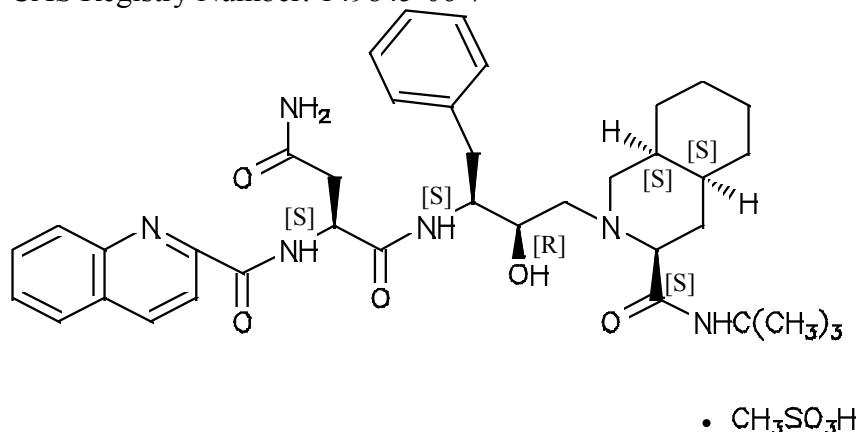


NAME OF THE MEDICINE

INVIRASE®

Saquinavir mesylate

CAS Registry Number: 149845-06-7



DESCRIPTION

INVIRASE is available as film-coated tablets containing 571.5 mg of saquinavir mesylate equivalent to 500 mg saquinavir free base.

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

The chemical name for saquinavir mesylate 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)-carboxamide methanesulfonate. The molecular formula is C₃₈H₅₀N₆O₅ • CH₄O₃S. Saquinavir mesylate has a molecular weight of 766.96.

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

Each 500 mg film-coated tablet also contains the inactive ingredients: lactose, microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, talc, iron oxide yellow CI 77492, iron oxide red CI 77491 and triacetin.

PHARMACOLOGY

Pharmacodynamics

Mechanism of action: 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.

Antiviral activity in vitro: Saquinavir demonstrates antiviral activity against both laboratory strains and clinical isolates of HIV-1; with typical EC₅₀ and EC₉₀ 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 EC₅₀ 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 antiretroviral therapy (ART) naïve patients [(saquinavir/ritonavir (1600 mg/100 mg) daily, n=349; (1000 mg/100 mg) bd, n=92)]. Baseline resistance analyses were conducted on 26 patients experiencing virological rebound. Data from 2 patients was excluded either because protease inhibitor (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 bd, 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) bd 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 1). 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 optimized background was taken into account ($p=0.0011$, see Table 2). 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 1: 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 2: Virological response (log₁₀ 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.

Pharmacokinetics

Absorption and Bioavailability: 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) bd and receiving 3 consecutive dosings under fasting conditions or after a high-fat meal (46 g fat, 1091

kcal), the AUC₀₋₁₂ 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 bd or 1000/100 mg bd provides saquinavir systemic exposures over a 24-hour period similar to, or greater than those achieved with FORTOVASE 1200 mg tds (see Table 3).

Table 3: 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);

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-glycoprotein, 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 bd. Mean exposure ratios were estimated to be 1.10 for AUC_{0-∞} 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 and Elimination: 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.

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) bd 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 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% CI) was 0.7 (0.3 - 1.6) for both AUC₀₋₁₂ 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 PRECAUTIONS: *Hepatic Impairment*).

Effect of gender, race and age: 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) bd in male and female patients is found to be well-tolerated and effective.

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

INVIRASE pharmacokinetics has not been investigated in elderly patients (> 65 years) or paediatric patients (< 12 years) – See PRECAUTIONS: *Use in Elderly Patients and Paediatric Use*.

CLINICAL TRIALS

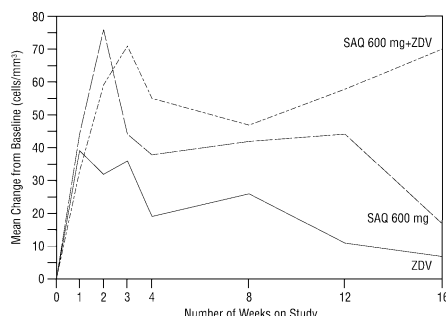
Advanced Patients without Prior Zidovudine Therapy

A dose-ranging study (Italy, V13330) conducted in 92 zidovudine-naïve patients (mean baseline CD₄ = 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 CD₄ changes over 16 weeks, treatment with the combination of saquinavir 600 mg tds + zidovudine (n = 14) produced greater CD₄ cell increases than zidovudine

monotherapy (see Fig 1). The CD₄ 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.

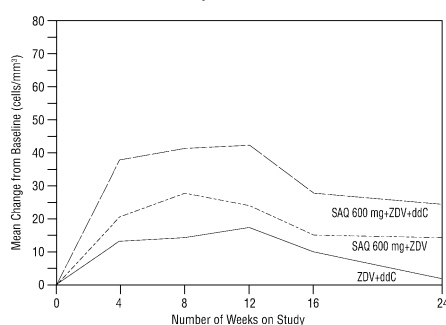
Fig. 1. Mean CD₄ Changes (cells/mm³) from Baseline in Study V13330 (Italy)



Advanced Patients with Prior Zidovudine Therapy

In ACTG229/NV14255, 295 patients (mean baseline CD₄ = 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 CD₄ changes over 24 weeks, the triple combination (n = 89) produced greater increases in CD₄ cell counts (see Fig 2) compared with that of zalcitabine + zidovudine. There were no significant differences in CD₄ changes among patients receiving saquinavir + zidovudine and zalcitabine + zidovudine. Based on surrogate markers, including CD₄ 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 CD₄ Changes (cells/mm³) 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 CD₄ cell count was 272 cells/mm³ and median baseline plasma HIV-RNA was 4.0 log₁₀ copies/mL in the FORTOVASE/ritonavir arm. Median baseline CD₄ cell count was 280 cells/mm³ and median

baseline plasma HIV-RNA was 3.9 log₁₀ copies/mL in the indinavir/ritonavir arm. At 48 weeks, the median increases in CD₄ cell counts were 85 and 73 cells/mm³ 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 CD₄ count and median baseline plasma HIV-RNA were 241 cells/mm³ and 4.4 log₁₀ copies/mL in the FORTOVASE/ritonavir arm, and 239 cells/mm³ and 4.6 log₁₀ 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 CD₄ count of 106 cells/mm³ for the lopinavir/ritonavir arm, and 110 cells/mm³ 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 boosted INVIRASE treatment groups (see results in Table 4). 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. (Also see PRECAUTIONS: *Cardiac Conduction and Repolarisation Abnormalities*)

Table 4 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 boosted INVIRASE treatment groups, 1000/100 mg bd and 1500/100 mg bd, respectively. (Also see PRECAUTIONS: *Cardiac Conduction and Repolarisation Abnormalities*).

There was no torsade de pointes and no QT prolongation >500 msec in the study. In several subjects, association of syncope or presyncope 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.

INDICATIONS

INVIRASE (saquinavir) is indicated for the treatment of HIV/AIDS in adults and children 12 years of age and older. Clinical studies indicate that saquinavir should be used only in combination with ritonavir and other antiretroviral therapies (see CLINICAL TRIALS).

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 CLINICAL TRIALS).

CONTRAINDICATIONS

Boosted INVIRASE is contraindicated in patients with hypersensitivity to saquinavir, ritonavir or to any of the excipients in the film-coated tablet.

Boosted INVIRASE is contraindicated in patients with severe hepatic impairment.

Boosted INVIRASE should not be given together with other medicines that may interact and result in potentially life threatening side effects associated with concomitantly administered medicines. Medicines which have both pharmacokinetic interactions and prolong the QT and/or PR interval and should not be given with boosted INVIRASE are included in Table 5 (See also PRECAUTIONS: *Cardiac Conduction and Repolarisation Abnormalities* and *Interactions with Other Medicines*).

Boosted INVIRASE is contraindicated in patients with 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.

Table 5: Medicines that are Contraindicated with Boosted INVIRASE

Medicine class	Medicines within class that are contraindicated with INVIRASE / ritonavir	Potential side effect
Antiarrhythmics	Amiodarone, flecainide, propafenone	Life-threatening cardiac arrhythmia
Antihistamines	Astemizole, terfenadine	Life-threatening cardiac arrhythmia
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Acute ergot toxicity
GI Motility Agents	Cisapride	Life-threatening cardiac arrhythmia
HMG-CoA Reductase Inhibitors	Simvastatin, lovastatin	Rhabdomyolysis
Neuroleptics	Pimozide	Life-threatening cardiac arrhythmia
Sedatives/Hypnotics	Triazolam, oral midazolam	Prolonged/increased sedation
Antimycobacterial Agents	Rifampicin	Severe hepatocellular toxicity

PRECAUTIONS

Information for Patients

INVIRASE should be given only in combination with ritonavir (boosted).

INVIRASE should NOT be given without ritonavir (unboosted).

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 PRECAUTIONS: *Interactions with Other Medicines*).

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.

Hepatic Impairment

No dosage adjustment is necessary for HIV-infected patients with moderate hepatic impairment based on limited data (see PHARMACOLOGY: *Pharmacokinetics in Special Population* and DOSAGE AND ADMINISTRATION: *Special Dosage Instructions*). 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.

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 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.

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 boosted INVIRASE (see CONTRAINDICATIONS).

It is not recommended to administer boosted INVIRASE 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. Boosted INVIRASE 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.

Boosted INVIRASE should be discontinued if significant arrhythmias, QT or PR prolongation 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 the drug. Therefore, the recommended dose of boosted INVIRASE should not be exceeded. Boosted INVIRASE at a dose of 2000 mg once daily with ritonavir 100 mg once daily has not been studied with regard to the risk of QT prolongation and is not recommended.

Patients initiating therapy with boosted INVIRASE: An ECG should be performed prior to initiation of treatment. Patients with a QT interval > 450 msec should not use boosted INVIRASE. For patients with a QT interval < 450 msec, an on-treatment ECG is suggested after approximately 3 to 4 days of therapy and for patients with a QT interval > 480 msec or prolongation over pre-treatment by > 20 msec should discontinue boosted INVIRASE.

Patients stable on boosted INVIRASE 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 boosted INVIRASE where no alternative therapy is available and the benefits outweigh the risks: An ECG should be performed prior to initiation of the concomitant therapy, and patients with a QT interval > 450 msec should not initiate the concomitant therapy (see PRECAUTIONS: *Interactions with other Medicines*). 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 boosted INVIRASE or the concomitant therapy or both.

Lactose Intolerance

Each 500mg 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.

Paediatric Use

Due to the significantly lower saquinavir plasma levels in children compared with adults, unboosted INVIRASE should not be used in children.

The safety and efficacy of boosted INVIRASE in HIV-infected patients younger than 12 years have not been established.

Limited information is available in children treated with unboosted saquinavir soft gel capsules (FORTOVASE). When FORTOVASE (50 mg/kg bid) is co-administered with nelfinavir or ritonavir in children, saquinavir exposures are greatly increased, and when combined with ritonavir, may provide saquinavir exposures up to 2-fold greater than those achieved with FORTOVASE 1200 mg tid in adults.

Use in Elderly Patients

Only limited experience is available in patients older than 60 years.

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 ADVERSE EFFECTS).

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) bd.

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.

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) bd.

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) bd. 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.

Interactions with Other Medicines

Most medicine interaction studies with saquinavir have been completed with unboosted saquinavir film-coated tablets (INVIRASE) and saquinavir soft gel capsules (FORTOVASE). A limited number of studies have been completed with boosted saquinavir.

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-glycoprotein (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.

Ritonavir can affect the pharmacokinetics of other medicines because it is a potent inhibitor of CYP3A4 and P-gp. Therefore, when saquinavir is co-administered with ritonavir (boosted INVIRASE), consideration should be given to the potential effects of ritonavir on other medicines, such as the contraindication of flecainide and propafenone (see the Product Information for NORVIR[®]).

Based on the finding of dose-dependent prolongations of QT and PR intervals in healthy volunteers receiving boosted INVIRASE (see CONTRAINDICATIONS; PRECAUTIONS: *Cardiac Conduction and Repolarisation Abnormalities* and CLINICAL TRIALS: *Effects on Electrocardiogram*) 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, 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 boosted INVIRASE should be avoided when alternative treatment options are available. Medicines showing both pharmacokinetic interactions with boosted INVIRASE and additive effects on QT and PR interval prolongation are strictly contraindicated. Regarding the combination of boosted INVIRASE with other medicines known to prolong the QT and PR interval see CONTRAINDICATIONS and PRECAUTIONS: *Cardiac Conduction and Repolarisation Abnormalities*.

Nucleoside reverse transcriptase inhibitors (NRTIs)

Didanosine: The effects of a single dose of didanosine 400 mg on the pharmacokinetics of saquinavir in 8 healthy subjects who received saquinavir soft gel capsules (FORTOVASE) / ritonavir (1600/100 mg) daily for 2 weeks were investigated. Didanosine decreased saquinavir AUC and C_{max} approximately 30% and 25%, respectively, and had essentially no effect on C_{min} of saquinavir. These changes are of doubtful clinical significance.

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

Zalcitabine and/or Zidovudine: Concomitant use of unboosted INVIRASE with zalcitabine and/or zidovudine has been studied in adults. Pharmacokinetic data suggest that the absorption, metabolism and elimination of each of the medicines are unchanged when they are used concomitantly. No pharmacokinetic interaction studies have been completed with these agents given in combination with boosted INVIRASE.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

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

Efavirenz: Limited data support the use of efavirenz with boosted INVIRASE. No clinically relevant alterations of either saquinavir or efavirenz concentrations were noted in a study in 24 healthy subjects who received FORTOVASE/ritonavir/efavirenz (1600/200/600 mg) daily. Two additional studies in HIV patients investigated the effect of concomitant administration of efavirenz with either a twice-daily boosted regimen (INVIRASE/ritonavir (1000/100 mg), n = 32) or a once-daily boosted regimen (FORTOVASE/ritonavir (1200/100 mg), n = 35). No clinically significant alterations of either saquinavir or efavirenz concentrations were noted in either study.

INVIRASE should not be given with efavirenz as the sole PI. Co-administration of efavirenz (600 mg) and unboosted saquinavir soft gel capsules (FORTOVASE) 1200 mg tds to 12 subjects decreased saquinavir AUC by 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. Because of these results, INVIRASE should only be given in combination with efavirenz if the saquinavir blood levels are increased by the addition of other antiretroviral agents such as ritonavir.

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

HIV protease inhibitors (PIs)

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

Indinavir: Co-administration of indinavir (800 mg tds) and a single dose (600 - 1200 mg) of unboosted INVIRASE or saquinavir soft gel capsules (FORTOVASE) in 6 healthy volunteers resulted in a 4.6 - 7.2-fold increase in plasma saquinavir AUC₀₋₂₄. Indinavir plasma concentrations remained unchanged.

The administration of low dose ritonavir increases the concentration of indinavir, which 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.

Lopinavir/ritonavir: The pharmacokinetic parameters of saquinavir, ritonavir and lopinavir have been investigated in HIV-infected patients treated with either saquinavir /ritonavir (1000/100 mg) bd in combination with two or three NRTIs (n=32) or saquinavir (1000 mg bd) and the fixed combination of lopinavir/ritonavir (400/100 mg) bd (n=45). Lopinavir did not alter the pharmacokinetics of boosted saquinavir. Steady-state saquinavir AUC₀₋₁₂ were 15130 and 16977 ng·h/ml, C_{max} 2410 and 2300 ng/ml and C_{min} 427 and 543 ng/ml in patients with and without lopinavir, respectively. The ritonavir exposure was significantly lower in patients taking lopinavir but its effectiveness as a boosting agent was not modified. Concentrations of lopinavir did not appear to be affected when lopinavir/ritonavir and saquinavir are combined, based on historical comparison with lopinavir/ritonavir alone. No dose adjustment is required when boosted INVIRASE is combined with lopinavir.

Use lopinavir/ritonavir with caution as additive effects on QT and/or PR interval prolongation may occur with ritonavir-boosted Invirase (see CONTRAINDICATIONS and PRECAUTIONS: *Cardiac Conduction and Repolarisation Abnormalities*).

Nelfinavir: The effect of multiple dose boosted INVIRASE/ritonavir (1000/100 mg) bd on the steady-state pharmacokinetics of nelfinavir (1250 mg bd) was evaluated in 12 HIV-infected patients. The geometric mean ratios of nelfinavir AUC_{0-12h} and C_{max} in the presence and absence of boosted INVIRASE was 0.94 (90% CI: 0.72 to 1.22) and 0.95 (90% CI: 0.77 to 1.16) respectively. The nelfinavir M8 metabolite AUC_{0-12h} and C_{max} were increased by 2.25-fold (90% CI: 1.47 to 3.44) and 1.74-fold (90% CI: 1.25 to 2.40) respectively, in the presence of boosted INVIRASE but did not alter the safety profile of nelfinavir.

The effect of multiple dose nelfinavir (1250 mg bd) on the steady-state pharmacokinetics of INVIRASE/ritonavir (1000/100 mg) bd was evaluated in 12 HIV-infected patients. The geometric mean ratios of saquinavir AUC_{0-12h} and C_{max} in the presence and absence of nelfinavir were 1.13 (90% CI: 0.73 to 1.74) and 1.09 (90% CI: 0.73 to 1.61) respectively.

Boosted INVIRASE combined with nelfinavir administered to 24 HIV-infected patients for a short treatment duration of 7 days was tolerated.

Ritonavir: The recommended dose of ritonavir with boosted INVIRASE is 100 mg bd (1000 mg INVIRASE bd). 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.

Ritonavir extensively inhibits the metabolism of saquinavir resulting in greatly increased saquinavir plasma concentrations. Saquinavir steady-state AUC_{0-24} and C_{max} values obtained from 10 patients, who received INVIRASE 600 mg tds, were 2598 ng·h/mL and 197 ng/mL, respectively.

INVIRASE, given at a dose of 1000 mg bd in combination with ritonavir 100 mg bd resulted in steady-state saquinavir plasma concentrations as follows (n = 24): AUC_{0-24} 29214 ng·h/mL, C_{max} 2623 ng/mL and C_{min} 371 ng/mL.

In HIV-infected patients, saquinavir soft gel capsules (FORTOVASE) or INVIRASE, given in combination with ritonavir at doses of 1000/100 mg bd, provide saquinavir systemic exposures, over a 24-hour period, similar to, or greater than, those achieved with FORTOVASE 1200 mg tds.

Saquinavir has not been shown to alter the pharmacokinetics of ritonavir following single or multiple oral doses in healthy volunteers.

Tipranavir: Concomitant use of saquinavir/ritonavir with tipranavir in a dual-boosted regimen resulted in a significant decrease in plasma concentrations of saquinavir. The clinical relevance of this reduction has not been established, therefore, the co-administration of boosted INVIRASE with tipranavir is not recommended. Currently, there are no safety and efficacy data available from the use of this combination.

HIV fusion inhibitors

Enfuvirtide: No clinically significant interaction was noted from a study in 12 HIV patients who received enfuvirtide concomitantly with saquinavir soft gel capsules (FORTOVASE) / ritonavir (1000/100 mg) bd.

Antiarrhythmics

Bepridil, systemic lignocaine, quinidine: Concentrations of these medicines may be increased when co-administered with boosted INVIRASE. These anti-arrhythmics are contraindicated in combination with boosted INVIRASE due to potentially life threatening cardiac arrhythmia (see CONTRAINDICATIONS and PRECAUTIONS: *Cardiac Conduction and Repolarisation Abnormalities*).

Amiodarone, flecainide and propafenone: Concentrations of these medicines may be increased when co-administered with boosted INVIRASE. Due to a potential for life-threatening cardiac arrhythmia, amiodarone, flecainide and propafenone are contraindicated with boosted INVIRASE (see CONTRAINDICATIONS).

Anticoagulants

Warfarin: Concentrations of warfarin may be affected. It is recommended that the International Normalised Ratio (INR) be monitored if warfarin is given with boosted INVIRASE.

Anticonvulsants

Carbamazepine, phenobarbital, phenytoin: The interaction between boosted INVIRASE and these medicines has not been evaluated. These medicines will induce CYP3A4 and may decrease saquinavir concentrations with INVIRASE therapy.

Antidepressants

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

Nefazodone: Will inhibit CYP3A4 and may increase saquinavir concentrations. If nefazodone is used concomitantly with INVIRASE, monitoring for saquinavir toxicity is recommended.

Trazodone: Concomitant use of trazodone and boosted INVIRASE may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. Trazodone is contraindicated in combination with boosted INVIRASE due to potentially life threatening cardiac arrhythmia (see CONTRAINDICATIONS and PRECAUTIONS: *Cardiac Conduction and Repolarisation Abnormalities*).

Antihistamines

Terfenadine, astemizole: Co-administration of terfenadine and unboosted saquinavir soft gel capsules (FORTOVASE) leads to an increase in plasma terfenadine exposure (AUC) associated with a prolongation of the QTc interval. Hence, terfenadine is contraindicated in patients receiving boosted INVIRASE. As similar interactions are likely, boosted INVIRASE must not be administered with astemizole (see CONTRAINDICATIONS).

Anti-infectives

Clarithromycin: The interaction between boosted INVIRASE and clarithromycin has not been evaluated. Co-administration of clarithromycin (500 mg bd) and saquinavir soft gel capsules (FORTOVASE) (1200 mg tds) to 12 healthy volunteers resulted in steady-state saquinavir AUC and C_{max} values which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two medicines are co-administered for a limited time at the doses studied.

Erythromycin: The interaction between boosted INVIRASE and erythromycin has not been evaluated. Co-administration of erythromycin (250 mg daily) and saquinavir soft gel capsules (FORTOVASE) (1200 mg tds) to 22 HIV-infected patients resulted in steady-state saquinavir AUC and C_{max} values which were 99% and 106% higher than those seen with saquinavir alone. No dose adjustment is required when the two medicines are co-administered. Use erythromycin with caution as additive effects on QT and/or PR interval prolongation may occur with boosted INVIRASE (see CONTRAINDICATIONS and PRECAUTIONS: *Cardiac Conduction and Repolarisation Abnormalities*).

Streptogramin antibiotics (e.g. quinupristin/dalfopristin): Streptogramin antibiotics will inhibit CYP3A4 and may increase saquinavir concentrations after administration of boosted INVIRASE. If these medicines are used concomitantly with boosted INVIRASE, monitoring for saquinavir toxicity is recommended.

Antifungals

Ketoconazole: Data from a drug-drug interaction study involving 200 mg/day ketoconazole and INVIRASE/ritonavir (1000/100 mg) bd in 20 healthy subjects indicated that C_{max} and AUC_{0-12h} of

both saquinavir and ritonavir at steady-state are not altered. This indicates that no dose adjustment for either INVIRASE or ritonavir is required when co-administered with ≤ 200 mg ketoconazole.

The effect of INVIRASE/ritonavir (1000/100 mg) bd on the pharmacokinetics of ketoconazole (200 mg/day) was studied in 12 healthy subjects. The C_{\max} and AUC_{0-24h} of ketoconazole at steady-state increased by 45% (90% CI: 32% to 59%) and 168% (90% CI: 146% to 193%) respectively, in the presence of INVIRASE/ritonavir (1000/100 mg) bd. These results should be taken into account when dosing ketoconazole with boosted INVIRASE. Hence, high doses of ketoconazole (> 200 mg/day) are not recommended.

Itraconazole: The interaction between boosted INVIRASE and itraconazole has not been evaluated. Itraconazole is a moderately potent inhibitor of CYP3A4, therefore if itraconazole is used concomitantly with INVIRASE, monitoring for saquinavir toxicity is recommended.

Fluconazole/miconazole: No specific interaction studies with either of these medicines have been performed. Fluconazole and miconazole, both CYP3A4 inhibitors, may increase plasma concentrations of saquinavir, therefore, if these medicines are used concomitantly with INVIRASE, monitoring for saquinavir toxicity is recommended.

Antimycobacterials

Rifabutin: Unboosted INVIRASE, when used in a combination regimen with other ART, should not be administered concurrently with rifabutin, as co-administration results in significantly reduced plasma concentrations of saquinavir.

The effect of multiple dose rifabutin on the pharmacokinetics of INVIRASE/ritonavir (1000/100 mg bd) was assessed in 25 healthy volunteers. Rifabutin appeared to slightly reduce the AUC_{0-12hr} and C_{\max} of saquinavir by 13% (90% CI: -31% to 9%) and 15% (90% CI: -32% to 7%), respectively, for healthy volunteers receiving rifabutin 150 mg once every three days (q3d) with INVIRASE/ritonavir (1000/100 mg bd). No effect of rifabutin on ritonavir AUC_{0-12hr} (90% CI: -10% to 9%) and C_{\max} (90% CI: -8% to 7%) were observed. No dose adjustment of INVIRASE/ritonavir (1000/100 mg bd) is required if boosted INVIRASE is administered in combination with rifabutin.

The effect of multiple dose INVIRASE/ritonavir (1000/100 mg bd) on the pharmacokinetics of rifabutin was evaluated in 2 groups of healthy volunteers. In the first group (n=14), rifabutin 150 mg q3d was co-administered with INVIRASE /ritonavir (1000/100 mg bd); the AUC_{0-72hr} and C_{\max} of the active moiety (rifabutin + 25-O-desacetyl rifabutin) increased by 134% (90% CI: 109% to 162%) and 130% (90% CI: 98% to 167%), respectively, in comparison to those when rifabutin 150 mg daily was administered alone. Whereas, the exposure of rifabutin increased by 53% (90% CI: 36% to 73%) for AUC_{0-72hr} and by 86% (90% CI: 57% to 119%) for C_{\max} . In the second group (n=13), rifabutin 150 mg q4d was co-administered with INVIRASE/ritonavir (1000/100 mg bd); the AUC_{0-96hr} and C_{\max} of the active moiety increased by 60% (90% CI: 43% to 79%) and 111% (90% CI: 75% to 153%), respectively, in comparison to those when rifabutin 150 mg daily was administered alone. In this second group, the exposure of rifabutin was not affected for AUC_{0-96hr} (90% CI: -10% to 13%) and increased by 68% (90% CI: 38% to 105%) for C_{\max} .

Hence, the recommended dose of rifabutin is 150 mg every 4 days (q4d) when used in combination with INVIRASE/ritonavir (1000/100 mg bd). Monitoring of neutropenia and liver enzyme levels is recommended for patients receiving boosted INVIRASE (1000/100 mg bd) and 150mg rifabutin (q4d).

Based on extrapolation from existing data, twice weekly dosing of rifabutin (e.g. Monday, Thursday) is not recommended with INVIRASE/ritonavir (1000/100 mg bd) as this would lead to pharmacokinetic exposure of rifabutin active moiety approximating that achieved at 300 mg rifabutin daily which may lead to a higher incidence or severity of rifabutin associated adverse events.

Rifampicin: Rifampicin should not be administered in patients taking boosted INVIRASE as part of an ART regimen due to the risk of severe hepatocellular toxicity observed in a drug-drug interaction study in healthy volunteers (see CONTRAINDICATIONS and ADVERSE EFFECTS: *Clinical Trials*).

A study in 20 HIV patients with tuberculosis who were receiving saquinavir soft gel capsules (FORTOVASE) / ritonavir (1600/200 mg) daily, demonstrated that rifampicin reduced the AUC of saquinavir by approximately 50%. However, observed concentrations of saquinavir were generally within the therapeutic range. Concentrations of saquinavir remained within the therapeutic range in 2 HIV patients with tuberculosis receiving either INVIRASE/ritonavir (1000/100mg) bd and 450 mg daily rifampicin, or INVIRASE/ritonavir (400/400 mg) bd and 600 mg daily rifampicin. In a phase I, randomised, open-label, multiple dose study involving 28 healthy volunteers, 11 of 17 (65%) healthy volunteers exposed concomitantly to rifampicin 600 mg daily and INVIRASE/ritonavir (1000/100 mg) bd developed severe hepatocellular toxicity during the 28-day study period.

Benzodiazepines

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

Midazolam:

Unboosted saquinavir: Co-administration of a single oral dose of midazolam 7.5 mg after 3 or 5 days of saquinavir soft gel capsules (FORTOVASE) 1200 mg tds, to 12 healthy volunteers in a double blind cross-over study, increased midazolam C_{max} by 235% and AUC by 514%. Saquinavir increased the elimination half-life of oral midazolam from 4.3 to 10.9 hours and the absolute bioavailability from 41% to 90%. Volunteers experienced impairment in psychomotor skills and an increase in sedative effects. When combined with intravenous midazolam (0.05 mg/kg) saquinavir decreased the clearance of midazolam by 56% and increased its elimination half-life from 4.1 to 9.5 hours.

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

Calcium channel blockers

Felodipine, nifedipine, nicardipine, diltiazem, nimodipine, verapamil, amlodipine, nisoldipine, isradipine: Concentrations of these medicines may be increased when co-administered with boosted INVIRASE. Caution is warranted and clinical monitoring of patients is recommended.

Corticosteroids

Dexamethasone: The interaction between boosted INVIRASE and dexamethasone has not been evaluated. Dexamethasone will induce CYP3A4 and may decrease saquinavir concentrations. Use with caution, INVIRASE may be less effective in patients taking these medicines concomitantly.

Fluticasone and budesonide: Ritonavir inhibits CYP3A4, by which systemically resorbed corticosteroid is usually metabolised. When administered with moderate or low dose ritonavir, increased systemic exposure has been reported with fluticasone (intranasal or by inhalation) and budesonide (oral) leading to Cushing's syndrome and adrenal suppression.

Beclomethasone: Consideration should be given to switching subjects requiring intranasal or inhaled corticosteroid therapy to beclomethasone.

Ergot derivatives

Dihydroergotamine, ergonovine, ergotamine, methylergonovine: Boosted INVIRASE is contraindicated in combination with ergot derivatives due to the potential of acute ergot toxicity (see CONTRAINDICATIONS).

Digitalis glycosides

Digoxin: Co-administration of a single oral dose of digoxin 0.5 mg after 2 weeks of INVIRASE/ritonavir (1000/100 mg) bd to 16 healthy volunteers in a cross-over study increased digoxin C_{max} by 27% and AUC_{0-72} by 49%. Caution should be exercised when boosted INVIRASE and digoxin are co-administered. The dose of digoxin should be reduced and the serum concentration of digoxin monitored.

Gastrointestinal motility agents

Cisapride: Co-administration of cisapride and boosted INVIRASE may lead to an increase in cisapride exposure (AUC) associated with a prolongation of QTc interval. Hence, cisapride is contraindicated in patients receiving boosted INVIRASE due to potentially life threatening cardiac arrhythmia (see CONTRAINDICATIONS and PRECAUTIONS: *Cardiac Conduction and Repolarisation Abnormalities*).

Histamine H2-receptor antagonists

Ranitidine: The interaction between boosted INVIRASE and ranitidine has not been evaluated. There was a statistically significant increase in saquinavir exposure when unboosted INVIRASE was dosed in the presence of both ranitidine and food, relative to saquinavir dosed with food alone. This resulted in AUC values which were 67% higher. This increase is not thought to be clinically relevant and no dose adjustment of INVIRASE is recommended.

HMG-CoA reductase inhibitors

Plasma concentrations of HMG-CoA reductase inhibitors mainly metabolised by CYP3A4, such as simvastatin and lovastatin, can increase markedly if co-administered with boosted saquinavir. Since increased concentrations of simvastatin and lovastatin can cause, in rare cases, severe adverse events such as myalgia and rhabdomyolysis, the combination of boosted INVIRASE with these medicines should not be used (see CONTRAINDICATIONS). The HMG-CoA reductase inhibitors atorvastatin and cerivastatin are also metabolised by CYP3A4 and a clinically relevant interaction of saquinavir with these medicines cannot be excluded; the lowest possible dose should be administered and the patient carefully monitored for signs/symptoms of myopathy (muscle weakness, muscle pain, rising plasma creatinine kinase levels).

Immunosuppressants

Cyclosporin, tacrolimus, rapamycin: Concentrations of these medicines may be increased when co-administered with boosted INVIRASE. Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with boosted INVIRASE.

Narcotic analgesics

Methadone: Co-administration of INVIRASE/ritonavir (1000/100 mg) bd with methadone 60 – 120 mg daily in 12 HIV negative methadone patients resulted in a 19% decrease in methadone AUC. None of the patients experienced withdrawal symptoms in this study. No dosage adjustment is required when boosted INVIRASE is combined with methadone. Use with caution as additive effects on QT and/or PR interval prolongation may occur with boosted INVIRASE (see CONTRAINDICATIONS and PRECAUTIONS: *Cardiac Conduction and Repolarisation Abnormalities*).

Neuroleptics

Pimozide: Co-administration of pimozide and boosted INVIRASE may lead to an increase in pimozide exposure (AUC) associated with additive effects on QT and/or PR interval prolongation (see CONTRAINDICATIONS and PRECAUTIONS: *Cardiac Conduction and Repolarisation Abnormalities*). Hence, pimozide is contraindicated in patients receiving boosted INVIRASE (see CONTRAINDICATIONS).

Oral contraceptives

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

Phosphodiesterase type 5 (PDE5) inhibitors

Sildenafil: The co-administration of saquinavir soft gel capsules (FORTOVASE) at steady-state (1200 mg tds) with sildenafil (100 mg single dose), a substrate of CYP3A4, resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes and priapism. Sildenafil had no effect on saquinavir pharmacokinetics. Use sildenafil with caution at reduced doses of no more than 25 mg every 48 hours with increased monitoring of adverse events when administered concomitantly with boosted INVIRASE.

Tadalafil: Concentrations of tadalafil may be increased when co-administered with boosted INVIRASE. 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 boosted INVIRASE.

Vardenafil: Concentrations of vardenafil may be increased when co-administered with boosted INVIRASE. 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 boosted INVIRASE.

Proton pump inhibitors

Concomitant administration of omeprazole (40 mg qd) and INVIRASE/ritonavir (1000/100 mg) bd to 18 healthy volunteers resulted in steady-state saquinavir AUC and C_{max} values which were 82% (90% CI: 44% to 131%) and 75% (90% CI: 38% to 123%) higher than those seen with boosted INVIRASE alone. The plasma levels of ritonavir did not change significantly after omeprazole use. No data are available on the concomitant administration of boosted INVIRASE and other pump inhibitors. If omeprazole or another proton pump inhibitor is used concomitantly with boosted INVIRASE, monitoring for potential saquinavir toxicities is recommended.

Others

The effects of chronic alcohol ingestion on saquinavir metabolism have not been studied.

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

Garlic capsules: The interaction between boosted INVIRASE and garlic capsules has not been evaluated. Co-administration of garlic capsules (dose approximately equivalent to two 4 gram cloves of garlic daily) and unboosted saquinavir 1200 mg tds to 9 healthy volunteers resulted in a decrease of the saquinavir AUC by 51% and a decrease of the mean trough levels at 8 hours post dose by 49%. Saquinavir mean C_{max} levels decreased by 54%. Therefore, patients on INVIRASE 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 (*Hypericum perforatum*): The interaction between boosted INVIRASE and St. John's wort has not been evaluated. Certain herbal products can also contain components that may inhibit or induce CYP3A4 or P-gp and can therefore lead to a change in saquinavir pharmacokinetics. Herbal preparations containing St. John's wort (*Hypericum perforatum*) should not be used while taking 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.

Medicines that are substrates of CYP3A4: Although specific studies have not been performed, co-administration of boosted INVIRASE with medicines that are mainly metabolised by the CYP3A4 pathway (e.g. dapsone, disopyramide, quinine, fentanyl and alfentanil) may result in elevated plasma concentrations of these medicines. Therefore these combinations should be given with caution.

Medicines that are substrates of P-glycoprotein (P-gp): Concomitant use of boosted INVIRASE with medicines that are substrates of P-gp (e.g. azithromycin) may lead to elevated plasma concentrations of these medicines, hence monitoring for toxicity is recommended.

Inhibitors of CYP3A4: An increase in plasma concentrations of saquinavir could occur with other compounds that are inhibitors of the CYP3A4 isoenzyme. If such medicines are used concomitantly with INVIRASE, monitoring for saquinavir toxicity may be necessary.

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 (e.g. metoclopramide) could lead to lower saquinavir plasma concentrations.

ADVERSE 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 bd) used in combination with low dose ritonavir (100 mg bd) for at least 48 weeks was studied in 311 patients. Adverse reactions (including marked laboratory abnormalities) from these pivotal studies are summarized in Table 6.

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 6: 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 ($\geq 10\%$), Common ($\geq 1\%$ and $< 10\%$)
Within each frequency grouping, adverse effects are presented in order of decreasing seriousness.

Body System	Adverse Reactions	
	Frequency of Reaction	
	Grades 3 & 4	All Grades
<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		Paresthesia, 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

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, bucca 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.

Hepato-biliary 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.

DOSAGE AND ADMINISTRATION

INVIRASE should be used only in combination with ritonavir.

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

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 PHARMACOKINETICS).

For the recommended dose and possible adverse effects of other antiretroviral agents used in combination therapy, please see the complete prescribing information for these medicines.

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 with INVIRASE should be interrupted. INVIRASE is not recommended at doses less than 600 mg tds. For combination treatment involving some other antiretrovirals (e.g. ritonavir) dose modifications of the protease inhibitors may be required since plasma levels might increase (see PRECAUTIONS: *Interactions with Other Medicines*).

For dosage instructions in special populations, please refer to PRECAUTIONS: *Hepatic Impairment, Renal Impairment, Paediatric Use and Use in Elderly Patients*.

OVERDOSAGE

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.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

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. INVIRASE tablets are available in bottles of 120.

INVIRASE tablets should be stored below 30°C.

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

Disposal of Medicines

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.

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription only medicine

NAME AND ADDRESS OF THE SPONSOR



Roche Products Pty Limited
ABN 70 000 132 865
4-10 Inman Road
Dee Why NSW 2099

Customer enquiries: 1800 233 950

TGA Approval Date: 17 Aug 2010