AUSTRALIAN PRODUCT INFORMATION
Invirase® (Saquinavir mesilate)

1. NAME OF THE MEDICINE

Saquinavir mesilate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Invirase film-coated tablets contain 571.5 mg of saquinavir mesilate equivalent to 500 mg saquinavir free base.

Excipients with known effect

Lactose monohydrate

For the full list of excipients, see section 6.1.

Note: Saquinavir soft gel capsules (Fortovase) are no longer marketed in Australia.

3. PHARMACEUTICAL FORM

Invirase 500 mg film-coated tablets are light orange to brownish orange, oval, cylindrical and biconvex. The tablets are marked "SQV 500" on one side and "ROCHE" on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Invirase (saquinavir) is indicated for the treatment of HIV/AIDS in adults. Saquinavir must be used only in combination with ritonavir and other antiretroviral therapies (see section 5.1).

This indication is based on changes in surrogate markers. At present there are no results from controlled clinical trials evaluating the effect of regimens containing saquinavir on HIV disease progression or survival (see section 5.1).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

Invirase must be given in combination with ritonavir (ritonavir-boosted Invirase). Please also see the complete product information for ritonavir.

The recommended dose of Invirase is 1000 mg twice daily (2000 mg total daily dose) with ritonavir 100 mg twice daily in combination with other antiretroviral agents.

For treatment-naïve patients initiating treatment with Invirase, the recommended starting dose of Invirase is 500 mg twice daily with ritonavir 100 mg twice daily for the first 7 days of treatment. After 7 days, the recommended dose of Invirase is 1000 mg twice daily with ritonavir 100 mg twice daily.

Patients switching immediately from treatment with another protease inhibitor (PI) taken with ritonavir or from a non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimen,

except rilpivirine (see section 4.3), without a wash-out period, should initiate and continue Invirase at the standard recommended dose of 1000 mg twice daily with ritonavir 100 mg twice daily.

Ritonavir should be taken at the same time as Invirase and within 2 hours after a meal. Note that food increases the bioavailability of Invirase and that in particular, a full meal has a greater effect than a light meal (see section 5.2).

For the recommended dose and possible adverse effects of other antiretroviral agents used in combination therapy, please see the complete product information for these medicines. For patients already taking ritonavir as part of their antiretroviral regimen, no additional ritonavir is needed.

As with all antiretroviral therapies, adherence to the prescribed regimen is strongly recommended.

Special Dosage Instructions

For serious toxicities that may be associated with Invirase, the treatment should be interrupted. Invirase should not be administered at less than the recommended dose (see section 4.2). For combination treatment involving some other antiretrovirals, dose modifications of the protease inhibitors may be required since plasma levels might increase (see section 4.5).

For dosage instructions in special populations, please refer to section 4.4.

4.3 CONTRAINDICATIONS

Please also refer to the full product information for ritonavir which is used in combination with Invirase.

Invirase is contraindicated in patients with:

- hypersensitivity to saquinavir or to any of the excipients in the film-coated tablet (see section 6.1).
- severe hepatic impairment (see section 4.4).
- congenital or documented acquired QT prolongation, and electrolyte disturbances particularly uncorrected hypokalaemia. Familial history of sudden death at a young age may be suggestive of congenital QT prolongation.

Invirase is contraindicated with other medicines that may interact and result in potentially life threatening side effects associated with concomitantly administered medicines. Examples of medicines which are contraindicated with Invirase are included in Table 1.

Table 1: Examples of medicines that are known to be contraindicated with Invirase/ritonavir

Medicines within class that are known to be contraindicated with Invirase/ritonavir		**Side effect**
Medicine class	**Examples**	
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Potentially increased alfuzosin concentrations can result in hypotension and potentially life-threatening cardiac arrhythmia

Medicines within class that are known to be contraindicated with Invirase/ritonavir		**Side effect**
Medicine class	**Examples**	
Antiarrhythmics	Class IA: (e.g. Quinidine) Class IB (e.g. Lidocaine (systemic)) Class IC (e.g. Amiodarone, flecainide, propafenone, bepridil, dofetilide)	Life-threatening cardiac arrhythmia
Antidepressant	Trazodone	Increased Trazodone concentrations can result in potentially life-threatening cardiac arrhythmia. Hypotension, nausea, dizziness and syncope have been observed.
Antihistamines	Astemizole, terfenadine, mizolastine	Potentially life-threatening cardiac arrhythmia
Antiinfectives	Clarithromycin Erythromycin Halofantrine	Potentially life- threatening cardiac arrhythmia.
Antimycobacterial Agents	Rifampicin	Severe hepatocellular toxicity
Antipsychotics	Lurasidone Pimozide, clozapine, haloperidol, chlorpromazine, sertindole, thioridazine, ziprasidone Quetiapine	Potentially serious and/or life-threatening reactions Potentially life-threatening cardiac arrhythmia Increased quetiapine-related toxicity
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Acute ergot toxicity
GI Motility Agents	Cisapride	Potentially life-threatening cardiac arrhythmia
HIV protease inhibitors (PIs)	Atazanavir	Potentially life- threatening cardiac arrhythmia
NNRTI	Rilpivirine: switching from rilpivirine to Invirase; as well as concomitant use	Potentially life-threatening cardiac arrhythmia
HMG-CoA Reductase Inhibitors	Simvastatin, lovastatin	Rhabdomyolysis
Immunosuppressant	Tacrolimus	Potentially life-threatening cardiac arrhythmia
Sedatives/Hypnotics	Triazolam, oral midazolam	Prolonged/increased sedation
Tyrosine kinase inhibitors	Dasatinib Sunitinib	Potentially life- threatening cardiac arrhythmia

Medicines within class that are known to be contraindicated with Invirase/ritonavir		Side effect
Medicine class	**Examples**	
Other medicinal products that are substrate of CYP3A4	Dapsone Disopyramide Quinine	Potentially life- threatening cardiac arrhythmia

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Information for Patients

Invirase must be given only in combination with ritonavir (see section 4.2). Please refer to the ritonavir full prescribing information for additional precautionary measures. Invirase is not recommended for use in combination with any other pharmacoenhancer (e.g. cobicistat), as dosing recommendations have not been established.

Invirase should NOT be given without ritonavir.

Invirase may interact with other medicines, therefore, patients should consult their doctor before taking other medications (prescription or non-prescription).

Alternative or additional contraceptive measures should be used when oestrogen-based oral contraceptives are co-administered (see section 4.5).

Patients should also be advised that they may experience toxicities associated with co-administered medications.

Patients should be informed that Invirase 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 be advised that Invirase does not reduce the risk of transmitting HIV to others through sexual contact or contamination through blood.

Patients should have regular visits with their doctor for blood tests and monitoring of blood glucose concentrations.

Use in Hepatic Impairment

Invirase is contraindicated in patients with severe hepatic impairment (see section 4.3).

No dosage adjustment is necessary for HIV-infected patients with moderate hepatic impairment based on limited data (see sections 4.2 and 5.2). In patients with underlying hepatitis B or C, cirrhosis, chronic alcoholism and/or other underlying liver abnormalities, there have been reports of worsening liver disease and development of portal hypertension while on treatment with Invirase. Associated symptoms include jaundice, ascites, oedema and, in some cases, oesophageal varices. Several of these patients died. A causal relationship between Invirase therapy and development of portal hypertension has not been established. Careful monitoring for signs and symptoms of liver toxicity, and tests of liver function (including transaminases) are recommended.

Use in Renal Impairment

Clinical studies with saquinavir included patients with a range of renal impairment from mild to moderate (highest creatinine value measured: 143 µmol/L). In these patients, exposure to saquinavir was not correlated with laboratory markers of renal impairment. No data are available in patients with more severe renal impairment. Although renal clearance is only a minor elimination pathway for saquinavir, clinical judgment should be exercised when administering Invirase to patients with renal insufficiency.

Diabetes and Hyperglycaemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycaemia have been reported during post-marketing surveillance in HIV-infected patients receiving PI therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycaemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued PI therapy, hyperglycaemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made.

Fat Redistribution

Redistribution and/or accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump) and breast enlargement, "cushingoid appearance" and loss of body fat from the face, limbs and upper trunk (peripheral lipodystrophy) have been reported in HIV positive patients receiving antiretroviral therapy (ART). It has also been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, and hyperglycaemia. The severity of these metabolic abnormalities differs within and between the three classes of antiretrovirals (PIs, NRTIs, and NNRTIs). A higher risk of lipodystrophy has been associated with older age, longer duration of ART, stavudine use, hypertriglyceridaemia and hyperlactaemia. Clinical examination should include evaluation for physical signs of fat redistribution. Measurement of serum lipids and blood glucose is recommended. In case of such metabolic abnormalities, a switch in ART may be considered, and/or the addition of treatments designed to directly correct these abnormalities (e.g. lipid lowering agents). The mechanisms of these events and long-term consequences, such as an increased risk of cardiovascular disease, are currently unknown.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome has been reported in patients treated with combination antiretroviral therapy, including Invirase. During the initial phase of combination antiretroviral treatment in patients with severe immune deficiency, a systemic inflammatory reaction to asymptomatic or residual opportunistic pathogens or self-antigens may arise and cause serious clinical conditions or aggravation of symptoms, which may necessitate further evaluation and treatment.

Autoimmune disorders have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

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. A causal relationship has been suggested. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Patients with Diarrhoea

The effects of diarrhoea on the absorption and clinical efficacy of saquinavir have not been studied systematically. The possibility that severe or prolonged diarrhoea may impair the efficacy of Invirase should be kept in mind.

Cardiac Conduction and Repolarisation Abnormalities

Dose-dependent prolongations of QT and PR intervals have been observed in healthy volunteers receiving Invirase/ritonavir (see section 4.3).

It is not recommended to administer Invirase/ritonavir to patients concurrently with other medicinal products that prolong the QT interval. Caution is advised if concomitant use is considered necessary and an ECG performed if signs of cardiac arrhythmias occur. Invirase/ritonavir should be used with caution in patients with underlying structural heart disease, pre-existing conduction system abnormalities, and ischemic heart disease or cardiomyopathies, as they may be at increased risk for developing cardiac conduction abnormalities.

Invirase/ritonavir should be discontinued if significant arrhythmias, QT or PR prolongations occur. Generally, women and elderly patients may be more susceptible to drug-associated effects on the QT interval. 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. 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.

<u>Patients initiating therapy with Invirase/ritonavir</u>

An ECG should be performed prior to initiation of treatment. Patients with a QT interval > 450 msec should not initiate treatment with Invirase/ritonavir. For patients with a QT interval < 450 msec, an on-treatment ECG is recommended.

For treatment-naïve patients initiating treatment with Invirase 500 mg twice daily and ritonavir 100 mg twice daily for the first 7 days of treatment followed by Invirase 1000 mg twice daily and ritonavir 100 mg twice daily is recommended. With a baseline QT interval < 450 msec, an on-treatment ECG is suggested after approximately 10 days of therapy.

Patients with a QT interval increased to > 480 msec, or prolongation over pre-treatment by > 20 msec, should discontinue Invirase/ritonavir (see section 5.1).

Patients stable on Invirase/ritonavir and requiring concomitant medication with potential to increase the QT interval or patients on medication with potential to increase the QT interval and requiring concomitant Invirase/ritonavir where no alternative therapy is available and the benefits outweigh the risks: An ECG should be performed prior to initiation of the concomitant therapy, and patients with a QT interval > 450 msec should not initiate the concomitant therapy (see section 4.5). If baseline QT interval < 450 msec, an on-treatment ECGs 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 Invirase/ritonavir or the concomitant therapy or both.

Lactose Intolerance

Each 500 mg film-coated tablet contains 38.5 mg lactose (monohydrate). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption (autosomal recessive disorder) should not take Invirase.

Drug Interactions

Saquinavir could interact and modify the pharmacokinetics of other drugs that are substrates for CYP3A4 and/or P-glycoprotein (P-gp) and should be used with caution. The example of drugs which are known to or have potential to interact with saquinavir are listed in sections 4.5 and 4.3.

Paediatric Use

The safety and efficacy of Invirase/ritonavir in HIV-infected patients younger than 2 years have not been established. No dose recommendation for children 2 to < 16 years of age could be established that are both reliably effective and below thresholds of concern for QT and PR interval prolongation.

Limited information is available in children. Unboosted Invirase should not be used in children due to the significantly lower saquinavir plasma levels in children compared with adults.

Use in the Elderly

Only limited experience is available in patients older than 60 years. No data are available to establish a dose recommendation in elderly patients.

Effects on Laboratory Tests

No data available.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Most medicine interaction studies with saquinavir have been completed without the administration of ritonavir (i.e. unboosted) with saquinavir soft gel capsules (Fortovase). Observations from medicine interaction studies conducted with unboosted saquinavir might not be representative of the effects seen with the boosted saquinavir therapy. Furthermore, results seen with Fortovase may not be predictive for Invirase and vice versa.

The metabolism of saquinavir is mediated by cytochrome P450, with the specific isoenzyme, CYP3A4, responsible for 90% of the hepatic metabolism. Additionally, saquinavir is a substrate for P-gp. Therefore, medicines that either share or modify CYP3A4 and/or P-gp, may modify the pharmacokinetics of saquinavir. Similarly, saquinavir might also modify the pharmacokinetics of other medicines that are substrates for CYP3A4 or P-gp.

Drugs with additive effects on QT and PR interval prolongation

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 with the following medicinal classes: Anti-arrhythmics class IA or class III, neuroleptics, tricyclic anti-depressive agents, phosphodiesterase type 5 (PDE5) inhibitors, certain antimicrobials and anti-histaminics and medicines which affect cardiac conduction (see also below under individual medicine

interactions). This effect might lead to an increased risk of ventricular arrhythmias, notably torsade de pointes. Therefore, concurrent administration of these agents with Invirase/ritonavir should be avoided when alternative treatment options are available. Medicines showing both pharmacokinetic interactions with Invirase/ritonavir and additive effects on QT and PR interval prolongation are strictly contraindicated. The combination of Invirase/ritonavir with other medicines known to prolong the QT and PR interval is not recommended and should be used with caution if concomitant use is deemed necessary (see sections 4.3 and 4.4).

Inhibitors of CYP3A4

An increase in plasma concentrations of saquinavir could occur with other compounds that are inhibitors of the CYP3A4 isoenzyme. In a clinical study, ketoconazole (a potent CYP3A4 inhibitor) did not increase PK exposure of saquinavir when it was co-administered with ritonavir, suggesting that a second CYP3A4 inhibitor in a therapy may not further elevate the plasma levels of saquinavir. However, clinical monitoring of patients for saquinavir toxicity is recommended when Invirase is coadministered with CYP3A4 inhibitors (see Table 2: Examples of known and predicted Drug-Drug Interactions).

Ritonavir can affect the pharmacokinetics of other medicines because it is a potent inhibitor of CYP3A4 and P-gp and is also an enzyme inducer of several cytochrome P450 isozymes (see Table 1: Medicines that are contraindicated with Invirase/ritonavir and the Product Information for ritonavir).

Inducers of CYP3A4 or P-gp

Other medicines that induce CYP3A4 may also reduce saquinavir plasma concentrations.

Medicines reducing gastrointestinal transit time

It is unknown whether medicines that reduce the gastrointestinal transit time could lead to lower saquinavir plasma concentrations.

Table 2 Examples of known and predicted *Drug-Drug Interactions*

Medicinal product by therapeutic area (dose of Invirase used in study)	**Interaction**	**Recommendations concerning co-administration**
Antiretroviral agents ***Nucleoside reverse transcriptase inhibitors (NRTIs)***		
Zalcitabine and/or Zidovudine	• No pharmacokinetic interaction studies have been completed with Invirase/ritonavir • 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.	• No dose adjustment required.

Medicinal product by therapeutic area (dose of Invirase used in study)	**Interaction**	**Recommendations concerning co-administration**
Didanosine 400 mg single dose (saquinavir soft gel capsules/ritonavir 1600/100 mg qd for 2 weeks, in eight healthy subjects	• Saquinavir AUC ↓ 30 % Saquinavir C_{max} ↓ 25 % Saquinavir C_{min} ↔	• Clinical significance not known • No dose adjustment required.
Tenofovir disoproxil fumarate 300 mg qd (saquinavir/ritonavir 1000/100 mg bid) 18 HIV-infected patients	• Saquinavir AUC ↓ 1 % Saquinavir C_{max} ↓ 7 % Saquinavir C_{min} ↔	• No clinically significant effect on saquinavir exposure. • No dose adjustment required.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Delavirdine	• Interaction with Invirase/ritonavir not studied. • There are limited safety and no efficacy data available from the use of this combination. • With unboosted saquinavir AUC ↑ 348 %. • 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. • Concomitant use only if the benefit outweighs the risk.
Efavirenz 600 mg qd saquinavir/ritonavir 1000/100 mg bid (n=32) Efavirenz 600 mg and unboosted saquinavir 1200 mg tds to 12 subjects	*Boosted saquinavir:* • Saquinavir ↔ • Efavirenz ↔ *Unboosted saquinavir:* • Saquinavir AUC ↓ 62% and C_{max} by 50%. The concentrations of efavirenz were also decreased by about 10%, /but this was not suggested to be clinically significant.	• No dose adjustment required. • Limited data support the use of saquinavir with efavirenz when co-administered with ritonavir.
Nevirapine	• Interaction with Invirase/ritonavir not studied. • Unboosted saquinavir: Saquinavir AUC ↓ 24 % Nevirapine AUC ↔	• Clinical significance not known • No dose adjustment required.

Medicinal product by therapeutic area (dose of Invirase used in study)	**Interaction**	**Recommendations concerning co-administration**
HIV protease inhibitors (PIs)		
Fosamprenavir 700 mg bid (saquinavir/ritonavir 1000/100 mg bid, in 18 HIV-infected patients)	• 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/ritonavir Indinavir 800 mg tid (saquinavir 600-1200 mg soft gel capsules single dose) six healthy volunteers	• Low dose ritonavir increases the concentration of indinavir. • *Unboosted saquinavir* Saquinavir AUC ↑ 4.6-7.2 fold Indinavir plasma concentration ↔ • No safety and efficacy data available for this combination.	• Increased concentrations of indinavir may result in urological complaints e.g. haematuria, flank pain, dysuria, passing urinary calculi. Adequate fluid intake (≥ 1.5 L daily) is recommended as a potential preventative measure, and reduction of indinavir dose is appropriate if nephrolithiasis develops. • Appropriate doses of combination not established.
Lopinavir Saquinavir soft gel capsules/ritonavir 1000/100 mg bid in combination with 2 or 3 NRTIs in 32 HIV-infected patients Saquinavir soft gel capsules 1000 mg bid and the fixed combination of lopinavir/ritonavir 400/100 mg bid in 45 HIV-infected patients	Saquinavir ↔ Ritonavir ↓ (effectiveness as boosting agent not modified). Lopinavir ↔ (based on historical comparison with unboosted lopinavir).	• Use lopinavir/ritonavir with caution as additive effects on QT and/or PR interval prolongation may occur with Invirase (see section 4.4). • For patients already taking ritonavir as part of their antiretroviral regimen, no additional ritonavir is needed.
Nelfinavir 1250 mg bid (saquinavir/ritonavir 1000/100 mg bid) Multiple dose saquinavir/ritonavir (1000 mg / 100 mg bid) nelfinavir (1250 mg bid) in 12 HIV-infected patients.	• Saquinavir AUC ↑ 13 % (90 % CI: 27↓ - 74↑) Saquinavir C_{max} ↑ 9 % (90 % CI: 27↓ - 61↑)	• Combination not recommended.

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 ↔ (see section 5.2). • Higher doses of ritonavir have been shown to be associated with an increased incidence of adverse events. • In some cases, 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	• The approved combination regimen is saquinavir 1000 mg bid with ritonavir 100 mg bid.
Tipranavir/ritonavir Dual-boosted protease inhibitor combination therapy in multiple-treatment experienced HIV-positive adults	• Saquinavir C_{min} ↓ 78 %	• Concomitant administration of tipranavir, co-administered with low dose ritonavir, with saquinavir/ritonavir, is not recommended as the clinical relevance of this reduction has not been established. • If the combination is nevertheless considered necessary, monitoring of the saquinavir plasma levels is strongly encouraged.
HIV fusion inhibitor		
Enfuvirtide (saquinavir soft gel capsules/ritonavir 1000/100 mg bid) 12 HIV patients.	• 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} ↑ approx 10 fold Maraviroc C_{max}: ↑ approx 5 fold 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.

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
Antiarrhythmics		
Ibutilide Sotalol	• Interaction with Invirase/ritonavir has not been studied. No pharmacokinetic interaction is expected.	• Use with caution due to possible cardiac arrhythmias
Anticoagulant		
Warfarin	• Concentrations of warfarin may be affected.	• INR (international normalised ratio) monitoring recommended.
Anticonvulsants		
Carbamazepine Phenobarbital Phenytoin	• Interaction with Invirase/ritonavir has not been studied. However, these medicinal products will induce CYP3A4 if unboosted Invirase is taken, and may therefore decrease saquinavir concentrations.	• Use with caution. • Monitoring of saquinavir plasma concentration is recommended.
Antidepressants		
Tricyclic antidepressants (e.g. amitriptyline imipramine) Clomipramine Maprotiline	• Invirase/ritonavir may increase concentrations of tricyclic antidepressants.	• Therapeutic concentration monitoring is recommended for tricyclic antidepressants. • Use with caution due to possible cardiac arrhythmias
Nefazodone	• Interaction with Invirase/ritonavir not studied. • Nefazodone inhibits CYP3A4. Saquinavir concentrations may be increased.	• Use with caution due to possible cardiac arrhythmias • Clinical monitoring for saquinavir toxicity is recommended.
Anti-gout preparation		
Colchicine	• Concomitant use of colchicine and Invirase/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 Invirase/ritonavir is not recommended, especially in the case of renal or hepatic impairment

Medicinal product by therapeutic area (dose of Invirase used in study)	**Interaction**	**Recommendations concerning co-administration**
Fusidic acid	• Interaction with Invirase/ritonavir not studied. • Co-administration of fusidic acid and Invirase/ritonavir can cause increased plasma concentration of both fusidic acid and saquinavir/ritonavir.	• Concomitant use of fusidic acid and saquinavir/ritonavir is not recommended due to potential for increased mutual toxicity.
Streptogramin antibiotics (quinupristin/dalfopristin)	• Interaction with Invirase/ritonavir not studied. • Streptogramin antibiotics such as quinupristin/dalfopristin will inhibit CYP3A4 and may increase saquinavir concentrations.	• Clinical monitoring for saquinavir toxicity recommended. • Use with caution due to possible cardiac arrhythmias.
Pentamidine Sparfloxacin	• Interaction with Invirase/ritonavir not studied	• Use with caution due to possible cardiac arrhythmias.
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	• 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. • Clinical monitoring for saquinavir toxicity recommended.
Fluconazole/miconazole	• Interaction with Invirase/ritonavir has not been studied. • Both drugs are CYP3A4 inhibitors and may increase the plasma concentration of saquinavir.	• Use with caution due to possible cardiac arrhythmias. • Clinical monitoring for saquinavir toxicity recommended.

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
Antimycobacterials		
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	• Dose adjustment of rifabutin (150 mg qod) is recommended when used in combination with Invirase. • Monitoring of neutropenia and liver enzyme levels is recommended due to an expected increase in exposure to rifabutin.
Benzodiazepines		
Midazolam parenteral	• No data are available on concomitant use of Invirase/ritonavir with intravenous midazolam • Studies of other CYP3A modulators and intravenous midazolam suggest a possible 3 to 4-fold increase in midazolam plasma levels.	• 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 a 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.

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
Alprazolam Clorazepate Diazepam Flurazepam	• Concentrations of these medicinal products may be increased when co-administered with Invirase/ritonavir.	• Careful monitoring of patients with regard to the benzodiazepam effects is warranted. • A decrease in the dose of the benzodiazepine may be required.
Calcium channel blockers		
Felodipine, nifedipine, nicardipine, diltiazem, nimodipine, verapamil, amlodipine, nisoldipine, isradipine	• Concentrations of these medicinal products may be increased when co-administered with Invirase.	• Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroids		
Dexamethasone	• Interaction with Invirase/ritonavir not studied. • Dexamethasone induces CYP3A4 and may decrease saquinavir concentrations.	• Use with caution. Saquinavir may be less effective in patients taking these products concomitantly.
Fluticasone propionate 50 mcg qid, intranasal (ritonavir 100 mg bid) budesonide	Fluticasone propionate ↑ • Intrinsic cortisol ↓ 86 % (90 % CI 82 %-89 %) Greater effects may be expected when fluticasone propionate is inhaled. • Systemic exposure to fluticasone and budesonide has been reported when either of these products is administered via oral inhalation or intranasal application with low dose ritonavir. • Several cases of Cushings disease associated with this interaction have been reported in the literature. • Consideration should be given to switching subjects requiring inhaled/intranasal corticosteroid therapy to beclomethasone.	• Concomitant administration of Invirase/ritonavir and fluticasone propionate and other corticosteroids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. • 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
Endothelin receptor antagonist		
Bosentan	• Interaction with Invirase/ritonavir not studied. • Concomitant use of bosentan and Invirase/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 Invirase/ritonavir, the patient's tolerability of bosentan should be monitored. • Monitoring the plasma levels of Invirase and concomitant HIV medications is recommended.
Medicinal products that are substrates of P-gp ***Digitalis glycosides***		
Digoxin 0.5 mg single dose after 2 weeks of Invirase/ritonavir 1000/100 mg twice daily to 16 healthy volunteers in a cross-over study	• 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.
Histamine H_2-receptor antagonist		
Ranitidine	• Interaction with Invirase/ritonavir not studied. • With unboosted saquinavir there was an increase in exposure of saquinavir when Invirase was dosed in the presence of both ranitidine and food, relative to Invirase dosed with food alone. This resulted in AUC values of saquinavir, which were 67 % higher. This increase is not thought to be clinically relevant	• No dose adjustment is recommended as a clinically relevant interaction would not be anticipated with Invirase/ritonavir.

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
HMG-CoA reductase inhibitors		
Pravastatin Fluvastatin	• Interaction with Invirase/ritonavir not studied. • Pravastatin, fluvastatin are not metabolised by CYP3A4, and interactions are not expected with protease inhibitors including ritonavir. • Interaction via effects on transport proteins cannot be excluded.	• Interaction unknown. • If no alternative treatment is available, use with careful monitoring. • If treatment with a HMG-CoA reductase inhibitor is indicated, either pravastatin or fluvastatin are recommended
Atorvastatin, cerivastatin	• Atorvastatin / cerivastatin are less dependent on CYP3A4 for metabolism.	• When used with Invirase, the lowest possible dose of atorvastatin and cerivastatin should be administered and the patient should be carefully monitored for signs/symptoms of myopathy (muscle weakness, muscle pain, rising plasma creatinine kinase).
Immunosuppressants		
Cyclosporin Rapamycin	• Concentrations of these medicinal products may increase several fold when co-administered with Invirase.	• Careful therapeutic drug monitoring is necessary for immunosuppressants when co-administered with Invirase.
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.
Narcotic analgesics		
Methadone 60-120 mg qd (saquinavir/ritonavir 1000/100 mg bid) once a day in 12 HIV negative methadone maintenance patients	• Methadone AUC ↓ 19 % (90 % CI 9 % to 29 %) None of the 12 patients experienced withdrawal symptoms.	• No dosage adjustment is required when Invirase is combined with methadone. • Use with caution as additive effects on QT

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
		and/or PR interval prolongation may occur.
Oral contraceptives		
Ethinyl estradiol	• Concentration of ethinyl estradiol may be decreased when co-administered with Invirase/ritonavir.	• Alternative or additional contraceptive measures should be used when oestrogen-based oral contraceptives are co-administered.
Phosphodiesterase type 5 (PDE5) inhibitors		
Sildenafil	• Interaction with Invirase/ritonavir not studied. • However sildenafil is a substrate of CYP3A4 and co administration of sildenafil 100 mg single dose with unboosted saquinavir (1200 mg tid) lead to: Saquinavir ↔ Sildenafil C_{max} ↑ 140 % Sildenafil AUC ↑ 210 % Sildenafil had no effect on saquinavir pharmacokinetics.	• Use sildenafil with caution at reduced doses of no more than 25 mg every 48 hours with increased monitoring of adverse events.
Vardenafil	• Interaction with Invirase/ ritonavir has not been evaluated. • Concentrations of vardenafil may be increased when co-administered with Invirase.	• Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring of adverse events
Tadalafil	• Interaction with Invirase/ ritonavir has not been evaluated. • Concentrations of tadalafil may be increased when co-administered with Invirase.	• Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring of adverse events
Proton pump inhibitors		
Omeprazole 40 mg qd (saquinavir/ritonavir 1000/100 mg bid in 8 healthy volunteers)	• Saquinavir AUC ↑ 82 % (90 % CI 44-131 %) Saquinavir C_{max} ↑ 75 % (90 % CI 38-123 %) Ritonavir ↔	• If omeprazole is taken concomitantly with Invirase, monitoring for potential saquinavir toxicities is recommended. • Use with caution due to possible cardiac arrhythmias.

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
Other proton pump inhibitors	• No data are available on the concomitant administration of Invirase/ritonavir and other proton pump inhibitors.	• If other proton pump inhibitors are taken concomitantly with Invirase, monitoring for potential saquinavir toxicities is recommended
Others		
Grapefruit juice	• Interaction with Invirase/ritonavir not studied. • Co-administration of unboosted saquinavir and grapefruit juice as single administration in healthy volunteers resulted in: Saquinavir ↑ 50 % (normal strength grapefruit juice) Saquinavir ↑ 100 % (double strength grapefruit juice)	• No dose adjustment is recommended as a clinically relevant interaction would not be anticipated with Invirase/ritonavir
Garlic capsules	• Interaction with Invirase/ritonavir not studied. • With unboosted saquinavir resulted in: Saquinavir AUC ↓ 51 % Saquinavir C_{trough} ↓ 49 % (8 hours post dose) Saquinavir C_{max} ↓ 54 %	• Patients on saquinavir treatment should 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	• Interaction with Invirase/ ritonavir not studied • Plasma levels of saquinavir can be reduced by concomitant use of the herbal preparation St. John's wort (*Hypericum perforatum*). This is due to induction of drug metabolising enzymes and/or transport proteins by St. John's wort induce CYP3A4 or P-gp.	• Herbal preparations containing St. John's wort *(hypericum perforatum)* should not be used concomitantly with Invirase due to the risk of decreased plasma concentrations and loss of virologic responses and possible resistance to one or more components of the antiretroviral regimen.
Other potential interactions ***Medicinal products that are substrates of CYP3A4***		
e.g. 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.	• Combinations should be given with caution

Medicinal product by therapeutic area (dose of Invirase used in study)	Interaction	Recommendations concerning co-administration
Gastroenterological medicinal products		
Metoclopramide	• Interaction with Invirase/ ritonavir not studied. • It is unknown whether medicinal products which reduce the gastrointestinal transit time could lead to lower saquinavir plasma concentrations.	
Vasodilators (peripheral)		
Vincamine i.v.		• Use with caution due to potential cardiac arrhythmias

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Fertility and reproductive performance were not affected in rats at plasma exposures (AUC values) approximately 33% of those achieved in humans at the recommended clinical dose of Invirase/ritonavir (1000/100 mg) twice daily.

Use in Pregnancy: Category B1

Reproduction studies conducted with saquinavir in rats and rabbits have shown no embryotoxicity or teratogenicity at plasma exposures (based on AUC) approximately 32% of those achieved in humans at the recommended clinical dose of Invirase/ritonavir (1000/100 mg) twice daily. Only small amounts of saquinavir were shown to cross the placental barrier in these species. In a perinatal and postnatal study in rats, at plasma exposures similar to those in the teratogenicity study, there was no effect on the survival, growth and development of offspring to weaning.

Because animal reproduction studies are not always predictive of human response and clinical experience in pregnant women is limited, caution should be exercised before Invirase is prescribed during pregnancy.

Use in Lactation

It is not known whether saquinavir is excreted in animal or human milk. Because many medicines are excreted in human milk, and because of the potential for serious adverse reactions to saquinavir in nursing infants, breast feeding should be stopped during treatment with Invirase.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies have been conducted on the ability to drive and to use machines whilst using Invirase. There is no evidence that Invirase may alter the patient's ability to drive and use machines, however, the adverse event profile of Invirase should be taken into account (see section 4.8).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

The most frequently reported adverse effects, with at least a possible relationship to boosted Invirase (i.e. adverse reactions) were nausea, diarrhoea, fatigue, vomiting, flatulence and abdominal pain.

Adverse Reactions from Clinical Trials with Boosted Saquinavir

Limited data are available from 2 studies where the safety of saquinavir soft gel capsules (Fortovase) (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 (including marked laboratory abnormalities) from these pivotal studies are summarised in Table 3.

Adverse effects from clinical trials with saquinavir soft gel capsules (Fortovase) are given for completeness, however, due to the higher bioavailability of Fortovase, these adverse effects might not be predictive of the safety profile of Invirase.

Table 3: Incidences of Adverse Reactions and Marked Laboratory Abnormalities from MaxCmin1 and MaxCmin2 Studies (Fortovase).

The following descriptors are used to describe the frequency of adverse reactions tabulated below: Very Common (≥ 10%), Common (≥ 1% and < 10%). Within each frequency grouping, adverse effects are presented in order of decreasing seriousness.

Body System **Frequency of Reaction**	**Adverse Reactions**	
	Grades 3 & 4	**All Grades**
Blood and the lymphatic system disorders		
Common	Anaemia	Anaemia
Immune system disorders		
Common		Hypersensitivity
Metabolism and nutrition disorders		
Common	Diabetes mellitus	Diabetes mellitus, anorexia, increased appetite
Psychiatric disorders		
Common		Decreased libido, sleep disorder
Nervous System Disorders		
Common		Paraesthesia, peripheral neuropathy, dizziness, dysgeusia, headache
Respiratory, thoracic and mediastinal disorders		
Common		Dyspnoea
Gastrointestinal disorders		
Very common		Diarrhoea, nausea

Body System **Frequency of Reaction**	**Adverse Reactions**	
	Grades 3 & 4	**All Grades**
Common	Diarrhoea, nausea, vomiting	Vomiting, abdominal distension, abdominal pain, upper abdominal pain, constipation, dry mouth, dyspepsia, eructation, flatulence, lip dry, loose stools
Skin and subcutaneous tissue disorders		
Common	Acquired lipodystrophy	Acquired lipodystrophy, alopecia, dry skin, eczema, lipoatrophy, pruritus, rash
Musculoskeletal and connective tissue disorders		
Common		Muscle spasms
General disorders and administration site conditions		
Common	Fatigue	Asthenia, fatigue, increased fat tissue, malaise
Investigations		
Very common		Increased alanine aminotransferase, increased aspartate aminotransferase, increased blood cholesterol, increased blood triglycerides, increased low density lipoprotein, decreased platelet count
Common		Increased blood amylase, increased blood bilirubin, increased blood creatinine, decreased haemoglobin, decreased lymphocyte count, decreased white blood cell count

Additionally, for completeness, the following adverse reactions reported in clinical trials with unboosted saquinavir and not mentioned in the table above are listed below by body system.

General disorders and administration site conditions: chest pain, fever, intoxication, mucosal damage, oedema, pyrexia, retrosternal pain, shivering, wasting syndrome, weight decrease.

Cardiovascular disorders: Cyanosis, heart murmur, heart valve disorder, hypertension, hypotension, syncope, thrombophlebitis, distended vein.

Endocrine/Metabolic disorders: Appetite decrease, appetite disturbance, dehydration, hyperglycaemia, weight increase, xerophthalmia.

Gastrointestinal disorders: Ascites, buccal mucosa ulceration, cheilitis, dysphagia, eructation, faeces bloodstained, faeces discoloured, gastralgia, gastritis, gastrointestinal inflammation, intestinal obstruction, gingivitis, glossitis, haemorrhage rectum, haemorrhoids,

hepatomegaly, hepatosplenomegaly, melaena, pelvic pain, painful defecation, pancreatitis, parotid disorder, salivary gland disorders, stomatitis, tooth disorder, vomiting.

Hepatobiliary disorders: Jaundice, portal hypertension, exacerbation of chronic liver disease with Grade 4 elevated liver function test.

Investigations: Blood creatinine phosphokinase increased, blood glucose increased, blood glucose decreased, raised transaminase values.

Blood and the lymphatic system: Anaemia, haemolytic anaemia, microhaemorrhages, neutropenia, pancytopenia, splenomegaly, thrombocytopenia.

Musculoskeletal and connective tissue disorders: Arthralgia, arthritis, back pain, muscle cramps, musculoskeletal disorders, musculoskeletal pain, myalgia, polyarthritis, stiffness, tissue changes, trauma.

Nervous system disorders: Ataxia, frequent bowel movements, confusion, convulsions, coordination abnormal, dysarthria, dysesthesia, extremity numbness, heart rate disorder, hyperaesthesia, hyperreflexia, hypoaesthesia, hyporeflexia, intracranial haemorrhage, dry mouth, face numbness (facial pain), paresis, poliomyelitis, progressive multifocal leukoencephalopathy, seizures, spasms, tremor.

Neoplasms benign, malignant and unspecified (including cysts and polyps): Skin papilloma, acute myeloid leukaemia.

Psychiatric disorders: Agitation, amnesia, anxiety, confusional state, depression, excessive dreaming, euphoria, hallucination, insomnia, intellectual ability reduced, irritability, lethargy, libido disorder, overdose effect, psychic disorder, somnolence, speech disorder, suicide attempt.

Reproductive system: Enlarged prostate, vaginal discharge.

Resistance mechanism: Abscess, angina tonsillaris, candidiasis, herpes simplex, herpes zoster, staphylococcal infection, other bacterial infections, mycotic infections, influenza, lymphadenopathy, tumour.

Respiratory: Bronchitis, cough, epistaxis, haemoptysis, laryngitis, pharyngitis, pneumonia, respiratory disorder, rhinitis, sinusitis, upper respiratory tract infection.

Skin and cutaneous tissue disorders: Acne, dermatitis, dermatitis bullous skin eruption, drug eruption, seborrheic dermatitis, erythema, folliculitis, furunculosis, hair changes, hot flushes, photosensitivity reaction, skin pigment changes, maculopapular rash, severe cutaneous reaction associated with increased liver function tests, skin disorder, skin nodule, skin ulceration, Stevens-Johnson syndrome, increased sweating, urticaria, verruca, xeroderma.

Special senses: Blepharitis, earache, ear pressure, eye irritation, dry eye syndrome, decreased hearing, otitis, taste alteration, tinnitus, visual disturbance.

Renal and urinary disorders: Micturition disorder, urinary tract infection, nephrolithiasis.

Vascular disorders: Vasoconstriction.

Post-Marketing Experience with Saquinavir

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

Nervous system disorders: Somnolence; convulsions.

Immune system disorders: Hypersensitivity.

Hepatobiliary disorders: Hepatitis.

Metabolism and nutrition disorders:

- Diabetes mellitus or hyperglycaemia, sometimes associated with ketoacidosis;
- Metabolic abnormalities such as hypertriglyceridemia; hypercholesterolemia; insulin resistance; hyperlactatemia;
- Lipodystrophy (including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsicervical fat accumulation (buffalo hump)).

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antiviral agent, ATC code: J05A E01

The chemical name for saquinavir mesilate is cis-N-tert-Butyl-decahydro-2[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)- L-asparginyl]amino]butyl]-(4aS,8aS)-isoquinoline-

3(S)-carboxyamide methanesulfonate. The molecular formula is C38H50N6O5 • CH4O3S. Saquinavir mesilate has a molecular weight of 766.96.

Saquinavir mesilate is a white to off-white, fine powder with an aqueous solubility of 220 mg/100 mL at 25°C.

Mechanism of Action

Invirase is a highly selective inhibitor of the Human Immunodeficiency Virus enzyme, HIV proteinase (HIV protease).

The HIV protease is an essential viral enzyme required for the specific cleavage of viral gag and gag-pol polyproteins. These viral polyproteins contain a type of cleavage site, which is only recognised by HIV and closely related viral proteases. Saquinavir has been designed as a peptide-like structural mimetic of the viral cleavage site. Saquinavir is a selective and reversible inhibitor of the HIV protease that prevents the creation of mature infectious virus particles.

Pharmacodynamic effect

Antiviral activity *in vitro*

Saquinavir demonstrates antiviral activity against both 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, using acutely infected T cell lines or primary human lymphocytes / monocytes. *In vitro* antiviral activity was observed against a panel of HIV-1 group M non-clade B isolates (A, AE, C, D, F, G and H) and HIV-2 with EC_{50} values ranging from 0.3 – 2.4 nM. In the presence of 50% human serum or alpha-1 acid glycoprotein (1 mg/ml), the antiviral activity of saquinavir decreases by an average factor of 25-fold and 14-fold, respectively.

Resistance

In vitro resistance:

In vitro selection of resistance from wild-type HIV-1 virus

The most commonly reported mutations, G48V and L90M, were observed to develop during *in vitro* passage of HIV-1 wild-type virus in the presence of increasing concentrations of saquinavir. Recombinant virus harbouring the G48V and L90M mutations exhibited 7.9-fold and 3.4-fold reductions in viral susceptibility to saquinavir, respectively. Protease mutations such as M36I, I54V, K57R, and L63V developed less frequently in the presence of saquinavir.

In vivo resistance:

Treatment naïve patients

Four studies have investigated boosted saquinavir regimens in ART naïve patients [saquinavir/ritonavir (1600 mg/100 mg) daily, n=349; (1000 mg/100 mg) twice daily, n=92]. Baseline resistance analyses were conducted on 26 patients experiencing virological rebound. Data from 2 patients was excluded either because PI mutations were present at baseline or a signature protease mutation (D30N) associated with another PI subsequently developed. Virus from 2 patients (2/24) developed protease mutations (M36I and M46i/m, respectively). These mutations are not typically associated with saquinavir resistance. No specific saquinavir-associated protease mutations were observed to develop following virological failure.

Treatment experienced patients

Baseline and on-therapy genotype was evaluated for 22 previously PI-experienced patients who experienced virological failure after receiving a boosted saquinavir regimen (MaxCmin 1 and 2 studies; 1000/100 mg twice daily, n=171). Virus from 8 patients (8/22; 36%) developed additional protease mutations following virological failure. The relative incidence of each mutation was: I84V (n=4, 18%); F53L, A71V or G73S (n=2, 9%); L10V, M46I, I54V, V82A or L90M (n=1, 4.5%).

Antiviral activity according to baseline genotype and phenotype

Genotypic and phenotypic clinical cut-offs predicting the clinical efficacy of boosted saquinavir have been derived from retrospective analyses of 2 open-label randomised clinical studies (RESIST 1 and 2) and a large independent hospital cohort study.

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.

A clinical hospital cohort study (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-naïve patients. The presence of 3 or more mutations was associated with reduced response to saquinavir/ritonavir.

To confirm the association between the number of these saquinavir-associated resistance mutations and virological response using an independent dataset, the association was investigated using data for patients receiving boosted saquinavir in the RESIST 1 and 2 clinical studies. The RESIST 1 and 2 studies enrolled a more heavily treatment experienced patient population, including 54% who had received prior saquinavir. This analysis confirmed the association between the number of saquinavir-associated mutations (p=0.0133, see Table 4). In addition, 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.

Virological response to HAART relies upon the activity of the individual antiretroviral components. The association between the number of saquinavir mutations at baseline and the activity of the concomitant antiretroviral components of the regimen was assessed using baseline phenotypic susceptibility data. The association between the number of baseline saquinavir resistance-associated mutations and response was highly significant when the activity of the optimised background was taken into account (p=0.0011, see Table 5). Patients receiving saquinavir in the presence of active concomitant ART and having fewer saquinavir-associated mutations had an improved response compared to patients receiving fewer active co-medication and higher numbers of saquinavir-associated mutations.

Table 4: Virological response to boosted saquinavir 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	Log_{10} Change in Baseline Plasma HIV-1 RNA at Weeks 12-20	n=114	Log_{10} 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

SQV = saquinavir

* 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

** Saquinavir naïve is defined as the patient who had never previously received a saquinavir-based regimen. Saquinavir-experienced patients had received prior saquinavir-based therapy (with or without boosting with ritonavir). Consequently, saquinavir-experienced patients were being retreated with a saquinavir-based therapy. Of note, patients receiving a saquinavir-based therapy at study entry (i.e. continuing a failing saquinavir based regimen) were excluded from the analysis.

Table 5: Virological response (log_{10} change in viral load) at week 4 stratified by the activity of concomitant antiretrovirals and the number of saquinavir-associated mutations

PSS of OBT	Number of Saquinavir-Associated Resistance Mutations at Baseline (n=114)								
	0	1	2	3	4	5	6	7	**Total**
0	-	-	-2.62	-0.32	-0.38	0.06	-0.51	0.24	**-0.32**
1	-	-	-1.44	-1.09	-0.32	-0.38	0.12	-	**-0.44**
2	-1.45	-0.92	-1.44	-1.58	-0.92	-0.79	0.16	-	**-1.34**
>2	-2.64	-1.78	-	-1.97	-2.05	-2.21	-0.94	-	**-2.01**
Total	**-2.04**	**-1.69**	**-1.57**	**-1.41**	**-0.75**	**-0.44**	**0.08**	**0.24**	**-1.17**

p-value = 0.0011 (model including PSS and saquinavir-associated resistance mutations)
PSS = Phenotypic Sensitivity Score (zero = no active background antiretroviral co-medication);
OBT = Optimised Background Treatment

Hypersusceptibility to Mutant Virus:

Hypersusceptibility of some resistant viruses to inhibition with saquinavir has been described, for example in the presence of the 30N substitution (with or without additional substitutions at residues 46, 71 or 88). This was also observed in complexes of substitutions showing resistance to amprenavir including 50V in presence or absence of 46I and 47V. A high proportion of viruses with substitutions at residue 82 either retain susceptibility (37%) or show enhanced activity (8%) to saquinavir. The clinical significance of hypersusceptibility to saquinavir has not been established.

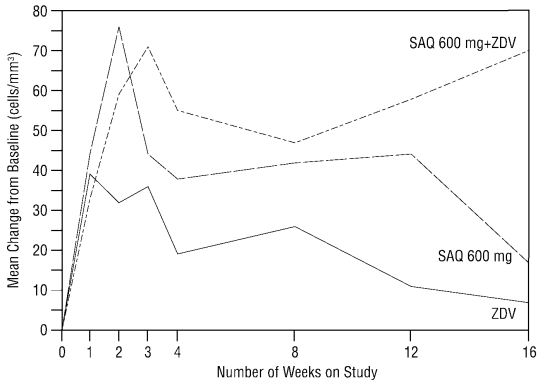
Clinical Trials

Advanced Patients without Prior Zidovudine Therapy

A dose-ranging study (Italy, V13330) conducted in 92 zidovudine-naïve patients (mean baseline CD_4 = 179) studied saquinavir at doses of 75 mg, 200 mg and 600 mg tds in combination with zidovudine 200 mg tds compared to saquinavir 600 mg tds alone and zidovudine alone.

In analyses of average CD_4 changes over 16 weeks, treatment with the combination of saquinavir 600 mg tds + zidovudine (n = 14) produced greater CD_4 cell increases than zidovudine monotherapy (see Fig 1). The CD_4 changes of zidovudine in combination with doses of saquinavir lower than 600 mg tds were no greater than that of zidovudine alone. The number of patients studied was too limited to permit adequate comparison of the efficacies of saquinavir 1800 mg daily versus recommended doses of zidovudine as monotherapy.

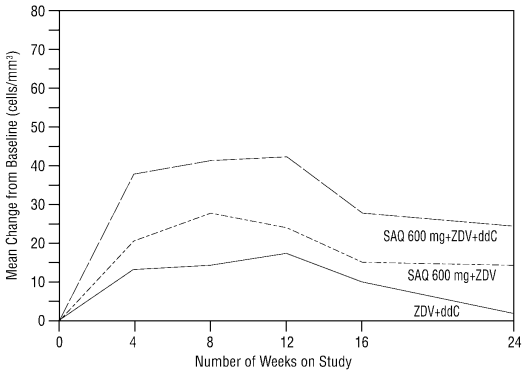
Fig. 1. Mean CD_4 Changes (cells/mm^3) from Baseline in Study V13330 (Italy)



Advanced Patients with Prior Zidovudine Therapy

In ACTG229/NV14255, 295 patients (mean baseline CD_4 = 165) with a history of prolonged zidovudine treatment (median 713 days) were randomised to receive either saquinavir 600 mg tds + zalcitabine + zidovudine (triple combination), saquinavir 600 mg tds + zidovudine or zalcitabine + zidovudine. In analyses of average CD_4 changes over 24 weeks, the triple combination (n = 89) produced greater increases in CD_4 cell counts (see Fig 2) compared with that of zalcitabine + zidovudine. There were no significant differences in CD_4 changes among patients receiving saquinavir + zidovudine and zalcitabine + zidovudine. Based on surrogate markers, including CD_4 count and plasma HIV-RNA response but not quality of life measures, the combination of saquinavir 1800 mg daily with zidovudine and zalcitabine was superior to saquinavir + zidovudine and zidovudine + zalcitabine but longer term follow-up information including morbidity and mortality information are lacking.

Fig. 2. Mean CD_4 Changes (cells/mm^3) from Baseline in Study ACTG229/NV14255



Only limited and transient antiviral activity has been demonstrated with Invirase monotherapy. Therefore, Invirase must be given in combination with other antiretrovirals.

Saquinavir in Combination with Ritonavir

MaxCmin1 study

In the MaxCmin1 study, the safety and efficacy of saquinavir soft gel capsules (Fortovase) / ritonavir (1000/100 mg) bd in combination with 2 NRTIs/NNRTIs was compared with indinavir/ritonavir (800/100 mg) bd in combination with 2 NRTIs/NNRTIs. Median baseline CD_4 cell count was 272 cells/mm^3 and median baseline plasma HIV-RNA was 4.0 $\log_{10}$ copies/mL in the Fortovase/ritonavir arm. Median baseline CD_4 cell count was 280 cells/mm^3 and median baseline plasma HIV-RNA was 3.9 $\log_{10}$ copies/mL in the indinavir/ritonavir arm. At 48 weeks, the median increases in CD_4 cell counts were 85 and 73 cells/mm^3 for the Fortovase and indinavir arms, respectively. For the intent-to-treat (ITT) analysis at week 48 (switch = failure) the proportion of patients in the saquinavir containing arm with viral load below the limit of detection (< 400 copies/mL) was 69% (n = 102) compared with 53% in the indinavir containing arm.

MaxCmin2 study

In the MaxCmin2 study, the safety and efficacy of saquinavir soft gel capsules (Fortovase) / ritonavir (1000/100 mg) bd in combination with 2 NRTIs/NNRTIs was compared with lopinavir/ritonavir (400/100 mg) bd in combination with 2 NRTIs/NNRTIs in over 324 subjects. Values for median baseline CD_4 count and median baseline plasma HIV-RNA were 241 cells/mm^3 and 4.4 $\log_{10}$ copies/mL in the Fortovase/ritonavir arm, and 239 cells/mm^3 and 4.6 $\log_{10}$ copies/mL in the lopinavir/ritonavir arm, respectively.

In the primary efficacy analysis, incidence of virological failure, including all subjects that took at least one dose of the study medication (ITT/exposed population) 29 failures were observed in the lopinavir/ritonavir arm and 53 failures in the Fortovase/ritonavir arm (hazard ratio HR: 0.5; 95% CI: 0.3 – 0.8). The better outcome in the lopinavir/ritonavir arm was associated with lower failure rates among subjects no longer taking their assigned treatment and better compliance with the protocols intention to use ART strategies aimed at suppressing viral replication at all times. Comparable findings were made in the analysis where discontinuation of the assigned treatment was regarded as virological failure (ITT/exposed population/discontinuation = failure; HR: 0.6; 95% CI: 0.4 – 0.9). In this analysis the better outcome in the lopinavir/ritonavir arm was associated with a reduced risk of discontinuation of the assigned treatment due to factors not linked to antiviral activity.

At 48 weeks, the proportion of subjects with HIV-RNA below the limit of detection (< 50 copies/mL) was 53% (n = 161) for the Fortovase arm versus 60% (n = 163) for the lopinavir arm in the ITT, switch equals failure analysis, and 74% (n = 114) for the Fortovase arm versus 70% (n = 141) for the lopinavir arm in the on-treatment analysis (*p* = ns for both comparisons). At the cut off level of HIV-RNA < 400 copies/mL, the probability of viral suppression was lower in the Fortovase/ritonavir arm from week 24 and onwards in the ITT/exposed population analysis and from week 36 in the ITT/exposed population/ discontinuation analysis. No statistical differences were observed in the on-treatment analysis.

Over 48 weeks a similar strong immunological response was seen in both arms with median increases in CD_4 count of 106 cells/mm^3 for the lopinavir/ritonavir arm, and 110 cells/mm^3 for the Fortovase/ritonavir arm.

More subjects in the Fortovase/ritonavir arm (30%) than in the lopinavir/ritonavir arm (14%) prematurely discontinued the assigned treatment (p = 0.001). The primary reasons for premature discontinuation were non-fatal adverse events and subject's choice.

No difference in the incidence of adverse events of Grade 3 and/or 4 was seen between the two arms.

Effects on Electrocardiogram

The effect of 1000/100 mg bd (therapeutic dose) and 1500/100 mg bd (supra-therapeutic dose) of Invirase/ritonavir on the QT interval was evaluated over 20 hours on day 3 of dosing 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). The day 3 time point was chosen since the pharmacokinetic exposure was maximum on that day in a previous 14-day multiple dose pharmacokinetic study. These doses of Invirase/ritonavir on day 3 in this study resulted in a mean C_{max} of approximately 3-fold and 4-fold, respectively, higher than the mean C_{max} observed with Invirase/ritonavir 1000/100 mg bd in HIV patient population at steady-state. On day 3, the upper 1-sided 95% CI 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 Invirase/ritonavir treatment groups (see results in Table 6). The supra-therapeutic dose of Invirase/ritonavir appeared to have a greater effect on the QT interval than the therapeutic dose of Invirase/ritonavir. Majority (89% and 80% in therapeutic dose and supra-therapeutic dose, respectively) of subjects had the QTcS of < 450 msec and none had the QTc interval of > 500 msec. (see section 4.4).

Table 6 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

Treatment	Post-Dose Time Point	Maximum Mean ddQTcS	Standard Error	Upper 95%-CI of ddQTcS
Invirase/ritonavir 1000/100 mg bd	12 hours	18.86	1.91	22.01
Invirase/ritonavir 1500/100 mg bd	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 prolongation of > 200 msec was also observed in 40% and 47% of subjects receiving Invirase/ritonavir 1000/100 mg bd and 1500/100 mg bd, respectively, on day 3. Three percent of subjects in the active control moxifloxacin arm and 5% in the placebo arm experienced PR prolongation of > 200 msec. The maximum mean PR interval changes relative to the pre-dose baseline value were 25 msec and 34 msec in the two Invirase/ritonavir treatment groups, 1000/100 mg bd and 1500/100 mg bd, respectively (see section 4.4).

There was no torsade de pointes and no QT prolongation >500 msec in the study. In several subjects, association of syncope or pre-syncope with PR prolongation could not be ruled out. The clinical significance 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 bd should be avoided.

The effect of treatment initiation with a dosing regimen of Invirase/ritonavir 500 /100 mg bd in combination with 2 NRTIs for the first 7 days of treatment followed by Invirase/ritonavir 1000/100 mg bd 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 pre-dose baseline in QTcF ($\Delta QTcF_{dense}$). 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 7), based on cross-study comparison in a different population. Only 2/21 (9%) patients across all study days had maximum QTcF change from dense pre-dose baseline ≥ 30 msec following administration of the modified Invirase/ritonavir regimen in the treatment-naïve HIV-1 infected patient population; and the maximum mean change from dense pre-dose baseline in QTcF was < 10 msec 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 7). The proportion of patients with a reported PR interval prolongation > 200 msec in this study ranged from 3/22 (14%) (day 3) to 8/21 (38%) (day14).

Following the modified Invirase/ritonavir regimen, SQV exposure during the first week peaked on Day 3 and declined to the lowest exposure on Day 7 with RTV induction effects, while Day 14 SQV PK parameters (following full doses of Invirase/ritonavir in the second week) approached the range of historical mean values for SQV steady-state values in HIV-1 infected patients (Table 7). 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 7 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 $\Delta QTcF_{dense}$ msec (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 $\Delta QTcF_{dense} \geq 30$ msec (%)	0	0	0	2/21 (9%)	0	29/57 (51%)

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

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The absolute bioavailability of saquinavir 200 mg capsules is very low: following administration of a 600 mg oral dose to healthy volunteers, in the presence of food, the mean absolute bioavailability was 4% (range: 1% - 9%). The low bioavailability is thought to be due to a combination of incomplete absorption (approximately 30%) and extensive first pass metabolism. Gastric pH has been shown not to play a major role in the large increase in bioavailability when given with food.

In healthy volunteers, the extent of absorption (as reflected by AUC) after a 600 mg oral dose of saquinavir given 30 minutes before food to fasted subjects, was substantially increased when the same dose was given following a full breakfast (including eggs, bacon, cereal, toast, coffee or tea) from 110 ng.h/mL to 390 ng.h/mL. The presence of food also increased the time taken to achieve maximum concentration from 1.7 hours to 2.5 hours and substantially increased the mean maximum plasma concentrations (C_{max}) from 41 ng/mL to 173 ng/mL. This effect of food has been shown to be present for up to 2 hours after food intake (systemic exposure (AUC) was similar for doses given 5 minutes and 2 hours after a standardised meal). Therefore, Invirase should be taken within 2 hours after a meal.

In another study in healthy volunteers, it was shown that the increased extent of absorption of a 600 mg oral dose of saquinavir following a full breakfast was approximately double the absorption after a light breakfast (only cereal, toast, coffee or tea).

In a cross-over study, 22 HIV-infected patients treated with Invirase/ritonavir (1000/100 mg) twice daily and receiving 3 consecutive doses under fasting conditions or after a high-fat meal (46 g fat, 1091 kcal), the AUC_{0-12} of saquinavir was 10320 ng·h/mL and 34926 ng·h/mL, respectively. All but 1 of the patients achieved C_{trough} above the therapeutic threshold in the fasted state. Nevertheless, Invirase should be administered within 2 hours following a meal.

In HIV-infected patients, boosted saquinavir (Fortovase soft gel capsules or Invirase) at doses of 400/400 mg twice daily or 1000/100 mg twice daily provides saquinavir systemic exposures over a 24-hour period similar to, or greater than those achieved with Fortovase 1200 mg three time daily (see Table 8).

Table 8: Pharmacokinetic Parameters of Saquinavir at Steady-State after Administration of Different Regimens in HIV-infected Patients

Dosing regimen	**N**	**AUC_{τ}** (ng·h/mL)	**AUC_{24h}** (ng·h/mL)	**C_{min}** (ng/mL)
Invirase 600 mg tds	10	866	2598	79
Fortovase 1200 mg tds	31	7249	21747	216
Invirase 400 mg bd + ritonavir 400 mg bd	7	16000	32000	480
Invirase 1000 mg bd + ritonavir 100 mg bd	24	14607	29214	371
Fortovase 1000 mg bd + ritonavir 100 mg bd	24	19085	38170	433
Invirase 1000 mg bd + ritonavir 100 mg bd Fasting conditions	22	10320	20640	313
Invirase 1000 mg bd + ritonavir 100 mg bd High fat meal	22	34926	69852	1179

Fortovase: saquinavir soft gel capsules; τ: dosing interval (8 hrs if tds, 12 hrs if bd)

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

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_{τ} (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)

No differences in gastrointestinal absorption were noted between HIV-positive subjects with and without diarrhoea, and administration of saquinavir had no effect on these parameters.

Saquinavir is a substrate for the MDR1 Multidrug Transporter (P-gp).

Bioequivalence of Invirase 500 mg film-coated tablets and Invirase 200 mg capsules was demonstrated in 94 healthy male and female volunteers who received 1000 mg (either as two 500 mg tablets or five 200 mg capsules) under fed conditions in combination with 100 mg ritonavir twice daily. Mean exposure ratios were estimated to be 1.10 for $AUC_{0-\infty}$ and 1.19 for C_{max} of saquinavir with corresponding 90% CI of 1.04 - 1.16 and 1.14 - 1.25, respectively.

Distribution

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. Saquinavir shows a high degree of protein binding (approximately 98%) which is independent of concentrations over the range 15 - 700 ng/mL. Saquinavir does not enter the cerebrospinal fluid readily and concentrations are low compared with plasma, as would be expected from saquinavir's high protein binding.

Metabolism

Saquinavir is metabolised extensively via the hepatic route. Values > 96% of a radiolabelled intravenous dose appeared in the faeces after 4 days. *In vitro* studies identified that the metabolism of saquinavir is cytochrome P450-mediated, with the specific isoenzyme CYP3A4 responsible for more than 90% of the hepatic metabolism. Renal excretion is a very minor route of elimination for saquinavir (< 4%). The metabolic profile of saquinavir has been investigated in bile, plasma and microsomes in rats and in microsomes from other species, including man. Saquinavir is rapidly metabolised to a range of mono- and di-hydroxylated inactive compounds.

Excretion

Systemic clearance is rapid, 80 L/hr; which is close to hepatic plasma flow. Systemic clearance was constant after intravenous doses of 6, 36 and 72 mg infused over 3 hours. The mean residence time of saquinavir was found to be 7 hours.

After single and multiple oral doses of capsules (25 - 600 mg tds) in the presence of food, the increase in exposure (50-fold) was greater than directly proportional to the increase in dose (24-fold). Accumulation following multiple dosing (25 - 600 mg tds) in HIV-infected patients is modest. AUC was increased by 150% at steady-state compared to single doses.

Pharmacokinetics in Special Populations

Patients with renal impairment

No pharmacokinetic investigations of Invirase in patients with renal insufficiency have been performed.

Patients with hepatic impairment

The effect of hepatic impairment on the steady-state pharmacokinetics of Invirase/ritonavir (1000 /100 mg) twice daily for 14 days, was investigated in 7 HIV-infected patients with moderate liver impairment (Child Pugh Grade B score 7 - 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% CI) was 0.7 (0.3 - 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. No dose adjustment is warranted for saquinavir in HIV-infected patients with moderate hepatic impairment (see section 4.4).

Effect of gender, race and age

Gender

No effect of gender was observed on the pharmacokinetics of Invirase 200 mg capsule administered as a 600 mg single dose in 71 healthy volunteers. A gender difference was observed with females showing higher saquinavir exposure than males (AUC 56%, C_{max} 26%) in the bioequivalence study comparing Invirase 500 mg film-coated tablets with Invirase 200 mg capsules (boosted therapies). There was no evidence that age and body-weight explained the gender difference in this study. A clinically significant difference in safety profile and efficacy between men and women has not been reported with the approved dosage regimen. Treatment with Invirase/ritonavir (1000/100 mg) twice daily in male and female patients is found to be well-tolerated and effective.

Race

The influence of race on the pharmacokinetics of Invirase has not been determined.

Elderly

Invirase pharmacokinetics have not been investigated in elderly patients (> 65 years).

Paediatric

Invirase pharmacokinetics have not been investigated in paediatric patients (< 12 years) (see section 4.4*).*

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Saquinavir, with and without metabolic activation as appropriate, was not mutagenic in the *Salmonella typhimurium* reverse-mutation assay or in the chinese hamster lung V79/HPRT test, was not clastogenic in the mouse micronucleus assay *in vivo* or in human peripheral blood leucocytes *in vitro,* and did not induce DNA damage in primary rat hepatocytes.

Carcinogenicity

Carcinogenicity studies found no indication of carcinogenic activity in rats and mice administered saquinavir 125 – 1000 mg/kg/d and 200 – 2500 mg/kg/d, respectively, for approximately 2 years. The plasma exposures (area under the curve [AUC] values) in the respective species were up to approximately 37% and 85% of those obtained in humans at the recommended clinical dose of Invirase/ritonavir (1000/100 mg) twice daily.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate
Microcrystalline cellulose
Povidone
Croscarmellose sodium
Magnesium stearate
Hypromellose
Titanium dioxide
Purified talc
Iron oxide yellow CI 77492
Iron oxide red CI 7749
Triacetin.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Invirase tablets should be stored below 30^{o}C.

6.5 NATURE AND CONTENTS OF CONTAINER

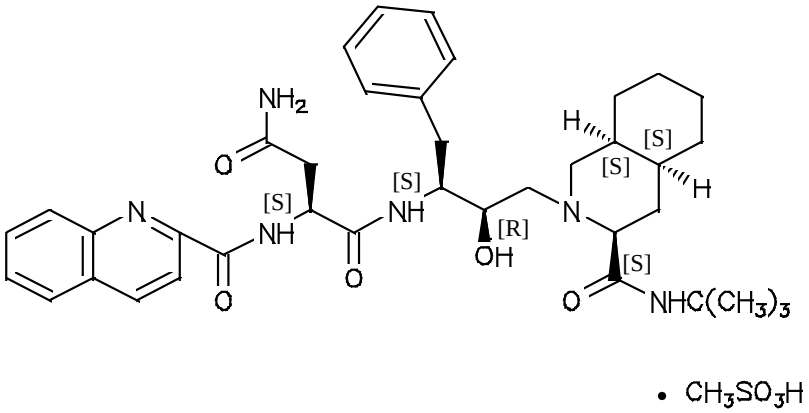
Invirase tablets are available in bottles of 120.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure



CAS number: 149845-06-7

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription only medicine

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

7 July 2006

10. DATE OF REVISION OF THE TEXT

6 November 2018

Summary Table of Changes

Section Changed	Summary of new information
1, 2 and 6.1	Changes consequential to revision of Australian Approved Names
8	Change to Sponsor address
All sections	Reformat to comply with new PI form, update cross references and add mandatory text. Editorial changes and corrections