required.
HIV CCR5 antagonist		
Maraviroc 100 mg bid (saquinavir/ritonavir 1000/100 mg bid)	Maraviroc AUC_{12} ↑ 8.77 Maraviroc C_{max}: ↑ 3.78 Saquinavir/ritonavir concentrations not measured, no effect is expected.	No dose adjustment of saquinavir/ritonavir is required. Dose of maraviroc should be decreased to 150 mg bid with monitoring.
Cobicistat containing medicinal products		
Cobicistat	Interaction with Invirase/ritonavir not studied. Cobicistat is not recommended in combination with regimens containing ritonavir due to similar effects of cobicistat and ritonavir on CYP3A.	It is not recommended to coadminister Invirase/ritonavir with cobicistat containing products (see section 4.4).
Other medicinal products ***Alpha-1 adrenoreceptor antagonist***		
Alfuzosin	Concomitant use of alfuzosin and saquinavir/ritonavir is expected to increase plasma levels of alfuzosin.	Contraindicated in combination with Invirase/ritonavir due to potential increase in alfuzosin concentration which can result in hypotension and potentially life-threatening cardiac arrhythmia.
Antiarrhythmics		
Bepridil Lidocaine (systemic) Quinidine Hydroquinidine (saquinavir/ritonavir)	Concentrations of bepridil, systemic lidocaine, quinidine or hydroquinidine may be increased when co-administered with Invirase/ritonavir.	Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Amiodarone flecainide propafenone (saquinavir/ritonavir)	Concentrations of amiodarone, flecainide or propafenone may be increased when co-administered with Invirase/ritonavir.	Contraindicated in combination with saquinavir/ritonavir due to potentially life threatening cardiac arrhythmia (see section 4.3).

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
Dofetilide (saquinavir/ritonavir)	Although specific studies have not been performed, co-administration of Invirase/ritonavir with medicinal products that are mainly metabolised by CYP3A4 pathway may result in elevated plasma concentrations of these medicinal products.	Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Ibutilide Sotalol (saquinavir/ritonavir)		Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Anticoagulant		
Warfarin (saquinavir/ritonavir)	Concentrations of warfarin may be affected when co-administered with Invirase/ritonavir.	INR (international normalised ratio) monitoring recommended.
Anticonvulsants		
- Carbamazepine Phenobarbital Phenytoin (saquinavir/ritonavir)	Interaction with Invirase/ritonavir not studied. These medicinal products will induce CYP3A4 and may therefore decrease saquinavir concentrations	Use with caution. Monitoring of saquinavir plasma concentration is recommended (see section 4.4)
Antidepressants		
Tricyclic antidepressants (e.g. amitriptyline, imipramine, clomipramine) (saquinavir/ritonavir)	Invirase/ritonavir may increase concentrations of tricyclic antidepressants.	Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Maprotiline	Maprotiline's metabolism appears to involve the cytochrome P450 isozymes CYP2D6 and CYP 1A2 Associated with a prolongation of QTc intervals.	Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
- Nefazodone (saquinavir/ritonavir)	Interaction with saquinavir/ritonavir not evaluated. Nefazodone inhibits CYP3A4. Saquinavir concentrations may be increased.	Combination not recommended. Use with caution due to possible cardiac arrhythmias. Monitoring for saquinavir toxicity recommended (see section 4.4).
Trazodone (saquinavir/ritonavir)	Plasma concentrations of trazodone may increase. Adverse events of nausea, dizziness, hypotension and syncope have been observed following coadministration of trazodone and ritonavir.	Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4).

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
Anti-gout preparation		
Colchicine	Concomitant use of colchicine and saquinavir/ritonavir is expected to increase plasma levels of colchicine due to P-gp and/or CYP3A4 inhibition by the protease inhibitor.	Because of a potential increase of colchicine-related toxicity (neuromuscular events including rhabdomyolysis), its concomitant use with saquinavir/ritonavir is not recommended, especially in the case of renal or hepatic impairment (see section 4.4).
Antihistamines		
Terfenadine Astemizole (saquinavir/ritonavir)	Terfenadine AUC ↑, associated with a prolongation of QTc intervals. A similar interaction with astemizole is likely.	Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Mizolastine (saquinavir/ritonavir)		Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Anti-infectives		
Clarithromycin (saquinavir/ritonavir)	Interaction with Invirase/ritonavir not studied. Clarithromycin is a CYP3A4 substrate and is associated with QT prolongation.	Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Clarithromycin 500 mg bid (unboosted saquinavir 1200 mg tid)	Saquinavir AUC ↑ 177 % Saquinavir C_{max} ↑ 187 % Clarithromycin AUC ↑ 40 % Clarithromycin C_{max} ↑ 40 %	Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Erythromycin (saquinavir/ritonavir)	Interaction with Invirase/ritonavir not studied. Erythromycin is a CYP3A4 substrate and is associated with QT prolongation.	Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Erythromycin 250 mg qid (unboosted saquinavir 1200 mg tid)	Saquinavir AUC ↑ 99 % Saquinavir C_{max} ↑ 106 %	Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
Fusidic acid (saquinavir/ritonavir)	Not studied. Co-administration of fusidic acid and Invirase/ritonavir can cause increased plasma concentration of both fusidic acid and saquinavir/ritonavir.	
Streptogramin antibiotics (saquinavir/ritonavir)	Interaction with Invirase/ritonavir not studied. Streptogramin antibiotics such as quinupristin/dalfopristin inhibit CYP3A4. Saquinavir concentrations may be increased.	Use with caution due to possible cardiac arrhythmias. Monitoring for saquinavir toxicity recommended (see section 4.4).
Halofantrine Pentamidine Sparfloxacin (saquinavir/ritonavir)		Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Antifungals		
Ketoconazole 200 mg qd (saquinavir/ritonavir 1000/100 mg bid)	Saquinavir AUC ↔ Saquinavir C_{max} ↔ Ritonavir AUC ↔ Ritonavir C_{max} ↔ Ketoconazole AUC ↑ 168% (90% CI 146%-193%) Ketoconazole C_{max} ↑ 45% (90% CI 32%-59%)	No dose adjustment required when saquinavir/ritonavir combined with ≤ 200 mg/day ketoconazole. High doses of ketoconazole (> 200 mg/day) are not recommended.
Itraconazole (saquinavir/ritonavir)	Interaction with Invirase/ritonavir not studied. Itraconazole is a moderately potent inhibitor of CYP3A4. An interaction is possible.	Use with caution due to possible cardiac arrhythmias. Monitoring for saquinavir toxicity recommended (see section 4.4).
Fluconazole/miconazole (saquinavir/ritonavir)	Interaction with Invirase/ritonavir not studied. Both drugs are CYP3A4 inhibitors and may increase the plasma concentration of saquinavir.	Use with caution due to possible cardiac arrhythmias. Monitoring for saquinavir toxicity recommended (see section 4.4).
Antimycobacterials		
Rifampicin 600 mg qd (saquinavir/ritonavir 1000/100 mg bid)	In a clinical study 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.	Rifampicin is contraindicated in combination with Invirase/ritonavir (see section 4.3).

Medicinal product by therapeutic area (dose of Invirase used in study)	**Interaction**	**Recommendations concerning co-administration**
Rifabutin 150 mg q3d (saquinavir/ritonavir 1000/100 mg bid) in healthy volunteers	Saquinavir AUC_{0-12} ↓ 13% (90% CI: 31↓ - 9↑) Saquinavir C_{max} ↓ 15% (90% CI: 32↓ - 7↑) Ritonavir AUC_{0-12} ↔ (90% CI: 10↓ - 9↑) Ritonavir C_{max} ↔ (90% CI: 8↓ - 7↑) Rifabutin active moiety* AUC_{0-72} ↑ 134% (90% CI 109%-162%) Rifabutin active moiety* C_{max} ↑ 130% (90% CI 98%-167%) Rifabutin AUC_{0-72} ↑ 53% (90% CI 36%-73%) Rifabutin C_{max} ↑ 86% (90% CI 57%-119%) * Sum of rifabutin + 25-O-desacetyl rifabutin metabolite	To prevent possible development of rifabutin resistance in TB and HIV co-infected patients, the recommended dose of rifabutin is 150 mg every other day or three times per week, with the dose of saquinavir/ritonavir unchanged (1000/100 mg bid). Monitoring of neutropenia and liver enzyme levels is recommended due to an expected increase in exposure to rifabutin.
Antipsychotics		
Lurasidone	Due to CYP3A inhibition by saquinavir/ritonavir, concentrations of lurasidone are expected to increase.	Concomitant administration of Invirase and lurasidone is contra-indicated as it may increase lurasidone-related toxicity (see section 4.3).
Quetiapine	Due to CYP3A inhibition by saquinavir/ritonavir, concentrations of quetiapine are expected to increase.	Concomitant administration of Invirase and quetiapine is contra-indicated as it may increase quetiapine-related toxicity. Increased plasma concentrations of quetiapine may lead to coma (see sectin 4.3).
Pimozide (saquinavir/ritonavir)	Concentrations of pimozide may be increased when co-administered with Invirase/ritonavir. Pimozide is a CYP3A4 substrate and is associated with QT prolongation,	Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Clozapine Haloperidol Chlorpromazine Mesoridazine Phenothiazines Sertindole Sultopride Thioridazine Ziprasidone (saquinavir/ritonavir)		Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
Benzodiazepines		
Midazolam 7.5 mg single dose (oral) (saquinavir/ritonavir 1000/100 mg bid)	Midazolam AUC ↑ 12.4 fold Midazolam C_{max} ↑ 4.3 fold Midazolam $t_{1/2}$ ↑ from 4.7 h to 14.9 h 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.	Co-administration of Invirase/ritonavir with orally administered midazolam is contraindicated (see section 4.3). Caution should be used with co-administration of Invirase and parenteral midazolam. 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 (saquinavir/ritonavir)	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 (saquinavir/ritonavir)	Concentrations of triazolam may be increased when co-administered with Invirase/ritonavir.	Contraindicated in combination with saquinavir/ritonavir, due to the risk of potentially prolonged or increased sedation and respiratory depression (see section 4.3).
Calcium channel blockers		
Felodipine, nifedipine, nicardipine, diltiazem, nimodipine, verapamil, amlodipine, nisoldipine, isradipine (saquinavir/ritonavir)	Concentrations of these medicinal products may be increased when co-administered with Invirase/ritonavir.	Caution is warranted and clinical monitoring of patients is recommended.

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
Corticosteroids		
- Dexamethasone (saquinavir/ritonavir)	Interaction with Invirase/ritonavir not studied. Dexamethasone induces CYP3A4 and may decrease saquinavir concentrations.	Use with caution. Monitoring of saquinavir plasma concentration is recommended (see section 4.4).
Fluticasone propionate 50 mcg qid, intranasal (ritonavir 100 mg bid)	Fluticasone propionate ↑ Intrinsic cortisol ↓ 86% (90% CI 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. Effects of high fluticasone systemic exposure on ritonavir plasma levels yet unknown.	Concomitant administration of boosted saquinavir and fluticasone propionate and other corticosteroids metabolised via the P450 3A pathway (e.g. budesonide) is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). 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. beclomethasone). In case of withdrawal of glucocorticoids progressive dose reduction may have to be performed over a longer period.
Endothelin receptor antagonist		
Bosentan	Not studied. Concomitant use of bosentan and saquinavir/ritonavir may increase plasma levels of bosentan and may decrease plasma levels of saquinavir/ritonavir.	Dose adjustment of bosentan may be required. When bosentan is administered concomitantly with saquinavir/ritonavir, the patient's tolerability of bosentan should be monitored. Monitoring of the patient's HIV therapy is also recommended.
Medicinal products that are substrates of P-glycoprotein ***Digitalis glycosides***		
Digoxin 0.5 mg single dose (saquinavir/ritonavir 1000/100 mg bid)	Digoxin AUC_{0-72} ↑ 49% Digoxin C_{max} ↑ 27% Digoxin levels may differ over time. Large increments of digoxin may be expected when saquinavir/ritonavir is introduced in patients already treated with digoxin.	Caution should be exercised when Invirase/ritonavir and digoxin are co-administered. The serum concentration of digoxin should be monitored and a dose reduction of digoxin should be considered if necessary.

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
Histamine H_2-receptor antagonist		
- Ranitidine (saquinavir/ritonavir) - Ranitidine (unboosted saquinavir)	Interaction with Invirase/ritonavir not studied. Saquinavir AUC ↑ 67 %	Increase not thought to be clinically relevant. No dose adjustment of saquinavir recommended.
HMG-CoA reductase inhibitors		
Pravastatin Fluvastatin (saquinavir/ritonavir)	Interaction not studied. Metabolism of pravastatin and fluvastatin is not dependent on CYP3A4. Interaction via effects on transport proteins cannot be excluded.	Interaction unknown. If no alternative treatment is available, use with careful monitoring (see section 4.4).
Simvastatin Lovastatin (saquinavir/ritonavir)	Simvastatin ↑↑ Lovastatin ↑↑ Plasma concentrations highly dependent on CYP3A4 metabolism.	Increased concentrations of simvastatin and lovastatin have been associated with rhabdomyolysis. These medicinal products are contraindicated for use with Invirase/ritonavir (see section 4.3).
Atorvastatin (saquinavir/ritonavir)	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 should be carefully monitored for signs/symptoms of myopathy (muscle weakness, muscle pain, rising plasma creatinine kinase, see section 4.4).
Immunosuppressants		
Tacrolimus	Tacrolimus is a substrate of CYP3A4 and P-glycoprotein. Concomitant use of tacrolimus and saquinavir/ritonavir is expected to increase plasma levels of tacrolimus. Tacrolimus may be associated with torsades de pointes.	Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Ciclosporin Rapamycin (saquinavir/ritonavir)	Concentrations of these medicinal products increase several fold when co-administered with Invirase/ritonavir.	Careful therapeutic drug monitoring is necessary for these immunosuppressants when co-administered with Invirase/ritonavir.

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
Long-acting beta2-adrenergic agonist		
Salmeterol	Concomitant use of salmeterol and saquinavir/ritonavir is expected to increase plasma levels of salmeterol.	Combination not recommended as may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia (see section 4,4).
Narcotic analgesics		
Methadone 60-120 mg qd (saquinavir/ritonavir 1000/100 mg bid)	Methadone AUC ↓ 19 % (90 % CI 9 % to 29 %) None of the 12 patients experienced withdrawal symptoms.	Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Oral contraceptives		
Ethinyl estradiol (saquinavir/ritonavir)	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 4.4).
Phosphodiesterase type 5 (PDE5) inhibitors		
Sildenafil (saquinavir/ritonavir) Sildenafil 100 mg (single dose) (unboosted saquinavir 1200 mg tid)	Interaction with Invirase/ritonavir not studied. Saquinavir ↔ Sildenafil Cmax ↑ 140 % Sildenafil AUC ↑ 210 % -Sildenafil is a substrate of CYP3A4.	Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Vardenafil (saquinavir/ritonavir)	Concentrations of vardenafil may be increased when co-administered with Invirase/ritonavir.	Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Tadalafil (saquinavir/ritonavir)	Concentrations of tadalafil may be increased when co-administered with Invirase/ritonavir.	Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).

Medicinal product by therapeutic area (dose of Invirase used in study)	**Interaction**	**Recommendations concerning co-administration**
Proton pump inhibitors		
Omeprazole 40 mg qd (saquinavir/ritonavir 1000/100 mg bid)	Saquinavir AUC ↑ 82% (90 % CI 44-131 %) Saquinavir C_{max} ↑ 75% (90 % CI 38-123 %) Ritonavir ↔	Combination not recommended.
Other proton pump inhibitors (saquinavir/ritonavir 1000/100 mg bid)	No data are available on the concomitant administration of Invirase/ritonavir and other proton pump inhibitors.	Combination not recommended.
Tyrosine kinase inhibitors		
All tyrosine kinase inhibitors with a risk of QT prolongation e.g. dasatinib, sunitinib	Interaction with Invirase/ritonavir not studied	Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Others		
Ergot alkaloids (e.g. ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (saquinavir/ritonavir)	Invirase/ritonavir may increase ergot alkaloids exposure, and consequently, increase the potential for acute ergot toxicity.	The concomitant use of Invirase/ritonavir and ergot alkaloids is contra-indicated (see section 4.3).
- Grapefruit juice (saquinavir/ritonavir)	Interaction with Invirase/ritonavir not studied.	
- Grapefruit juice (single dose) (unboosted saquinavir)	Saquinavir ↑ 50% (normal strength grapefruit juice) Saquinavir ↑ 100% (double strength grapefruit juice)	Increase not thought to be clinically relevant. No dose adjustment required.

Medicinal product by therapeutic area (dose of Invirase used in study)	**Interaction**	**Recommendations concerning co-administration**
- Garlic capsules (saquinavir/ritonavir)	Interaction with Invirase/ritonavir not studied.	
- Garlic capsules (dose approx. equivalent to two 4 g cloves of garlic daily) (unboosted saquinavir 1200 mg tid)	Saquinavir AUC ↓ 51 % Saquinavir Ctrough ↓ 49 % (8 hours post dose) Saquinavir Cmax ↓ 54 %.	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 (saquinavir/ritonavir)	Interaction with Invirase/ritonavir not studied.	
St. John's wort (unboosted saquinavir)	Plasma levels of unboosted 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***		
e.g. dapsone, disopyramide, quinine, fentanyl, and alfentanyl	Although specific studies have not been performed, co-administration of Invirase/ritonavir with medicinal products that are mainly metabolised by CYP3A4 pathway may result in elevated plasma concentrations of these medicinal products.	Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Gastroenterological medicinal products		
Metoclopramide	It is unknown whether medicinal products which reduce the gastrointestinal transit time could lead to lower saquinavir plasma concentrations.	
Cisapride (saquinavir/ritonavir)	Although specific studies have not been performed, co-administration of Invirase/ritonavir with medicinal products that are mainly metabolised by CYP3A4 pathway may result in elevated plasma concentrations of these medicinal products.	Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4).
Diphemanil (saquinavir/ritonavir)		Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4).

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
Vasodilators (peripheral)		
Vincamine i.v.		Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).

Key: ↓ reduced, ↑ increased, ↔ unchanged, ↑↑ markedly increased

4.6 Fertility, 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).

Breast-feeding**:** 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 women living with HIV do not breast-feed their infants 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, fatigue and visual impairment 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

a. Summary of the safety profile

Limited data is available from two clinical 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.

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.

The following adverse events were reported with the highest severity (grades 3 and 4): anaemia, diabetes mellitus, diarrhoea, nausea, vomiting and fatigue.

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.

b. Tabulated list of adverse reactions

Adverse reactions from two pivotal studies of saquinavir soft capsule (1000 mg twice daily) used in combination with low dose ritonavir (100 mg twice daily) for at least 48 weeks are summarised in Table 2. Also included are serious and non-serious adverse reactions from post-marketing spontaneous reports for which a causal relationship to saquinavir cannot be excluded.

Adverse reactions are presented according to the MedDRA system organ classification. The frequency groupings according to MedDRA convention are: Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000); not known (frequency cannot be estimated from the available data).

Table 2: Incidences of Adverse Reactions and marked laboratory abnormalities in clinical studies and post-marketing experience in adult patients.

Body System **Frequency of reaction**	**Adverse reactions**
Blood and the lymphatic system disorders	
Very common	Decreased platelet count
Common	Anaemia, decreased haemoglobin, decreased lymphocyte count, decreased white blood cell count
Uncommon	Neutropenia
Eye Disorders	
Uncommon	Visual impairment
Immune System Disorders	
Common	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Increased blood cholesterol, increased blood triglycerides
Common	Diabetes mellitus, anorexia, increased appetite
Uncommon	Decreased appetite
Psychiatric Disorders	
Common	Decreased libido, sleep disorder
Nervous System Disorder	
Common	Paraesthesia, peripheral neuropathy, dizziness, dysgeusia, headache
Uncommon	Somnolence, convulsions
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea
Gastrointestinal disorders	
Very common	Diarrhoea, nausea
Common	Vomiting, abdominal distension, abdominal pain, upper abdominal pain, constipation, dry mouth, dyspepsia, eructation, flatulence, lip dry, loose stools
Uncommon	Pancreatitis
Hepato-biliary disorders	
Very common	Increased alanine aminotransferase, increased aspartate aminotransferase, increased low density lipoprotein
Common	Increased blood bilirubin, increased blood amylase
Uncommon	Hepatitis, jaundice
Renal and urinary disorders	
Common	Increased blood creatinine
Uncommon	Renal impairment
Skin and subcutaneous tissue disorders	

Body System **Frequency of reaction**	**Adverse reactions**
Common	Alopecia, dry skin, eczema, lipoatrophy, pruritus, rash
Uncommon	Stevens Johnson syndrome, dermatitis bullous
Musculoskeletal and connective tissue disorders	
Common	Muscle spasms
General disorders and administration site conditions	
Common	Asthenia, fatigue, increased fat tissue, malaise
Uncommon	Mucosal ulceration

c. Description of selected adverse reactions

Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

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).

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).

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. Autoimmune disorders (such as Graves'disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

d. Paediatric population

Limited safety data are available from a paediatric study (NV20911, n=18) in which the safety of saquinavir hard capsules (50 mg/kg bid, not to exceed 1000 mg bid) used in combination with low dose ritonavir oral solution (3 mg/kg bid for body weight from 5 to <15 kg, 2.5 mg/kg bid for body weight from 15 to 40 kg and 100 mg bid for body weight >40 kg) has been studied in paediatric patients aged 4 months to 6 years old.

Four patients in the study experienced five adverse events that were considered related to trial treatment. These events were vomiting (3 patients), abdominal pain (1 patient) and diarrhoea (1 patient). No unexpected adverse events were observed in this study.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is limited experience of overdose with saquinavir. Whereas acute or chronic overdose of saquinavir alone did not result in major complications, in combination with other protease inhibitors, overdose symptoms and signs such as general weakness, fatigue, diarrhoea, nausea, vomiting, hair loss, dry mouth, hyponatraemia, weight loss and orthostatic hypotension have been observed. There is no specific antidote for overdose with saquinavir. Treatment of overdose with saquinavir should

consist of general supportive measures, including monitoring of vital signs and ECG, and observations of the patient's clinical status. If indicated, prevention of further absorption can be considered. Since saquinavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action: The HIV protease is an essential viral enzyme required for the specific cleavage of viral gag and gag-pol polyproteins. Saquinavir selectively inhibits the HIV protease, thereby preventing the creation of mature infectious virus particles.

QT and PR prolongation on electrocardiogram: The effects of therapeutic (1000/100 mg twice daily) and supra-therapeutic (1500/100 mg twice daily) doses of Invirase/ritonavir on the QT interval were evaluated in a 4-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg) study in healthy male and female volunteers aged 18 to 55 years old (N=59). On Day 3 of dosing, ECG measurements were done over a period of 20 hours. The Day 3 timepoint was chosen since the pharmacokinetic exposure was maximum on that day in a previous 14-day multiple dose pharmacokinetic study. On Day 3, mean C_{max} values were approximately 3-fold and 4-fold higher with the therapeutic and supra-therapeutic doses, respectively, relative to the mean C_{max} observed at steady state with the therapeutic dose administered to HIV patients. On Day 3, the upper 1-sided 95% confidence interval of the maximum mean difference in pre-dose baseline-corrected QTcS (study specific heart rate corrected QT) between the active drug and placebo arms was > 10 msec for the two ritonavir-boosted Invirase treatment groups (see results in Table 3). While the supra-therapeutic dose of Invirase/ritonavir appeared to have a greater effect on the QT interval than the therapeutic dose of Invirase/ritonavir, it is not sure if maximum effect for both doses has been observed. In the therapeutic and the supra-therapeutic arm 11% and 18% of subjects, respectively, had a QTcS between 450 and 480 msec. There was no QT prolongation > 500 msec and no torsade de pointes in the study (see also section 4.4).

Table 3: Maximum mean of ddQTcS† (msec) on day 3 for therapeutic dose of Invirase/ritonavir, supra-therapeutic dose of Invirase/ritonavir and active control moxifloxacin in healthy volunteers in Thorough QT (TQT) Study

Treatment	Post-Dose Time Point	Mean ddQTcS	Standard Error	Upper 95%-CI of ddQTcS
Invirase/ritonavir 1000/100 mg BID	12 hours	18.86	1.91	22.01
Invirase/ritonavir 1500/100 mg BID	20 hours	30.22	1.91	33.36
Moxifloxacin^	4 hours	12.18	1.93	15.36

† Derived difference of pre-dose baseline corrected QTcS between active treatment and placebo arms

^ 400 mg was administered only on Day 3

Note: QTcS in this study was $QT/RR^{0.319}$ for males and $QT/RR^{0.337}$ for females, which are similar to Fridericia's correction ($QTcF=QT/RR^{0.333}$).

In this study, PR interval of > 200 msec was also observed in 40% and 47% of subjects receiving Invirase/ritonavir 1000/100 mg twice daily and 1500/100 mg twice daily, respectively, on Day 3. PR intervals of > 200 msec were seen in 3% of subjects in the active control group (moxifloxacin) and 5% in the placebo arm. The maximum mean PR interval changes relative to the pre-dose baseline value

were 25 msec and 34 msec in the two ritonavir-boosted Invirase treatment groups, 1000/100 mg twice daily and 1500/100 mg twice daily, respectively (also see section 4.4).

Events of syncope/presyncope occurred at a higher than expected rate and were seen more frequently under treatment with saquinavir (11 of 13). The clinical relevance of these findings from this study in healthy volunteers to the use of Invirase/ritonavir in HIV-infected patients is unclear, but doses exceeding Invirase/ritonavir 1000/100 mg twice daily should be avoided.

The effect of treatment initiation with a dosing regimen of Invirase/ritonavir 500 /100 mg twice daily in combination with 2 NRTIs for the first 7 days of treatment followed by Invirase/ritonavir 1000 / 100 mg twice daily in combination with 2 NRTIs in the subsequent 7 days on QTc interval, PK, and viral load was evaluated in an open-label 2-week observational study in 23 HIV-1 infected, treatment-naïve patients initiating Invirase/ritonavir therapy. ECG and PK measurements were collected on Days 3, 4, 7, 10, and 14 of treatment with the modified Invirase/ritonavir treatment. The primary study variable was maximal change from dense predose baseline in QTcF (ΔQTcFdense). The modified Invirase/ritonavir regimen reduced mean maximum $\Delta QTcF_{dense}$ in the first week of treatment compared with the same value in healthy volunteers receiving the standard Invirase/ritonavir dosing regimen in the TQT study on Day 3, (Table 4) based on cross-study comparison in a different population. Only 2/21 (9%) patients across all study days had maximum QTcF change from dense predose baseline ≥ 30 ms following administration of the modified Invirase/ritonavir regimen in the treatment-naïve HIV-1 infected patient population; and the maximum mean change from dense predose baseline in QTcF was < 10 ms across all study days. These results suggest that the QTc liability is reduced with the modified Invirase/ritonavir dosing regimen, based on a cross-study comparison in a different population (Table 4). The proportion of patients with a reported PR interval prolongation > 200 ms in this study ranged from 3/22 (14%) (day 3) to 8/21 (38%) (day14).

Following the modified Invirase/ritonavir regimen, saquinavir exposure during the first week peaked on Day 3 and declined to the lowest exposure on Day 7 with ritonavir induction effects, while Day 14 saquinavir PK parameters (following full doses of Invirase/ritonavir in the second week) approached the range of historical mean values for saquinavir steady-state values in HIV-1 infected patients (Table 9). Mean Invirase C_{max} with the modified Invirase/ritonavir regimen was approximately 53-83% lower across study days in the HIV-1 infected patients relative to the mean C_{max} achieved in healthy volunteers in the TQT study on Day 3. Continuous declines in HIV-RNA were observed in all treatment-naïve patients receiving the modified Invirase/ritonavir dosing regimen over the 2-week treatment period, suggesting HIV viral suppression during the time of the study. No long-term efficacy was evaluated with the modified regimen.

Table 4: Summary of Electrocardiogram Parameters following administration of the Modified Invirase/ritonavir Regimen in Treatment Naïve HIV-1 infected Patients initiating treatment with Invirase/ritonavir

Parameter	**Day 3 500/100 mg (n=22)**	**Day 4 500/100 mg (n=21)**	**Day 7 500/100 mg (n=21)**	**Day 10 1000/100 mg (n=21)**	**Day 14 1000/100 mg (n=21)**	**TQT Study Day 3* (n=57)**
Mean Maximal $\Delta QTcF_{dense}$ ms (SD)	3.26 ± 7.01	0.52 ± 9.25	7.13 ± 7.36	11.97 ± 11.55	7.48 ± 8.46	32.2 ± 13.4
Patients with maximal $\Delta QTcF_{dense} \geq 30$ ms (%)	0	0	0	2/21 (9%)	0	29/57 (51%)

*Historical data from the thorough QT study conducted in healthy volunteers

Antiviral activity in vitro: Saquinavir demonstrates antiviral activity against a panel of laboratory strains and clinical isolates of HIV-1 with typical EC_{50} and EC_{90} values in the range 1-10 nM and 5-50 nM, respectively, with no apparent difference between subtype B and non-B clades. The

corresponding serum (50% human serum) adjusted EC_{50} ranged from 25-250 nM. Clinical isolates of HIV-2 demonstrated EC_{50} values in the range of 0.3-2.4 nM.

Resistance

Antiviral activity according to baseline genotype and phenotype:

Genotypic and phenotypic clinical cut-offs predicting the clinical efficacy of ritonavir boosted saquinavir have been derived from retrospective analyses of the RESIST 1 and 2 clinical studies and analysis of a large hospital cohort (Marcelin et al 2007).

Baseline saquinavir phenotype (shift in susceptibility relative to reference, PhenoSense Assay) was shown to be a predictive factor of virological outcome. Virological response was first observed to decrease when the fold shift exceeded 2.3-fold; whereas virological benefit was not observed when the fold shift exceeded 12-fold.

Marcelin et al (2007) identified nine protease codons (L10F/I/M/R/V, I15A/V, K20I/M/R/T, L24I, I62V, G73S/T, V82A/F/S/T, I84V, L90M) that were associated with decreased virological response to saquinavir/ritonavir (1000/100 mg twice daily) in 138 saquinavir naive patients. The presence of 3 or more mutations was associated with reduced response to saquinavir/ritonavir. The association between the number of these saquinavir-associated resistance mutations and virological response was confirmed in an independent clinical study (RESIST 1 and 2) involving a more heavily treatment experienced patient population, including 54% who had received prior saquinavir (p=0.0133, see Table 5). The G48V mutation, previously identified *in vitro* as a saquinavir signature mutation, was present at baseline in virus from three patients, none of whom responded to therapy.

Table 5: Virological response to saquinavir/ritonavir stratified by the number of baseline saquinavir-associated resistance mutations

Number of Saquinavir Associated Resistance Mutations at Baseline*	**Marcelin et al (2007) SQV Naive Population**		**RESIST 1 & 2 SQV Naive/Experienced Population**	
	N=138	**Change in Baseline Plasma HIV-1 RNA at Weeks 12-20**	**N=114**	**Change in Baseline Plasma HIV-1 RNA at Week 4**
0	35	-2.24	2	-2.04
1	29	-1.88	3	-1.69
2	24	-1.43	14	-1.57
3	30	-0.52	28	-1.41
4	9	-0.18	40	-0.75
5	6	-0.11	17	-0.44
6	5	-0.30	9	0.08
7	0	-	1	0.24

* *Saquinavir Mutation Score Mutations: L10F/I/M/R/V, I15A/V, K20I/M/R/T, L24I, I62V, G73S/T, V82A/F/S/T, I84V, L90M*

Clinical results from studies with treatment naïve and experienced patients

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.

Table 6: 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	82%	74%	81%	76%
Race (White/Black/Asian) %	86/9/1	82/12/4	75/19/1	74/19/2
Age, median, yrs	39	40	40	40
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)
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 7: Outcomes at Week 48 MaxCmin1 and MaxCmin2†

Outcomes	**MaxCmin1**		**MaxCmin2**	
	SQV/r	**IDV/r**	**SQV/r**	**LPV/r**
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	
Virological failure ITT/e*#	36/148 (24%)	41/158 (26%)	53/161 (33%)	29/163 (18%)
	P=0.76		P=0.002	
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, On Treatment	82/104 (79%)	73/93 (78%)	84/113 (74%)	97/138 (70%)
	P>0.05‡		P=0.48	
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

† Data from clinical study report

‡ Data from MaxCmin1 publication

Clinical results from paediatric studies

The pharmacokinetics, safety and activity of saquinavir have been evaluated in an open label, multicenter study in 18 children aged 4 months to less than 6 years old in which saquinavir (50 mg/kg bid up to the adult dose of 1000 mg bid) was administered in combination with ritonavir oral solution (3 mg/kg bid for body weight from 5 to <15 kg, 2.5 mg/kg bid for body weight from 15 to 40 kg and 100 mg bid for body weight >40 kg) plus ≥2 background ARVs. The infants and young children were stratified into 2 groups: Group A "Low Age Group" 4 months to less than 2 years old (n=5) and Group B "High Age Group" children 2 years to less than 6 years old (n=13).

In the "High Age Group", the number of patients with a viral load <400 copies/mL at week 48 was 11 of 13. The number of patients with viral load <50 copies/mL was 9 of 13 for the same period. The CD4 lymphocyte count expressed as percentage mean CD4 increased by a mean of 2.97% over the same 48 week period. The size of the study was too small to allow conclusions on clinical benefit.

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: In HIV-infected adult 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 8). The pharmacokinetics of saquinavir is stable during long-term treatment.

Table 8: 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	1,509 (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	5,208 (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 treatment-naïve HIV-1 infected patients initiating Invirase/ritonavir treatment with a modified Invirase/ritonavir dosing regimen of Invirase 500 mg two times daily with ritonavir 100 mg two times daily for the first 7 days of treatment and increased to Invirase 1000 mg two times daily with ritonavir 100 mg two times daily in the subsequent 7 days, saquinavir systemic exposures generally approached or exceeded the range of historical steady-state values with the standard Invirase/ritonavir 1000 mg/100 mg bid dosing regimen across study days (see Tables 9 and 8).

Table 9: Mean (CV%) PK Parameters following administration of the Modified Invirase/ritonavir Regimen in Treatment Naïve HIV-1 infected Patients initiating treatment with Invirase/ritonavir

Parameter	**Day 3 500/100 mg (n=22)**	**Day 4 500/100 mg (n=21)**	**Day 7 500/100 mg (n=21)**	**Day 10 1000/100 mg (n=21)**	**Day 14 1000/100 mg (n=21)**
AUC_{0-12} **(ng*hr/ml)**	27100 (35.7)	20300 (39.9)	12600 (54.5)	34200 (48.4)	31100 (49.6)
C_{max} (ng/ml)	4030 (29.1)	2960 (40.2)	1960 (53.3)	5300 (36.0)	4860 (46.8)
C_{12} **(ng/ml)**	899 (64.9)	782 (62.4)	416 (98.5)	1220 (91.6)	1120 (80.9)

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.

Biotransformation 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.

Patients with hepatic impairment: The effect of hepatic impairment on the steady state pharmacokinetics of saquinavir/ritonavir (1000 mg/100 mg twice daily for 14 days) was investigated in 7 HIV-infected patients with moderate liver impairment (Child Pugh Grade B score 7 to 9). The study included a control group consisting of 7 HIV-infected patients with normal hepatic function matched with the hepatically impaired patients for age, gender, weight and tobacco use. The mean (% coefficient of variation in parentheses) values for saquinavir AUC_{0-12} and C_{max} were 24.3 (102%) µg·hr/ml and 3.6 (83%) µg/ml, respectively, for HIV-infected patients with moderate hepatic impairment. The corresponding values in the control group were 28.5 (71%) µg·hr/ml and 4.3 (68%) µg/ml. The geometric mean ratio (ratio of pharmacokinetic parameters in hepatically impaired patients to patients with normal liver function) (90% confidence interval) was 0.7 (0.3 to 1.6) for both AUC_{0-12} and C_{max}, which suggests approximately 30% reduction in the pharmacokinetic exposure in patients with moderate hepatic impairment. Results are based on total concentrations (protein-bound and unbound). Concentrations unbound at steady-state were not assessed. No dosage adjustment seems warranted for patients with moderate hepatic impairment based on limited data. Close monitoring of safety (including signs of cardiac arrhythmia) and of virologic response is recommended due to increased variability of the exposure in this population (see sections 4.2 and 4.4).

Paediatric Patients: Steady state pharmacokinetic information is available from HIV-infected paediatric patients from study NV20911. In this study, 5 patients were <2 years and 13 between 2 to <6 years and received 50 mg/kg saquinavir bid (not to exceed 1000 mg bid) boosted with ritonavir at 3 mg/kg for patients with body weight ranging from 5 to <15 kg or 2.5 mg/kg for patients with body weight ranging from 15 to 40 kg (not to exceed 100 mg bid). Sixteen of 18 children could not swallow Invirase hard capsules and received medication by opening the capsules and mixing the contents with different vehicles. The pharmacokinetic exposure parameters for the “High Age Group” are listed in Table 10. Results of the “Low Age Group” are not shown as data are limited due to the small size of the group.

Table 10: Pharmacokinetic parameters of saquinavir at steady-state in HIV-infected pediatric patients

			Mean ± SD Saquinavir (%CV) Pharmacokinetic Parameters*		
Study	**Age Group** (Years)	**N**	**AUC_{0-12h} (ng•h/mL)**	**C_{trough} (ng/mL)**	**C_{max} (ng/mL)**
NV20911	2 to < 6 years	13	38000 ± 18100 (48%)	1860 ± 1060 (57%)	5570 ± 2780 (50%)

* All parameters normalized to a 50 mg/kg dose

Steady state saquinavir exposures observed in paediatric trials were substantially higher than historical data in adults where dose- and exposure-dependent QTc and PR prolongation were observed (see section 4.4).

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.

Mutagenesis: Mutagenicity and genotoxicity studies, with and without metabolic activation where appropriate, have shown that saquinavir has no mutagenic activity *in vitro* in either bacterial (Ames test) or mammalian cells (Chinese hamster lung V79/HPRT test). Saquinavir does not induce chromosomal damage *in vivo* in the mouse micronucleus assay or *in vitro* in human peripheral blood lymphocytes and does not induce primary DNA damage *in vitro* in the unscheduled DNA synthesis test.

Carcinogenesis: There was no evidence of carcinogenic activity after the administration of saquinavir mesilate for 96 to 104 weeks to rats and mice. The plasma exposures (AUC values) in rats (maximum dose 1000 mg/kg/day) and in mice (maximum dose 2500 mg/kg/day) were lower than the expected plasma exposures obtained in humans at the recommended clinical dose of ritonavir boosted Invirase.

Reproductive toxicity: Fertility, peri- and postnatal development were not affected, and embryotoxic / teratogenic effects were not observed in rats or rabbits at plasma exposures lower than those achieved in humans at the recommended clinical dose of ritonavir boosted Invirase. Distribution studies in these species showed that the placental transfer of saquinavir is low (less than 5% of maternal plasma concentrations).

Safety pharmacology: Cloned human cardiac potassium channel (hERG) trafficking *in vitro* was inhibited by 75% at 30μM of saquinavir. Saquinavir inhibited both hERG current and L-type Ca++ channel current with respective IC50s of 4.7 and 6.3 μM. In a myocardial distribution study in the rat an approximately 2-fold accumulation of saquinavir was observed in the heart compared to plasma after coadministration of saquinavir and ritonavir. The clinical relevance of these preclinical results are unknown, however cardiac conduction and repolarisation abnormalities in humans have been observed with saquinavir and ritonavir combination therapy (see section 4.4 and 5.1).

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 for disposal.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

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 latest renewal: 04 October 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
TEXT FOR 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
The film-coated tablets should be swallowed whole
Read the package leaflet before use

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

Keep out of the sight and reach 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 GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

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

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

TEXT FOR THE BOTTLE LABEL

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
The film-coated tablets should be swallowed whole
Read the package leaflet before use

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

Keep out of the sight and reach 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 GmbH
Emil-Barell-Strasse 1
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Germany

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

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable

B. PACKAGE LEAFLET

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 because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Invirase is and what it is used for

Invirase contains the active substance saquinavir which 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-1-infected adults. Invirase is prescribed for use in combination with ritonavir (Norvir) and other antiretroviral medicines.

2. What you need to know before you take Invirase

Do not take Invirase if you have:
- an allergy to saquinavir, ritonavir or any of the other ingredients (see “Invirase contains lactose” later in this section and “What Invirase contains” in Section 6)
- any heart problems that show on an electrocardiogram (ECG, electrical recording of the heart) - you may have been born with that
- a very slow heart rate (bradycardia)
- a weak heart (heart failure)
- a history of an irregular heart beat (arrhythmias)
- a salt imbalance in your blood, especially low blood concentrations of potassium (hypokalaemia), which is not currently controlled by treatment
- severe liver problems such as jaundice, hepatitis or liver failure - where your belly fills with fluid, you get confused or your oesophagus (the tube that runs from your mouth to your stomach) bleeds
- recently taken the HIV medicine rilpivirine.

Do not take Invirase if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Invirase.

Do not take Invirase if you are taking any of the following medicines:
Any medicine that can change your heart beat, such as:

- certain medicines for HIV - such as atazanavir, lopinavir, rilpivirine
- certain heart medicines - amiodarone, bepridil, disopyramide, dofetilide, flecainide, hydroquinidine, ibutilide, lidocaine, propafenone, quinidine, sotalol
- certain medicines for depression - amitriptyline, imipramine, trazodone, maprotiline
- medicines for other severe mental health problems - such as clozapine, haloperidol, mesoridazine, phenothiazines, sertindole, sultopride, thioridazine, ziprasidone
- certain medicines for infection - such as clarithromycin, dapsone, erythromycin, halofantrine, pentamidine, sparfloxacin
- certain strong pain killers (narcotics) - such as alfentanyl, fentanyl, methadone
- medicines for erectile dysfunction - sildenafil, vardenafil, tadalafil
- certain medicines that may be used for a variety of things: cisapride, diphemanil, mizolastine, quinine, vincamine.
- certain medicines used to prevent rejection of new organs after a transplant operation such as tacrolimus
- certain medicines used to treat the symptoms of Benign Prostatic Hyperplasia (an increase in size of the prostate) such as alfuzosin
- certain medicines commonly used for allergy symptoms such as terfenadine and astemizole
- certain medicines for severe mental health problems such as pimozide
- certain medicines (so called tyrosine kinase inhibitors) used to treat different types of cancer such as dasatinib and sunitinib.

Any of these other medicines:

- ergot alkaloids - for migraine attacks
- triazolam and midazolam (taken by mouth) - to help you sleep or for anxiety
- rifampicin - for preventing or treating tuberculosis
- simvastatin and lovastatin - for lowering blood cholesterol
- quetiapine – used to treat schizophrenia, bipolar disorder and major depressive disorder
- lurasidone – used to treat schizophrenia.

Do not take Invirase with any other drug unless you have talked to your doctor first. The drugs listed above might cause serious side effects if you take them together with Invirase.

Do not take Invirase if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Invirase.

Warnings and precautions
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.

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

Abnormal heart rhythms (arrhythmias):
Invirase can change how your heart beats - this can be serious. This can happen especially if you are female or elderly.

- If you are taking any medicine that decreases your blood potassium levels talk to your doctor before taking Invirase.
- **Contact your doctor immediately, if you get palpitations or an irregular heart beat during treatment.** Your doctor may wish to do an ECG to check your heart beat.

Other conditions
There are certain conditions, which you may have, or have had, which require special care before or while taking Invirase/ritonavir. Therefore, before taking this medicine, you should have told your

doctor if you suffer from diarrhoea, or if you have allergies (see Section 4) or if you have an intolerance to some sugars (see section “Invirase contains lactose”).

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

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

Infection: 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).

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

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.

Other medicines and Invirase
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

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 if you are taking any of the following medicines:" above). There are also some medicines that *require dosage reduction* of that medicine or Invirase or ritonavir (see section “Medicines that can interact with saquinavir or ritonavir include:” below). Ask your doctor or pharmacist for more information about taking Invirase/ritonavir with other medicines.

Medicines that can interact with saquinavir or ritonavir include:
- other HIV medicines - such as nelfinavir, indinavir, nevirapine, delavirdine, efavirenz, maraviroc, cobicistat
- some medicines affecting the immune system - such as ciclosporin, sirolimus (rapamycin), tacrolimus
- various steroids - such as dexamethasone, ethinyl estradiol, fluticasone
- certain heart medicines - such as calcium channel blockers, quinidine, digoxin
- medicines used to lower blood cholesterol - such as statins
- antifungals - ketoconazole, itraconazole, fluconazole, miconazole
- anticonvulsants - such as phenobarbital, phenytoin, carbamazepine
- sedative agents - such as midazolam administered by injection
- certain antibiotics - such as quinupristin/dalfopristin, rifabutin, fusidic acid

- medicines to treat depression - such as 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 - such as omeprazole or other proton pump inhibitors
- medicines used to treat asthma or other chest illness such as Chronic Obstructive Pulmonary Disease (COPD) such as salmeterol
- medicines for gout, such as colchicine
- medicines used to treat high blood pressure in the arteries of the lungs (a disease known as pulmonary arterial hypertension) such as bosentan.

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

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.

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.

Breast-feeding ***is not recommended*** in women living with HIV because HIV infection can be passed on to the baby in breast milk.

If you are breast-feeding or thinking about breast-feeding, you ***should discuss it with*** your doctor ***as soon as possible***.

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

Invirase contains lactose
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 this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Invirase comes as a 500 mg film-coated tablet. Your doctor will prescribe Invirase in combination with ritonavir (Norvir) and other HIV medicines.

How to take
- Take Invirase at the same time as your ritonavir (Norvir) capsules.
- Take your Invirase film-coated tablets with or after food.
- Swallow them whole with water.

How much to take

Standard dose
- Take two 500 mg film-coated tablets of Invirase twice a day.
- Take one 100 mg capsule of ritonavir (Norvir) twice a day.

If this is your first medicine for HIV or the first time you are taking ritonavir (Norvir)
You need to take a lower dose of Invirase for your first week.
Week 1:

- Take one 500 mg film-coated tablet of Invirase twice a day.
- Take one 100 mg capsule of ritonavir (Norvir) twice a day.

Week 2 onwards:

- Continue with the standard dose.

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.
If you have any further questions on the use of this medicine, ask your doctor or pharmascist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and lifestyle, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

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 persons)* 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 (e.g., blood or urine tests) have been reported very commonly.

Other 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), weakness, dizziness, libido problems, taste alteration, mouth ulcers, dry lips, abdominal discomfort, indigestion, weight loss,constipation, increased appetite, muscle spasms and shortness of breath.

Other less frequently reported side effects (*in more than one in one thousand persons but less than one in a hundred persons)* include: decreased appetite, visual disturbance, inflammation of the liver, fits, allergic reactions, blisters, sleepiness, abnormal renal function, inflammation of the pancreas, yellowing of the skin or whites of the eyes caused by liver problems and Steven's Johnson syndrome (a serious illness with blistering of the skin, eyes, mouth and genitals).

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.

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).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Invirase

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date (EXP) which is stated on the bottle and carton. The expiry date refers to the last day of that month.

Invirase does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other 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 (excipients) are microcrystalline cellulose, croscarmellose sodium, povidone, lactose (monohydrate) 38.5 mg, magnesium stearate, hypromellose, titanium dioxide (E171), talc, glycerol triacetate, iron oxide yellow (E172) and iron oxide red (E172) (see section 2 “Invirase contains lactose”).

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 one side and "ROCHE" on the other side. One plastic (HDPE) bottle contains 120 tablets.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.