

Annexes

Attached, please find the Summary of Product Characteristics (SmPC) for Invirase 500 mg film-coated tablets as a relevant example of the Invirase SmPCs for all approved strengths.

The wording of the Invirase SmPCs is identical in terms of the arrhythmogenic risk due to a dose-dependent prolongation of the QT and PR intervals.

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: Contains lactose monohydrate: 38.5 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Adults and adolescents over the age of 16 years:

In combination with ritonavir

The recommended dose of Invirase is 1000 mg (2 x 500 mg film-coated tablets) two times daily with ritonavir 100 mg two times daily in combination with other antiretroviral agents.

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

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).

Children under the age of 16 and adults over 60 years:

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

4.3 Contraindications

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

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

~~Invirase is contraindicated in patients with:~~

- ~~• hypersensitivity to the active substance or to any of the excipients~~
- ~~• 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)~~

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

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

- ~~• terfenadine, astemizole, pimozone, cisapride, amiodarone, propafenone and flecainide (potential for life threatening cardiac arrhythmia), see section 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).~~

4.4 Special warnings and precautions for use

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

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

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

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

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.

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

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

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

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

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

Osteonecrosis: Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to

combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

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

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). The magnitude of QT and PR prolongation may increase with increasing concentrations of saquinavir. Therefore, the recommended dose of Invirase/ritonavir should not be exceeded, and other medicinal products known to increase the plasma concentration of ritonavir-boosted Invirase should be used with caution. Concomitant use of ritonavir-boosted Invirase with other medicinal products that prolong the QT and/or PR interval is contraindicated (see section 4.3). Women and elderly patients may be more susceptible to drug-associated effects on the QT and/or PR interval. 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. 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.

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

Interaction with tipranavir: Concomitant use of boosted saquinavir and tipranavir, co-administered with low dose ritonavir in a dual-boosted regimen, results in a significant decrease in saquinavir plasma concentrations (see section 4.5). Therefore, the co-administration of boosted saquinavir and tipranavir, co-administered with low dose ritonavir, is not recommended.

Interaction with HMG-CoA reductase inhibitors: Caution must be exercised if Invirase/ritonavir is used concurrently with atorvastatin, which is metabolised to a lesser extent by CYP3A4. In this situation a reduced dose of atorvastatin should be considered. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5).

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

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

Interaction with efavirenz: The combination of saquinavir and ritonavir with efavirenz has been shown to be associated with an increased risk of liver toxicity; liver function should be monitored when saquinavir and ritonavir are co-administered with efavirenz. No clinically significant alterations

of either saquinavir or efavirenz concentration were noted in studies in healthy volunteers or in HIV-infected patients (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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 |
|--|--|--|
| <i>Antiretroviral agents</i> | | |
| <i>Nucleoside reverse transcriptase inhibitors (NRTIs)</i> | | |
| - Zalcitabine and/or Zidovudine (saquinavir/ritonavir) | - No pharmacokinetic interaction studies have been completed. 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. |
| - Zalcitabine and/or Zidovudine (unboosted saquinavir) | - Saquinavir ↔ Zalcitabine ↔ Zidovudine ↔ | |
| 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. |
| <i>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</i> | | |
| - 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, <i>or</i> saquinavir/ritonavir 1000/100 mg bid, <i>or</i> saquinavir/ritonavir 1200/100 mg qd) | Saquinavir ↔ Efavirenz ↔ | No dose adjustment required. |
| - Nevirapine (saquinavir/ritonavir) | - Interaction with Invirase/ritonavir not studied. | |
| - Nevirapine (unboosted saquinavir) | - Saquinavir AUC ↓ 24% Nevirapine AUC ↔ | - No dose adjustment required. |

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

| Medicinal product by therapeutic area (dose of Invirase used in study) | Interaction | Recommendations concerning co-administration |
|---|--|--|
| <i>HIV protease inhibitors (PIs)</i> | | |
| 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. | <u>Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |
| 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) - Indinavir 800 mg tid (saquinavir 600-1200 mg single dose) | - Low dose ritonavir increases the concentration of indinavir. - Saquinavir AUC ↑ 4.6-7.2 fold Indinavir ↔ No safety and efficacy data available for this combination. Appropriate doses of combination not established. | Increased concentrations of indinavir may result in nephrolithiasis. |
| Lopinavir/ritonavir 400/100 mg bid (saquinavir/ritonavir 1000/100 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) | No dose adjustment required. <u>Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |
| - Nelfinavir 1250 mg bid (saquinavir/ritonavir 1000/100 mg bid) | - Saquinavir AUC ↑ 13% (90% CI: 27↓ - 74↑) Saquinavir C _{max} ↑ 9% (90% CI: 27↓ - 61↑) Nelfinavir AUC ↓ 6% (90% CI: 28↓ - 22↑) Nelfinavir C _{max} ↓ 5% (90% CI: 23↓ - 16↑) | No dose adjustment required. <u>Combination not recommended.</u> |
| - Nelfinavir 750 mg tid (unboosted saquinavir 1200 mg tid) | - Saquinavir AUC ↑ 392% Saquinavir C _{max} ↑ 179% Nelfinavir AUC ↑ 18% Nelfinavir C _{max} ↔ | - Quadruple therapy, including saquinavir soft capsules and nelfinavir in addition to two nucleoside reverse transcriptase inhibitors gave a more durable response (prolongation of time to virological relapse) than triple therapy with either single protease inhibitor. Concomitant administration of nelfinavir and saquinavir soft capsules resulted in a moderate increase in the incidence of diarrhoea. |

| Medicinal product by therapeutic area (dose of Invirase used in study) | Interaction | Recommendations concerning co-administration |
|---|---|--|
| 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. |
| 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. |
| <i>HIV fusion inhibitor</i> | | |
| Enfuvirtide (saquinavir/ritonavir 1000/100 mg bid) | Saquinavir ↔ Enfuvirtide ↔ No clinically significant interaction was noted. | No dose adjustment required. |
| <i>Other medicinal products</i> | | |
| <i>Antiarrhythmics</i> | | |
| Bepidil Lidocaine (systemic) Quinidine <u>Hydroquinidine</u> (saquinavir/ritonavir) | Concentrations of bepridil, systemic lidocaine, or quinidine <u>or hydroquinidine</u> may be increased when co-administered with Invirase/ritonavir. | Caution is warranted. Therapeutic concentration monitoring is recommended, if available <u>Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |
| 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). |
| <u>Dofetilide</u> (saquinavir/ritonavir) | <u>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.</u> | <u>Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |
| <u>Ibutilide</u> <u>Sotalol</u> (saquinavir/ritonavir) | | <u>Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |
| <i>Anticoagulant</i> | | |
| Warfarin (saquinavir/ritonavir) | Concentrations of warfarin may be affected. | INR (international normalised ratio) monitoring recommended. |

| Medicinal product by therapeutic area (dose of Invirase used in study) | Interaction | Recommendations concerning co-administration |
|--|--|--|
| Anticonvulsants | | |
| - Carbamazepine Phenobarbital Phenytoin (saquinavir/ritonavir) | - Interaction with Invirase/ritonavir not studied. | |
| - Carbamazepine Phenobarbital Phenytoin (unboosted saquinavir) | - These medicinal products will induce CYP3A4 and may therefore decrease saquinavir concentrations. | |
| Antidepressants | | |
| Tricyclic antidepressants (e.g. amitriptyline, imipramine) (saquinavir/ritonavir) | Invirase/ritonavir may increase concentrations of tricyclic antidepressants. | Therapeutic concentration monitoring recommended. <u>Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |
| - Nefazodone (saquinavir/ritonavir) | - Interaction with saquinavir/ritonavir not evaluated. | |
| - Nefazodone (unboosted saquinavir) | - Nefazodone inhibits CYP3A4. Saquinavir concentrations may be increased. | - Monitoring for saquinavir toxicity recommended. <u>Combination not recommended.</u> |
| Trazodone (ritonavir) | Plasma concentrations of trazodone may increase. Adverse events of nausea, dizziness, hypotension and syncope have been observed following coadministration of trazodone and ritonavir. | <u>Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> Caution is warranted. A lower dose of trazodone should be considered. |
| Antihistamines | | |
| Terfenadine Astemizole (saquinavir/ritonavir) | Terfenadine AUC ↑, associated with a prolongation of QTc intervals. A similar interaction with astemizole is likely. | Terfenadine and astemizole are contraindicated with boosted or unboosted saquinavir (see section 4.3). |
| <u>Mizolastine</u> (saquinavir/ritonavir) | | <u>Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |
| Anti-infectives | | |
| - Clarithromycin (saquinavir/ritonavir) | - Interaction with Invirase/ritonavir not studied. | |
| - Clarithromycin 500 mg bid (unboosted saquinavir 1200 mg tid) | - Saquinavir AUC ↑ 177 % Saquinavir C _{max} ↑ 187 % Clarithromycin AUC ↑ 40 % Clarithromycin C _{max} ↑ 40 % | - <u>Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> No dose adjustment is required when co-administered for a limited time at the doses studied. |

| Medicinal product by therapeutic area (dose of Invirase used in study) | Interaction | Recommendations concerning co-administration |
|--|--|---|
| - Erythromycin (saquinavir/ritonavir) | - Interaction with Invirase/ritonavir not studied. | - <u>Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |
| - Erythromycin 250 mg qid (unboosted saquinavir 1200 mg tid) | - Saquinavir AUC ↑ 99 % Saquinavir C _{max} ↑ 106 % | - No dose adjustment required. |
| - Streptogramin antibiotics (saquinavir/ritonavir) | - Interaction with Invirase/ritonavir not studied. | - Monitoring for saquinavir toxicity recommended. |
| - Streptogramin antibiotics (unboosted saquinavir) | - Streptogramin antibiotics such as quinupristin/dalfopristin inhibit CYP3A4. Saquinavir concentrations may be increased. | |
| - <u>Halofantrine</u> <u>Pentamidine</u> <u>Sparfloxacin</u> (saquinavir/ritonavir) | - | - <u>Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |
| <i>Antifungals</i> | | |
| 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. | Monitoring for saquinavir toxicity recommended. |
| - Itraconazole (unboosted saquinavir) | - Itraconazole is a moderately potent inhibitor of CYP3A4. An interaction is possible. | |
| Fluconazole/miconazole (saquinavir/ritonavir) | Interaction with Invirase/ritonavir not studied. | |

| Medicinal product by therapeutic area (dose of Invirase used in study) | Interaction | Recommendations concerning co-administration |
|---|---|--|
| 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). |
| Rifabutin 150 mg q3d (saquinavir/ritonavir 1000/100 mg bid) | 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 | No dose adjustment of saquinavir/ritonavir 1000/100 mg bid is required if ritonavir-boosted Invirase is administered in combination with rifabutin. |
| Rifabutin 150 mg q4d (saquinavir/ritonavir 1000/100 mg bid) | Rifabutin active moiety* AUC ₀₋₉₆ ↑ 60% (90% CI 43%-79%) Rifabutin active moiety* C _{max} ↑ 111% (90% CI 75%-153%) Rifabutin AUC ₀₋₉₆ ↔ (90% CI 10↓ - 13↑) Rifabutin C _{max} ↑ 68% (90% CI 38%-105%) * Sum of rifabutin + 25-O-desacetyl rifabutin metabolite | The recommended dose of rifabutin is 150 mg twice weekly on set days (for example Mondays and Thursdays), with the dose of Invirase/ritonavir unchanged (1000/100 mg bid). Monitoring of neutropenia and the liver enzyme levels is recommended. Tapering the rifabutin dose to 150 mg every four days could be justified in cases of marked neutropenia. |
| 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 | 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 |

| Medicinal product by therapeutic area (dose of Invirase used in study) | Interaction | Recommendations concerning co-administration |
|--|---|--|
| | levels. | 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. |
| Corticosteroids | | |
| - Dexamethasone (saquinavir/ritonavir) | - Interaction with Invirase/ritonavir not studied. | |
| - Dexamethasone (unboosted saquinavir) | - Dexamethasone induces CYP3A4 and may decrease saquinavir concentrations. | - Use with caution. Saquinavir may be less effective in patients taking dexamethasone. |
| 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. |

| Medicinal product by therapeutic area (dose of Invirase used in study) | Interaction | Recommendations concerning co-administration |
|--|---|--|
| <i>Medicinal products that are substrates of P-glycoprotein</i> | | |
| <i>Digitalis glycosides</i> | | |
| 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. |
| <i>Histamine H₂-receptor antagonist</i> | | |
| - 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. |
| <i>HMG-CoA reductase inhibitors</i> | | |
| 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. |
| 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). |
| <i>Immunosuppressants</i> | | |
| Ciclosporin Tacrolimus Rapamycin (saquinavir/ritonavir) | Concentrations of these medicinal products increase several fold when co-administered with Invirase/ritonavir. | Careful therapeutic drug monitoring is necessary for immunosuppressants when co-administered with Invirase/ritonavir. |
| <i>Narcotic analgesics</i> | | |
| 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. | No dosage adjustment required. <u>Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |
| <i>Neuroleptics</i> | | |
| Pimozide (saquinavir/ritonavir) | Concentrations of pimozide may be increased when co-administered with Invirase/ritonavir. | Due to a potential for life threatening cardiac arrhythmias, Invirase/ritonavir is contra-indicated in combination with pimozide (see |

| Medicinal product by therapeutic area (dose of Invirase used in study) | Interaction | Recommendations concerning co-administration |
|---|--|--|
| <u>Clozapine</u> <u>Haloperidol</u> <u>Mesoridazine</u> <u>Phenothiazines</u> <u>Sertindole</u> <u>Sultopride</u> <u>Thioridazine</u> <u>Ziprasidone</u> (saquinavir/ritonavir) | | section 4.3). <u>Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |
| 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. |
| 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 C _{max} ↑ 140 % Sildenafil AUC ↑ 210 % - Sildenafil is a substrate of CYP3A4. | - Use sildenafil with caution at reduced doses of no more than 25 mg every 48 hours with increased monitoring of adverse events when administered concomitantly with Invirase/ritonavir. <u>Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |
| Vardenafil (saquinavir/ritonavir) | Concentrations of vardenafil may be increased when co-administered with Invirase/ritonavir. | Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring of adverse events when administered concomitantly with Invirase/ritonavir. <u>Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |
| Tadalafil (saquinavir/ritonavir) | Concentrations of tadalafil may be increased when co-administered with Invirase/ritonavir. | Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring of adverse events when administered concomitantly with Invirase/ritonavir. <u>Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |

| 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 ↔ | Monitoring for potential saquinavir toxicities is recommended. <u>Combination not recommended.</u> |
| 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. | If omeprazole or other proton pump inhibitors are taken concomitantly with Invirase/ritonavir, monitoring for potential saquinavir toxicities is recommended. <u>Combination not recommended.</u> |
| 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. |
| - 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 C _{trough} ↓ 49 % (8 hours post dose) Saquinavir C _{max} ↓ 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. |

| Medicinal product by therapeutic area (dose of Invirase used in study) | Interaction | Recommendations concerning co-administration |
|---|---|---|
| - St. John's wort (saquinavir/ritonavir) | - Interaction with Invirase/ritonavir not studied. | |
| - St. John's wort (unboosted saquinavir) | - Plasma levels of saquinavir can be reduced by concomitant use of the herbal preparation St. John's wort (<i>Hypericum perforatum</i>). 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. |
| <i>Other potential interactions</i> | | |
| <i>Medicinal products that are substrates of CYP3A4</i> | | |
| e.g. dapsone, disopyramide, quinine, fentanyl, and alfentanil (unboosted saquinavir) | 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. | These combinations should be given with caution. Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4). |
| <i>Gastroenterological medicinal products</i> <i>Medicinal products reducing gastrointestinal transit time</i> | | |
| Metoclopramide | It is unknown whether medicinal products which reduce the gastrointestinal transit time could lead to lower saquinavir plasma concentrations. | |
| <u>Cisapride (saquinavir/ritonavir)</u> | <u>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.</u> | <u>Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |
| <u>Diphemanil (saquinavir/ritonavir)</u> | | <u>Contraindicated in combination with Invirase/ritonavir due to potentially life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |
| <i>Vasodilators (peripheral)</i> | | |
| <u>Vincamine i.v.</u> | | <u>Contraindicated in combination with Invirase/ritonavir due to the potential for life threatening cardiac arrhythmia (see sections 4.3 and 4.4).</u> |

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).

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

Adverse reactions from clinical trials where saquinavir was boosted with ritonavir

Limited data is available from two studies where the safety of saquinavir soft capsule (1000 mg twice daily) used in combination with low dose ritonavir (100 mg twice daily) for at least 48 weeks was studied in 311 patients. Adverse reactions in these two pivotal studies are summarised in Table 2. The list also includes marked laboratory abnormalities that have been observed with the saquinavir soft capsule in combination with ritonavir (at 48 weeks).

Table 2: Incidences of Adverse Reactions and marked laboratory abnormalities from the MaxCmin1 and MaxCmin2 study. (Very common ($\geq 10\%$); common ($\geq 1\%$ and $< 10\%$))

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

Post-marketing experience with saquinavir

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

As these data come from the spontaneous reporting system, the frequency of the adverse reactions is unknown.

- Immune system disorders: Hypersensitivity.
- Metabolism and nutrition disorders:
 - Diabetes mellitus or hyperglycaemia sometimes associated with ketoacidosis (see section 4.4).
 - Lipodystrophy: Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsicervical fat accumulation (buffalo hump).
 - Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).
- Nervous system disorders: Somnolence, convulsions.
- Vascular disorders: There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophilic patients type A and B treated with protease inhibitors (see section 4.4).
- Hepato-biliary disorders: Hepatitis.
- Musculoskeletal, connective tissue and bone disorders: Increased CPK, myalgia, myositis and rarely, rhabdomyolysis have been reported with protease inhibitors, particularly in combination with nucleoside analogues. Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).
- Renal and urinary disorders: Renal impairment.
- In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

4.9 Overdose

There 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

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

[†] 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 prolongation 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 prolongations 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.

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 34). 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 34: 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 <u>Weeks 12-20</u> | N=114 | Change in Baseline Plasma HIV-1 RNA at <u>Week 4</u> |
| 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 45: Subject Demographics MaxCmin1 and MaxCmin2[†]

| | MaxCmin1 SQV/r N=148 | IDV/r N=158 | MaxCmin2 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 56: 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 $\geq 50,000$ copies/ml at week 4, $\geq 5,000$ 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

5.2 Pharmacokinetic properties

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

Absorption and bioavailability in adults: In HIV-infected patients, Invirase in combination with ritonavir at doses of 1000/100 mg twice daily provides saquinavir systemic exposures over a 24-hour period similar to or greater than those achieved with saquinavir soft capsules 1200 mg tid (see Table 67). The pharmacokinetics of saquinavir is stable during long-term treatment.

Table 67: 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 | AUC τ (ng·h/ml) | AUC ₀₋₂₄ (ng·h/ml) [†] | C _{max} (ng/ml) | C _{min} (ng/ml) |
|---|----|----------------------------|--|----------------------------|------------------------------------|
| Invirase (hard capsule) 600 mg tid | 10 | 866 (62) | 2,598 | 197 (75) | 75 (82) |
| saquinavir soft capsule 1200 mg tid | 31 | 7,249 (85) | 21,747 | 2,181 (74) | 216 (84) |
| Invirase (tablet) 1000 mg bid plus ritonavir 100 mg bid* (fasting condition) | 22 | 10,320 (2,530-30,327) | 20,640 | 1509 (355-4,101) | 313 (70-1,725) ^{††} |
| Invirase (tablet) 1000 mg bid plus ritonavir 100 mg bid* (high fat meal) | 22 | 34,926 (11,826-105,992) | 69,852 | 5208 (1,536- 14,369) | 1,179 (334-5,176) ^{††} |

τ = dosing interval, i.e. 8 hour for tid and 12 h for bid dosing.

C_{min} = the observed plasma concentration at the end of the dose interval.

bid = twice daily

tid = three times daily

* results are geometric mean (min - max)

[†] derived from tid or bid dosing schedule

^{††} C_{trough} values

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

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

Effective therapy in treatment naïve patients is associated with a C_{min} of approximately 50 ng/ml and an AUC₀₋₂₄ 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 AUC₀₋₂₄ of about 20,000 ng·h/ml.

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

Effect of food: In a cross-over study in 22 HIV-infected patients treated with Invirase/ritonavir 1000 mg/100 mg twice daily and receiving three consecutive doses under fasting conditions or after a high-fat, high-calorie meal (46 g fat, 1,091 Kcal), the AUC₀₋₁₂, C_{max} and C_{trough} values of saquinavir under fasting conditions were about 70 per cent lower than with a high-fat meal. All but one of the patients achieved C_{trough} values of saquinavir above the therapeutic threshold (100 ng/ml) in the fasted state. There were no clinically significant differences in the pharmacokinetic profile of ritonavir in fasting and fed conditions but the ritonavir C_{trough} (geometric mean 245 vs. 348 ng/ml) was lower in the fasting state compared to the administration with a meal. Invirase/ritonavir should be administered with or after food.

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

concentrations of saquinavir were negligible when compared to concentrations from matching plasma samples.

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

Special populations

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

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 AUC₀₋₁₂ 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 AUC₀₋₁₂ 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).

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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

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

Tablet coat:

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Plastic bottles (HDPE) containing 120 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

EU/1/96/026/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
(~~EMEA~~) <http://www.emea.europa.eu/>