CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-785 / S-002
20-828 / S-020, 019
20-628 / S-023

Trade Name: Fortovase

Generic Name: (saquinavir)

Sponsor: Hoffman La Roche Inc.

Approval Date: September 9, 2005

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21-785 / S-002
20-828 / S-020, 019
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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-785/S-001 NDA 21-785/S-002
NDA 20-828/S-019 NDA 20-828/S-020
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Hoffman-La Roche
Attention: Karen H. Noh, Pharm.D.
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Noh:

Please refer to your supplemental new drug applications dated March 7, 2005, received March 9, 2005 (NDA 21-785/S-001, NDA 20-828/S-019, and NDA 20-628/S-022) and your supplemental new drug applications dated March 11, 2005, received March 14, 2005 (NDA 21-785/S-002, NDA 20-828/S-020, and NDA 20-628/S-023) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invirase® (saquinavir mesylate) capsules and Invirase® (saquinavir mesylate) film coated tablets.

We acknowledge receipt of your submissions dated August 31, 2005, and September 1, 2005.

These supplemental new drug applications provide for revisions to the Invirase labeling to reflect drug interaction information with rifampin and drug interaction information between saquinavir/ritonavir and tenofovir, fosamprenavir, lopinavir, and atazanavir.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplements NDA 21-785/S-001, 20-828/S-019, 20-628/S-022 and NDA 21-785/S-002, 20-828/S-020 and 20-628/S-023.**" Approval of these submissions by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kenny Shade, Regulatory Project Manager, at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Center for Drug Evaluation and Research

Enclosure: approved draft labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeffrey Murray
9/8/2005 11:17:38 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-785 / S-002
20-828 / S-020, 019
20-628 / S-023

APPROVED LABELING

Roche

INVIRASE®

(saquinavir mesylate)

CAPSULES and TABLETS

R_x only

WARNING

INVIRASE® (saquinavir mesylate) capsules and tablets and FORTOVASE® (saquinavir) soft gelatin capsules are not bioequivalent and cannot be used interchangeably. INVIRASE may be used only if it is combined with ritonavir, which significantly inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal to those achieved with FORTOVASE. When using saquinavir as the sole protease inhibitor in an antiviral regimen, FORTOVASE is the recommended formulation (see CLINICAL PHARMACOLOGY: Drug Interactions).

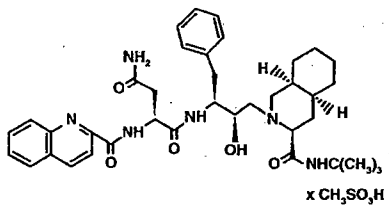
Product identification in this document includes: INVIRASE in reference to saquinavir mesylate; FORTOVASE in reference to saquinavir soft gel formulation, and saquinavir in reference to the active base.

DESCRIPTION

INVIRASE brand of saquinavir mesylate is an inhibitor of the human immunodeficiency virus (HIV) protease. INVIRASE is available as light brown and green, opaque hard gelatin capsules for oral administration in a 200-mg strength (as saquinavir free base). Each capsule also contains the inactive ingredients lactose, microcrystalline cellulose, povidone K30, sodium starch glycolate, talc, and magnesium stearate. Each capsule shell contains gelatin and water with the following dye systems: red iron oxide, yellow iron oxide, black iron oxide, FD&C Blue #2, and titanium dioxide.

INVIRASE is also available as a light orange to greyish- or brownish-orange, oval cylindrical, biconvex film coated tablet for oral administration in a 500-mg strength (as saquinavir free base). Each tablet also contains the inactive ingredients lactose, microcrystalline cellulose, povidone K30, croscarmellose sodium, and magnesium stearate. Each film coat contains hypromellose, titanium dioxide, talc, iron oxide yellow, iron oxide red, and triacetin.

The chemical name for saquinavir mesylate is N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide methanesulfonate with a molecular formula $C_{38}H_{50}N_6O_5 \cdot CH_4O_3S$ and a molecular weight of 766.96. The molecular weight of the free base is 670.86. Saquinavir mesylate has the following structural formula:



Saquinavir mesylate is a white to off-white, very fine powder with an aqueous solubility of 2.22 mg/mL at 25°C.

MICROBIOLOGY

Mechanism of Action

Saquinavir is an inhibitor of HIV protease. HIV protease is an enzyme required for the proteolytic cleavage of viral polyprotein precursors into individual functional proteins found in infectious HIV. Saquinavir is a peptide-like substrate analogue that binds to the protease active site and inhibits the activity of the enzyme. Saquinavir inhibition prevents cleavage of the viral polyproteins resulting in the formation of immature noninfectious virus particles.

Antiviral Activity

In vitro antiviral activity of saquinavir was assessed in lymphoblastoid and monocytic cell lines and in peripheral blood lymphocytes. Saquinavir inhibited HIV activity in both acutely and chronically infected cells. IC_{50} and IC_{90} values (50% and 90% inhibitory concentrations) were in the range of 1 to 30 nM and 5 to 80 nM, respectively. In the presence of 40% human serum, the mean IC_{50} of saquinavir against laboratory strain HIV-1 RF in MT4 cells was 37.7± 5nM representing a 4-fold increase in the IC_{50} value. In cell culture, saquinavir demonstrated additive to synergistic effects against HIV-1 in combination with reverse transcriptase inhibitors (didanosine, lamivudine, nevirapine, stavudine, zalcitabine and zidovudine) without enhanced cytotoxicity. Saquinavir in combination with the protease inhibitors amprenavir, atazanavir, or lopinavir resulted in synergistic antiviral activity. Saquinavir displayed antiviral activity in vitro against HIV-1 clades A-H (IC_{50} ranged from 0.9 to 2.5 nM). The IC_{50} and IC_{90} values of saquinavir against HIV-2 isolates in vitro ranged from 0.25 nM to 14.6 nM and 4.65 nM to 28.6 nM respectively.

Drug Resistance

HIV-1 mutants with reduced susceptibility to saquinavir have been selected during in vitro passage. Genotypic analyses of these isolates showed several substitutions in the HIV protease gene. Only the G48V and L90M substitutions were associated with reduced susceptibility to saquinavir, and conferred an increase in the IC_{50} value of 8- and 3-fold, respectively.

HIV-1 isolates with reduced susceptibility (≥4-fold increase in the IC_{50} value) to saquinavir emerged in some patients treated with INVIRASE. Genotypic analysis of these isolates identified resistance conferring primary mutations in the protease gene G48V and L90M, and secondary mutations L10I/R/V, I54V/L, A71V/T, G73S, V77I, V82A and I84V that contributed additional resistance to saquinavir. Forty-one isolates from 37 patients failing therapy with INVIRASE had a median decrease in susceptibility to saquinavir of 4.3-fold.

The degree of reduction in in vitro susceptibility to saquinavir of clinical isolates bearing substitutions G48V and L90M depends on the number of secondary mutations present. In general, higher levels of resistance are associated with greater number of mutations only in association with either or both of the primary mutations G48V and L90M. No data are currently available to address the development of resistance in patients receiving saquinavir/ritonavir.

Cross-resistance

Among protease inhibitors, variable crossresistance has been observed. In one clinical study, 22 HIV-1 isolates with reduced susceptibility (>4-fold increase in the IC_{50} value) to saquinavir following therapy with INVIRASE were evaluated for cross-resistance to amprenavir, indinavir, nelfinavir and ritonavir. Six of the 22 isolates (27%) remained susceptible to all 4 protease inhibitors, 12 of the 22 isolates (55%) retained susceptibility to at least one of the PIs and 4 out of the 22 isolates (18%) displayed broad cross-resistance to all PIs. Sixteen (73%) and 11 (50%) of the 22 isolates remained susceptible (<4-fold) to amprenavir and indinavir, respectively. Four of 16 (25%) and nine of 21 (43%) with available data remained susceptible to nelfinavir and ritonavir, respectively.

After treatment failure with amprenavir, cross-resistance to saquinavir was evaluated. HIV-1 isolates from 22/22 patients failing treatment with amprenavir and containing one or more mutations M46L/I, I50V, I54L, V32I, I47V, and I84V were susceptible to saquinavir.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetic properties of INVIRASE have been evaluated in healthy volunteers (n=351) and HIV-infected patients (n=270) after single- and multiple-oral doses of 25, 75, 200, and 600 mg tid and in healthy volunteers after intravenous doses of 6, 12, 36 or 72 mg (n=21). The pharmacokinetics of INVIRASE/ritonavir 400/400 mg bid and INVIRASE/ritonavir 1000/100 mg bid have also been evaluated in HIV-infected patients.

HIV-infected patients administered INVIRASE (600-mg tid) had AUC and maximum plasma concentration (C_{max}) values approximately 2-2.5 times those observed in healthy volunteers receiving the same treatment regimen.

Similar bioavailability was demonstrated when INVIRASE 500 mg FCT (2 x 500 mg) and INVIRASE 200 mg capsule (5 x 200 mg) were administered with low dose ritonavir (100 mg) under fed conditions. The ratio of mean exposures (90% confidence intervals) of tablets vs capsules were 1.10 (1.04-1.16) for $AUC_{0-\infty}$ and 1.19 (1.14-1.25) for C_{max}.

Absorption and Bioavailability in Adults

Absolute bioavailability of saquinavir administered as INVIRASE averaged 4% (CV 73%, range: 1% to 9%) in 8 healthy volunteers who received a single 600-mg dose (3 x 200 mg) of saquinavir mesylate following a high-fat breakfast (48 g protein, 60 g carbohydrate, 57 g fat; 1006 kcal). The low bioavailability is thought to be due to a combination of incomplete absorption and extensive first-pass metabolism. Following single 600-mg doses, the relative bioavailability of saquinavir as FORTOVASE compared to saquinavir administered as INVIRASE was estimated at 331% (95% CI 207% to 530%).

When administered as the sole protease inhibitor, it has been shown that FORTOVASE 1200 mg tid provides an 8-fold increase in AUC compared with INVIRASE 600 mg tid (see **Table 1**).

INVIRASE in combination with ritonavir at doses of 1000/100 mg bid or 400/400 mg bid provides saquinavir systemic exposures over a 24-hour period similar to or greater than those achieved with FORTOVASE 1200 mg tid (see **Table 1**).

Table 1 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 tid (arithmetic mean, %CV)	10	866 (62)	2598	79
FORTOVASE 1200 mg tid (arithmetic mean)	31	7249	21747	216
INVIRASE 400 mg bid + ritonavir 400 mg bid (arithmetic mean ± SD)	7	16000 ± 8000	32000	480 ± 360
INVIRASE 1000 mg bid + ritonavir 100 mg bid (geometric mean and 95% CI)	24	14607 (10218-20882)	29214	371 (245-561)
FORTOVASE 1000 mg bid + ritonavir 100 mg bid (geometric mean and 95% CI)	24	19085 (13943-26124)	38170	433 (301-622)

τ is the dosing interval (ie, 8h if tid and 12h if bid)

Food Effect

No food effect data are available for INVIRASE in combination with ritonavir.

The mean 24-hour AUC after a single 600-mg oral dose (6 x 100 mg) in healthy volunteers (n=6) was increased from 24 ng·h/mL (CV 33%), under fasting conditions, to 161 ng·h/mL (CV 35%) when INVIRASE was given following a high-fat breakfast (48 g protein, 60 g carbohydrate, 57 g fat; 1006 kcal). Saquinavir 24-hour AUC and C_{max} (n=6) following the administration of a higher calorie meal (943 kcal, 54 g fat) were on average 2 times higher than after a lower calorie, lower fat meal (355 kcal, 8 g fat). The effect of food has been shown to persist for up to 2 hours.

Saquinavir exposure was similar when FORTOVASE plus ritonavir (1000-mg/100-mg bid) were administered following a high-fat (45 g fat) or moderate-fat (20 g fat) breakfast.

Distribution in Adults

The mean steady-state volume of distribution following intravenous administration of a 12-mg dose of saquinavir (n=8) was 700 L (CV 39%), suggesting saquinavir partitions into tissues. Saquinavir was approximately 98% bound to plasma proteins over a concentration range of 15 to 700 ng/mL. In 2 patients receiving saquinavir mesylate 600 mg tid, cerebrospinal fluid concentrations were negligible when compared to concentrations from matching plasma samples.

Metabolism and Elimination in Adults

In vitro studies using human liver microsomes have shown that the metabolism of saquinavir is cytochrome P450 mediated with the specific isoenzyme, CYP3A4, responsible for more than 90% of the hepatic metabolism. Based on in vitro studies, saquinavir is rapidly metabolized to a range of mono- and di-hydroxylated inactive compounds. In a mass balance study using 600 mg ^{14}C-saquinavir mesylate (n=8), 88% and 1% of the orally administered radioactivity was recovered in feces and urine, respectively, within 5 days of dosing. In an additional 4 subjects administered 10.5 mg ^{14}C-saquinavir

intravenously, 81% and 3% of the intravenously administered radioactivity was recovered in feces and urine, respectively, within 5 days of dosing. In mass balance studies, 13% of circulating radioactivity in plasma was attributed to unchanged drug after oral administration and the remainder attributed to saquinavir metabolites. Following intravenous administration, 66% of circulating radioactivity was attributed to unchanged drug and the remainder attributed to saquinavir metabolites, suggesting that saquinavir undergoes extensive first-pass metabolism.

Systemic clearance of saquinavir was rapid, 1.14 L/h/kg (CV 12%) after intravenous doses of 6, 36, and 72 mg. The mean residence time of saquinavir was 7 hours (n=8).

Special Populations

Hepatic or Renal Impairment

Saquinavir pharmacokinetics in patients with hepatic or renal impairment has not been investigated (see **PRECAUTIONS**). Only 1% of saquinavir is excreted in the urine, so the impact of renal impairment on saquinavir elimination should be minimal.

Gender, Race, and Age

A gender difference was observed, with females showing higher saquinavir exposure than males (mean AUC increase of 56%, mean C_{max} increase of 26%), in the relative bioavailability study comparing INVIRASE 500 mg film coated tablets to the INVIRASE 200 mg capsules in combination with ritonavir. There was no evidence that age and body weight explained the gender difference in this study. A clinically significant difference in safety and efficacy between men and women has not been reported with the approved dosage regimen (saquinavir 1000-mg/ritonavir 100-mg bid).

The effect of race on the pharmacokinetics of saquinavir has not been investigated.

Pediatric Patients

The pharmacokinetics of saquinavir when administered as INVIRASE has not been sufficiently investigated in pediatric patients.

Geriatric Patients

The pharmacokinetics of saquinavir when administered as INVIRASE have not been sufficiently investigated in patients >65 years of age.

Drug Interactions (see **PRECAUTIONS: Drug Interactions**)

Several drug interaction studies have been completed with both INVIRASE and FORTOVASE. It is important to be aware that, when INVIRASE is coadministered with ritonavir, the occurrence and magnitude of drug interactions may differ from those seen with FORTOVASE when administered as the sole protease inhibitor. Because ritonavir is coadministered, prescribers should refer to the prescribing information for ritonavir regarding drug interactions associated with this drug.

Table 2 summarizes the effect of FORTOVASE on the geometric mean AUC and C_{max} of coadministered drugs. **Table 3** summarizes the effect of coadministered drugs on the geometric mean AUC and C_{max} of saquinavir.

Table 2 Effect of FORTOVASE or INVIRASE on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug	FORTOVASE or FORTOVASE/ ritonavir Dose	N	% Change for Coadministered Drug	
			AUC (95% CI)	C_{max} (95% CI)
Clarithromycin 500 mg bid x 7 days Clarithromycin 14-OH clarithromycin metabolite	1200 mg tid x 7 days	12V	 ↑45% (17-81%) ↓24% (5-40%)	 ↑39% (10-76%) ↓34% (14-50%)
Midazolam 7.5-mg oral single dose	1200 mg tid x 5 days	6V	↑514%	↑235%
Ketoconazole 400 mg once daily	1200 mg tid	12V	↔	↔
Enfuvirtide 90 mg SCq 12h (bid) for 7 days	1000/100 mg bid	12P	↔	↔
Nelfinavir 750-mg single dose	1200 mg tid x 4 days	14P	↑18% (5-33%)	↔
Rifabutin 300 mg once daily	1200 mg tid	14P	↑44%	↑45%
Ritonavir 400 mg bid x 14 days	400 mg bid x 14 days	8V	↔	↔
Sildenafil 100-mg single dose	1200 mg tid x 8 days	27V	↑210% (150-300%)	↑140% (80-230%)
Terfenadine$^{\phi}$ 60 mg bid x 11 days* Terfenadine Terfenadine acid metabolite	1200 mg tid x 4 days	12V	 ↑368% (257-514%) ↑120% (89-156%)	 ↑253% (164-373%) ↑93% (59-133%)
Efavirenz 600 mg	1200 mg tid	13V	↓12%	↓13%

↑ Denotes an average increase in exposure by the percentage indicated.
↓ Denotes an average decrease in exposure by the percentage indicated.
↔ Denotes no statistically significant change in exposure was observed.
* FORTOVASE or INVIRASE/ritonavir should not be coadministered with terfenadine (see **PRECAUTIONS: Drug Interactions**).
P Patient
V Healthy Volunteers
ϕ No longer marketed in the US.

Table 3 Effect of Coadministered Drugs on FORTOVASE or INVIRASE Pharmacokinetics

Coadministered Drug	FORTOVASE Dose	N	% Change for Saquinavir	
			AUC (95% CI)	C_{max} (95% CI)
Clarithromycin 500 mg bid x 7 days	1200 mg tid x 7 days	12V	↑177% (108-269%)	↑187% (105-300%)
Efavirenz 600 mg	1200 mg tid	13V	↓62%	↓50%
Indinavir 800 mg q8h x 2 days	1200-mg single dose	6V	↑364% (190-644%)	↑299% (138-568%)
Ketoconazole 400 mg once daily	1200 mg tid	12V	↑190%	↑171%
Nelfinavir 750 mg x 4 days	1200-mg single dose	14P	↑392% (271-553%)	↑179% (105-280%)
Rifabutin 300 mg once daily	1200 mg tid	14P	↓47%	↓39%
Ritonavir 100 mg bid	1000 mg bid†	24P	↑176%	↑153%
Ritonavir 400 mg bid x 14 days*	400 mg bid x 14 days†	8V	↑121% (7-359%)	↑64%§
Lopinavir/ritonavir Evidence from several clinical trials indicate that saquinavir concentrations achieved with saquinavir 1000 mg + lopinavir/ritonavir 400/100 mg BID are similar to those achieved following saquinavir/ritonavir 1000/100 mg BID.				

Coadministered Drug	INVIRASE or INVIRASE/Ritonavir Dose	N	% Change for Saquinavir	
			AUC (95% CI)	C_{max} (95% CI)
Atazanavir 300 mg once daily	1600 mg qd + 100 mg ritonavir qd	18P	↑60% (16-122%)	↑42% (10-84%)
Fosamprenavir 700 mg bid	1000 mg bid + 100 mg ritonavir bid	18P	↓15% (-33% to 9%)	↔
Rifabutin 150 mg every 3 days or 300 mg every 7 days	400 mg bid + 400 mg ritonavir bid	24P	↑19%	↑39%
Ritonavir 400 mg bid steady state*	400 mg bid steady state‡	7P	↑1587% (808-3034%)	↑1277% (577-2702%)
Ritonavir 100 mg bid	1000 mg bid‡	24P	↑1124%	↑1325%
Tenofovir 300 mg once daily	1000 mg bid + 100 mg ritonavir bid	18P	↔	↔

↑ Denotes an average increase in exposure by the percentage indicated.
↓ Denotes an average decrease in exposure by the percentage indicated.
* When ritonavir was combined with the same dose of either INVIRASE or FORTOVASE, actual mean plasma exposures (AUC_{12}, 18200 ng·h/mL, 20000 ng·h/mL, respectively) were not significantly different.
↔ Mean change < 10%
† Compared to standard FORTOVASE 1200 mg tid regimen (n=33).
‡ Compared to standard INVIRASE 600 mg tid regimen (n=114).
§ Did not reach statistical significance.
P Patient
V Healthy Volunteers

For information regarding clinical recommendations, see **PRECAUTIONS: Drug Interactions, Table 6.**

INDICATIONS AND USAGE

INVIRASE in combination with ritonavir and other antiretroviral agents is indicated for the treatment of HIV infection. The twice daily administration of INVIRASE in combination with ritonavir is supported by safety data from the MaxCmin 1 study (see **Table 7**) and pharmacokinetic data (see **Table 1**). The efficacy of INVIRASE with ritonavir or FORTOVASE (with or without ritonavir coadministration) has not been compared against the efficacy of antiretroviral regimens currently considered standard of care.

Description of Clinical Studies

In a randomized, double-blind clinical study (NV14256) in ZDV-experienced, HIV-infected patients, INVIRASE in combination with HIVID was shown to be superior to either INVIRASE or HIVID monotherapy in decreasing the cumulative incidence of clinical disease progression to AIDS-defining events or death. Furthermore, in a randomized study (ACTG229/NV14255), patients with advanced HIV infection with history of prolonged ZDV treatment and who were given INVIRASE 600 mg tid + ZDV + HIVID experienced greater increases in CD_4 cell counts as compared to those who received

INVIRASE + ZDV or HIVID + ZDV. It should be noted that HIV treatment regimens that were used in these initial clinical studies of INVIRASE are no longer considered standard of care.

FORTOVASE 1000 mg bid coadministered with ritonavir 100 mg bid was studied in a heterogeneous population of 148 HIV-infected patients (MaxCmin 1 study). At baseline 42 were treatment naïve and 106 were treatment experienced (of which 52 had an HIV RNA level <400 copies/mL at baseline). Results showed that 91/148 (61%) subjects achieved and/or sustained an HIV RNA level <400 copies/mL at the completion of 48 weeks.

CONTRAINDICATIONS

INVIRASE may be used only if it is combined with ritonavir, which significantly inhibits saquinavir's metabolism and provides plasma saquinavir levels at least equal to those achieved with FORTOVASE.

INVIRASE is contraindicated in patients with clinically significant hypersensitivity to saquinavir or to any of the components contained in the capsule or tablet.

INVIRASE/ritonavir should not be administered concurrently with terfenadine, cisapride, astemizole, pimozide, triazolam, midazolam or ergot derivatives. Inhibition of CYP3A4 by saquinavir could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions, such as cardiac arrhythmias or prolonged sedation (see **PRECAUTIONS: Drug Interactions**).

INVIRASE/ritonavir should not be given together with rifampin, due to the risk of severe hepatocellular toxicity if the three drugs are given together (see **PRECAUTIONS: Drug Interactions).**

INVIRASE when administered with ritonavir is contraindicated in patients with severe hepatic impairment.

INVIRASE should not be administered concurrently with drugs listed in **Table 4** (also see **PRECAUTIONS: Drug Interactions, Table 5**).

Table 4 Drugs That Are Contraindicated With INVIRASE/Ritonavir

Drug Class	**Drugs Within Class That Are Contraindicated With INVIRASE**
Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine
Antihistamines	Astemizole, terfenadine
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
Antimycobacterial Agents	Rifampin
GI Motility Agent	Cisapride
Neuroleptics	Pimozide

Sedative/Hypnotics	Triazolam, midazolam

WARNINGS

ALERT: Find out about medicines that should not be taken with INVIRASE. This statement is included on the product's bottle label.

Interaction with HMG-CoA Reductase Inhibitors

Concomitant use of INVIRASE with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including INVIRASE, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (eg, atorvastatin). Since increased concentrations of statins can, in rare cases, cause severe adverse events such as myopathy including rhabdomyolysis, this risk may be increased when HIV protease inhibitors, including saquinavir, are used in combination with these drugs.

Interaction with Rifampin

Rifampin should not be administered in patients taking ritonavir-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 **PRECAUTIONS: Drug Interactions**).

Interaction with St. John's Wort (hypericum perforatum)

Concomitant use of INVIRASE and St. John's wort (hypericum perforatum) or products containing St. John's wort is not recommended. Coadministration of protease inhibitors, including INVIRASE, with St. John's wort is expected to substantially decrease protease-inhibitor concentrations and may result in sub-optimal levels of INVIRASE and lead to loss of virologic response and possible resistance to INVIRASE or to the class of protease inhibitors.

Interaction with Garlic Capsules

Garlic capsules should not be used while taking saquinavir as the sole protease inhibitor due to the risk of decreased saquinavir plasma concentrations. No data are available for the coadministration of INVIRASE/ritonavir or FORTOVASE/ritonavir and garlic capsules.

Diabetes Mellitus and Hyperglycemia

New onset diabetes mellitus, exacerbation of preexisting diabetes mellitus and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease-inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for the treatment of these events. In some cases diabetic ketoacidosis has occurred. In those patients who discontinued protease-inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease-inhibitor therapy and these events has not been established.

PRECAUTIONS

General

INVIRASE (saquinavir mesylate) capsules and FORTOVASE (saquinavir) soft gelatin capsules are not bioequivalent and cannot be used interchangeably when used as the sole protease inhibitor. Only FORTOVASE should be used for the initiation of therapy that includes saquinavir as a sole protease inhibitor (see **DOSAGE AND ADMINISTRATION**) since FORTOVASE soft gelatin capsules provide greater bioavailability and efficacy than INVIRASE capsules.

If a serious or severe toxicity occurs during treatment with INVIRASE, INVIRASE should be interrupted until the etiology of the event is identified or the toxicity resolves. At that time, resumption of treatment with full-dose INVIRASE may be considered. For antiretroviral agents used in combination with INVIRASE, physicians should refer to the complete product information for these drugs for dose adjustment recommendations and for information regarding drug-associated adverse reactions.

Hepatic Effects

The use of INVIRASE (in combination with ritonavir) by patients with hepatic impairment has not been studied. In the absence of such studies, caution should be exercised, as increases in saquinavir levels and/or increases in liver enzymes may occur. 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.

Renal Effects

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

Hemophilia

There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors. In some patients additional factor VIII was required. In the majority of reported cases treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established.

Hyperlipidemia

Elevated cholesterol and/or triglyceride levels have been observed in some patients taking saquinavir in combination with ritonavir. Marked elevation in triglyceride levels is a risk factor for development of pancreatitis. Cholesterol and triglyceride levels should be monitored prior to initiating combination dosing regimen of FORTOVASE or INVIRASE with ritonavir, and at periodic intervals while on such therapy. In these patients, lipid disorders should be managed as clinically appropriate.

Lactose Intolerance

Each capsule contains lactose (anhydrous) 63.3 mg. This quantity should not induce specific symptoms of intolerance.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), facial wasting, peripheral wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. A causal relationship between protease-inhibitor therapy and these events has not been established and the long-term consequences are currently unknown.

Resistance/Cross-resistance

Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of INVIRASE therapy following loss of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors (see **MICROBIOLOGY**).

Information for Patients

A statement to patients and health care providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with INVIRASE.**

Patients should be informed that any change from INVIRASE to FORTOVASE or FORTOVASE to INVIRASE coadministered with a drug which inhibits its metabolism, such as ritonavir, should be made only under the supervision of a physician.

INVIRASE may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, nonprescription medication, or herbal products, particularly St. John's wort.

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 may be used only if it is combined with ritonavir, which significantly inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal to those achieved with FORTOVASE.**

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time.

Patients should be told that the long-term effects of INVIRASE are unknown at this time. They should be informed that INVIRASE therapy has not been shown to reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

Patients should be advised that INVIRASE administered with ritonavir should be taken within 2 hours after a full meal (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**). When INVIRASE is taken without food, concentrations of saquinavir in the blood are substantially reduced and may result in no antiviral activity. Patients should be advised of the importance of taking their medication every day, as prescribed, to achieve maximum benefit. Patients should not alter the dose or discontinue therapy without consulting their physician. If a dose is missed, patients should take the next dose as soon as possible. However, the patient should not double the next dose.

Laboratory Tests

Clinical chemistry tests, viral load, and CD_4 count should be performed prior to initiating INVIRASE therapy and at appropriate intervals thereafter. Elevated nonfasting triglyceride levels have been observed in patients in saquinavir trials. Triglyceride levels should be periodically monitored during therapy. For comprehensive information concerning laboratory test alterations associated with use of other antiretroviral therapies, physicians should refer to the complete product information for these drugs.

Drug Interactions

Several drug interaction studies have been completed with both INVIRASE and FORTOVASE. Observations from drug interaction studies with FORTOVASE may not be predictive for INVIRASE. Because ritonavir is coadministered, prescribers should also refer to the prescribing information for ritonavir regarding drug interactions associated with this agent.

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 (Pgp). Therefore, drugs that affect CYP3A4 and/or Pgp, may modify the pharmacokinetics of saquinavir. Similarly, saquinavir might also modify the pharmacokinetics of other drugs that are substrates for CYP3A4 or Pgp.

Drugs that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in **Table 4** under CONTRAINDICATIONS. Additional drugs that are not recommended for coadministration with INVIRASE and ritonavir are included in **Table 5**. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Drug interactions that have been established based on drug interaction studies are listed with the pharmacokinetic results in **Table 2**, which summarizes the effect of saquinavir, administered as FORTOVASE or INVIRASE, on the geometric mean AUC and C_{max} of coadministered drugs and **Table 3**, which summarizes the effect of coadministered drugs on the geometric mean AUC and C_{max} of saquinavir. Clinical dose recommendations can be found in **Table 6**. The magnitude of the interactions may be different when INVIRASE or FORTOVASE are given with ritonavir.

When coadministering INVIRASE/ritonavir with any agent having a narrow therapeutic margin, such as anticoagulants, anticonvulsants, and antiarrhythmics, special attention is warranted. With some agents, the metabolism may be induced, resulting in decreased concentrations. Examples and clinical dose recommendations can be found in **Table 6**.

Table 5 Drugs That Should Not Be Coadministered With INVIRASE/Ritonavir

Drug Class: Drug Name	Clinical Comment
Antiarrhythmics: Amiodarone, bepridil, flecainide, propafenone, quinidine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions.
Antihistamines: astemizole*, terfenadine*	CONTRAINDICATED due to potential for serious and/or life-threatening cardiac arrhythmias.
Ergot Derivatives: Dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Antimycobacterial Agents: rifampin	CONTRAINDICATED since the coadministration of this product with saquinavir in an antiretroviral regimen reduces the plasma concentrations of saquinavir. Rifampin should not be administered in patients taking ritonavir-boosted INVIRASE as part of an ART regimen due to the risk of severe hepatocellular toxicity.
Garlic Capsules	Garlic capsules should not be used while taking saquinavir (FORTOVASE) as the sole protease inhibitor due to the risk of decreased saquinavir plasma concentrations. No data are available for the coadministration of INVIRASE/ritonavir or FORTOVASE/ritonavir and garlic capsules.
GI Motility Agent: cisapride*	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	WARNING coadministration may lead to loss of virologic response and possible resistance to INVIRASE or to the class of protease inhibitors.

Drug Class: Drug Name	Clinical Comment
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	WARNING potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Sedatives/Hypnotics: triazolam, midazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

* No longer marketed in the US.

Table 6 Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (Information in the table applies to INVIRASE/ritonavir)

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Delavirdine	↑ Saquinavir Effect on delavirdine is not well established **INVIRASE/ritonavir** Interaction has not been evaluated	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz*, nevirapine	↓ Saquinavir ↓ Efavirenz **INVIRASE/ritonavir** Interaction has not been evaluated	INVIRASE should not be given as the sole protease inhibitor to patients. Appropriate doses of the combination of efavirenz or nevirapine and INVIRASE/ritonavir with respect to safety and efficacy have not been established.
HIV protease inhibitor: Atazanavir*	**INVIRASE/ritonavir** ↑ Saquinavir ↑ Ritonavir ↔ Atazanvir	No data are available on the combination of INVIRASE 1000 mg/ritonavir 100 mg bid with atazanavir 300 mg qd. Appropriate dosing

Concomitant Drug Class: **Drug Name**	**Effect on Concentration of Saquinavir or Concomitant Drug**	**Clinical Comment**
		recommendations for this combination, with respect to efficacy and safety, have not been established.
HIV protease inhibitor: Indinavir*	↑ Saquinavir Effect on indinavir is not well established **INVIRASE/ritonavir** Interaction has not been evaluated	Appropriate doses of the combination of indinavir and INVIRASE/ritonavir with respect to safety and efficacy have not been established.
HIV protease inhibitor: Nelfinavir*	↑ Saquinavir ↑ Nelfinavir **INVIRASE/ritonavir** Interaction has not been evaluated	Saquinavir 1200 mg bid with nelfinavir 1250 mg bid results in adequate plasma drug concentrations for both protease inhibitors.
HIV protease inhibitor: Ritonavir*	↑ Saquinavir ↔ Ritonavir	The recommended dose regimen when ritonavir is given to increase saquinavir concentrations is 1000 mg saquinavir plus ritonavir 100 mg twice daily.
HIV protease inhibitor: Lopinavir/ritonavir (coformulated capsule)*	↔ Saquinavir ↔ Lopinavir ↓ Ritonavir	Evidence from several clinical trials indicates that saquinavir concentrations achieved with the saquinavir and lopinavir/ritonavir combination are similar to those achieved following saquinavir/ritonavir 1000/100 mg. The recommended dose for this combination is saquinavir 1000 mg plus lopinavir/ritonavir 400/100 mg BID.
HIV fusion inhibitor:	FORTOVASE	No clinically significant

Concomitant Drug Class: **Drug Name**	**Effect on Concentration of Saquinavir or Concomitant Drug**	**Clinical Comment**
Enfuvirtide*	Interaction has not been evaluated FORTOVASE/ritonavir ↔ enfuvirtide	interaction was noted from a study in 12 HIV patients who received enfuvirtide concomitantly with FORTOVASE/ritonavir 1000/100 mg bid. No dose adjustments are required.
Other Agents		
Antiarrhythmics: Lidocaine (systemic)	↑ Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics given with INVIRASE/ritonavir
Anticoagulant: Warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin	↓ Saquinavir Effect on carbamazepine, phenobarbital, and phenytoin is not well established **INVIRASE/ritonavir** Interaction has not been evaluated	Use with caution, saquinavir may be less effective due to decreased saquinavir plasma concentrations in patients taking these agents concomitantly.
Anti-infective: Clarithromycin*	↑ Saquinavir ↑ Clarithromycin **INVIRASE/ritonavir** Interaction has not been evaluated	No dose adjustment is required when the two drugs are coadministered for a limited time at the doses studied (clarithromycin 500 mg bid and FORTOVASE 1200 mg tid for 7 days). For patients with renal impairment, the following dosage adjustments should be considered:

Concomitant Drug Class: **Drug Name**	**Effect on Concentration of Saquinavir or Concomitant Drug**	**Clinical Comment**
		• For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} <30 mL/min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antifungal: Ketoconazole*, itraconazole	↑ Saquinavir ↔ Ketoconazole **INVIRASE/ritonavir** Interaction has not been evaluated	No dose adjustment is required when the two drugs are coadministered for a limited time at the doses studied (ketoconazole 400 mg qd and FORTOVASE 1200 mg tid). A similar increase in plasma concentrations of saquinavir could occur with itraconazole.
Antimycobacterial Rifabutin*	↓ Saquinavir ↑ Rifabutin	INVIRASE should not be given as the sole protease inhibitor to patients. Appropriate doses of the combination of rifabutin and INVIRASE/ritonavir with respect to safety and efficacy have not been established.
Benzodiazepines: Alprazolam, clorazepate, diazepam, flurazepam	↑ Benzodiazepines	Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.
Calcium channel blockers: Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil,	↑ Calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.

Concomitant Drug Class: **Drug Name**	**Effect on Concentration of Saquinavir or Concomitant Drug**	**Clinical Comment**
amlodipine, nisoldipine, isradipine		
Corticosteroid: Dexamethasone	↓ Saquinavir **INVIRASE/ritonavir** Interaction has not been evaluated	Use with caution, saquinavir may be less effective due to decreased saquinavir plasma concentrations in patients taking these agents concomitantly.
Histamine H_2-receptor antagonist: Ranitidine	↑ Saquinavir **INVIRASE/ritonavir** Interaction has not been evaluated	The increase is not thought to be clinically relevant and no dose adjustment of FORTOVASE is recommended. Appropriate doses of the combination of ranitidine and INVIRASE/ritonavir with respect to safety and efficacy have not been established.
HMG-CoA reductase inhibitors: Simvastatin, lovastatin, atorvastatin	↑ HMG-CoA reductase inhibitors	The combination of INVIRASE/ritonavir with simvastatin and lovastatin should be avoided. Use lowest possible dose of atorvastatin and with careful monitoring or consider other HMG-CoA reductase inhibitors such as pravastatin, fluvastatin and rosuvastatin.
Immunosuppressants: Cyclosporine, tacrolimus, rapamycin	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with INVIRASE/ritonavir.
Narcotic analgesic: Methadone	↓ Methadone	Dosage of methadone may need to be increased when coadministered with INVIRASE/ritonavir.
Oral contraceptives: Ethinyl estradiol	↓ Ethinyl estradiol	Alternative or additional contraceptive measures

Concomitant Drug Class: **Drug Name**	**Effect on Concentration of Saquinavir or Concomitant Drug**	**Clinical Comment**
		should be used when estrogen-based oral contraceptives and INVIRASE/ritonavir are coadministered.
PDE5 inhibitors (phosphodiesterase type 5 inhibitors): Sildenafil*, vardenafil, tadalafil	↑ Sildenafil ↔ Saquinavir ↑ Vardenafil ↑ Tadalafil	Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring of adverse events when administered concomitantly with INVIRASE/ritonavir. Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring of adverse events when administered concomitantly with INVIRASE/ritonavir. Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring of adverse events when administered concomitantly with INVIRASE/ritonavir.
Tricyclic antidepressants: Amitriptyline, imipramine	↑ Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with INVIRASE/ritonavir.

*See **CLINICAL PHARMACOLOGY: Pharmacokinetics, Table 2** and **Table 3** for magnitude of interactions

Drugs That Are Mainly Metabolized by CYP3A4

Although specific studies have not been performed, coadministration with drugs that are mainly metabolized by CYP3A4 (eg, calcium channel blockers, dapsone, disopyramide, quinine, amiodarone, quinidine, warfarin, tacrolimus, cyclosporine, ergot derivatives, pimozide, carbamazepine, fentanyl, alfentanyl, alprazolam, and triazolam) may have elevated plasma concentrations when coadministered with saquinavir; therefore, these combinations should be used with caution. Since INVIRASE is

coadministered with ritonavir, the ritonavir label should be reviewed for additional drugs that should not be coadministered.

Inducers of CYP3A4

Coadministration with compounds that are potent inducers of CYP3A4 (eg, phenobarbital, phenytoin, dexamethasone, carbamazepine) may result in decreased plasma levels of saquinavir.

Rifampin:

In a Phase I, randomized, open-label, multiple-dose study involving 28 healthy volunteers, 11 of 17 (65%) healthy volunteers exposed concomitantly to rifampin 600 mg once daily and INVIRASE 1000 mg/ritonavir 100 mg given twice daily (ritonavir-boosted INVIRASE) developed severe hepatocellar toxicity during the 28 day study period. Therefore, rifampin should not be administered concomitantly in patients taking ritonavir-boosted INVIRASE as part of an ART regimen (see **CONTRAINDICATIONS**).

Carcinogenesis, Mutagenesis and Impairment of Fertility

Carcinogenesis

Carcinogenicity studies found no indication of carcinogenic activity in rats and mice administered saquinavir for approximately 2 years. Because of limited bioavailability of saquinavir in animals, the plasma exposures (AUC values) in the respective species were approximately 29% (using rat) and 65% (using mouse) of those obtained in humans at the recommended clinical dose boosted with ritonavir.

Mutagenesis

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

Impairment of Fertility

No adverse effects were reported in fertility and reproductive performance study conducted in rats. Because of limited bioavailability of saquinavir in animals, the maximal plasma exposures achieved in rats were approximately 26% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

Pregnancy

Teratogenic Effects: Category B

Reproduction studies conducted with saquinavir have shown no embryotoxicity or teratogenicity in both rats and rabbits. Because of limited bioavailability of saquinavir in animals and/or dosing limitations, the plasma exposures (AUC values) in the respective species were approximately 29% (using rat) and 21% (using rabbit) of those obtained in humans at the recommended clinical dose

boosted with ritonavir. Clinical experience in pregnant women is limited. Saquinavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to antiretroviral medications, including INVIRASE, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. It is not known whether saquinavir is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving antiretroviral medications, including INVIRASE.**

Pediatric Use

Safety and effectiveness of INVIRASE in HIV-infected pediatric patients younger than 16 years of age have not been established.

Geriatric Use

Clinical studies of INVIRASE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be taken when dosing INVIRASE in elderly patients due to the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS (SEE PRECAUTIONS)

INVIRASE may be used only if it is combined with ritonavir, which significantly inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal to those achieved with FORTOVASE. See **Concomitant Therapy with Ritonavir Adverse Reactions** for safety information with the recommended dosage regimen.

The safety of INVIRASE was studied in patients who received the drug either alone or in combination with zidovudine and/or HIVID (zalcitabine, ddC). The majority of adverse events were of mild intensity. The most frequently reported adverse events among patients receiving INVIRASE in clinical trials (excluding those toxicities known to be associated with zidovudine and HIVID when used in combinations) were diarrhea, abdominal discomfort, and nausea.

The following grade 2 to grade 4 adverse events, (considered at least possibly related to study drug or of unknown relationship) occurred in ≥2% of patients receiving INVIRASE 600 mg tid alone or in combination with zidovudine and/or HIVID: abdominal discomfort, abdominal pain, appetite disturbances, asthenia, buccal mucosa ulceration, diarrhea, dizziness, dyspepsia, extremity numbness, headache, mucosa damage, musculoskeletal pain, myalgia, nausea, paresthesia, peripheral neuropathy, pruritus, and rash.

Rare occurrences of the following serious adverse experiences have been reported during clinical trials of INVIRASE and were considered at least possibly related to use of study drugs: confusion, ataxia, and weakness; acute myeloblastic leukemia; hemolytic anemia; attempted suicide; Stevens-Johnson syndrome; seizures; severe cutaneous reaction associated with increased liver function tests; isolated elevation of transaminases; thrombophlebitis; headache; thrombocytopenia; exacerbation of chronic liver disease with Grade 4 elevated liver function tests, jaundice, ascites, and right and left upper quadrant abdominal pain; drug fever; bullous skin eruption and polyarthritis; pancreatitis leading to death; nephrolithiasis; thrombocytopenia and intracranial hemorrhage leading to death; peripheral vasoconstriction; portal hypertension; intestinal obstruction. These events were reported from a database of >6000 patients. Over 100 patients on INVIRASE therapy have been followed for >2 years.

Concomitant Therapy with Ritonavir Adverse Reactions

In combination with ritonavir the recommended dose of INVIRASE is 1000 mg two times daily with ritonavir 100 mg two times daily in combination with other antiretroviral agents. **Table 7** lists grades 2, 3 and 4 related adverse events that occurred in ≥2% of patients receiving FORTOVASE with ritonavir (1000/100 mg bid).

Table 7 Grade 2, 3 and 4 Related Adverse Events (All Causality) Reported in ≥2% of Adult Patients in the MaxCmin 1 Study of FORTOVASE in Combination with Ritonavir 1000/100 mg bid

	FORTOVASE 1000 mg plus Ritonavir 100 mg bid (48 weeks) N=148 n(%=n/N)
Endocrine Disorders	
Diabetes mellitus/hyperglycemia	4 (2.7)
Lipodystrophy	8 (5.4)
Gastrointestinal Disorders	
Nausea	16 (10.8)
Vomiting	11 (7.4)
Diarrhea	12 (8.1)
Abdominal Pain	9 (6.1)
Constipation	3 (2.0)
General Disorders and Administration Site Conditions	
Fatigue	9 (6.1)
Fever	5 (3.4)
Musculoskeletal Disorders	
Back Pain	3 (2.0)
Respiratory Disorders	
Pneumonia	8 (5.4)
Bronchitis	4 (2.7)
Influenza	4 (2.7)
Sinusitis	4 (2.7)
Dermatological Disorders	
Rash	5 (3.4)
Pruritus	5 (3.4)
Dry lips/skin	3 (2.0)
Eczema	3 (2.0)

Includes events with unknown relationship to study drug

Additionally, adverse events that occurred in clinical trials with FORTOVASE, which are not listed above, are listed for completeness. However, due to the higher bioavailability of FORTOVASE, these adverse events might not be predictive of the safety profile of INVIRASE.

Limited experience is available from three studies investigating the pharmacokinetics of the INVIRASE 500 mg film coated tablet compared to the INVIRASE 200 mg capsule in healthy volunteers (n=140). In two of these studies saquinavir was boosted with ritonavir; in the other study, saquinavir was administered as single drug. The INVIRASE tablet and the capsule formulations were similarly tolerated. The most common adverse events were gastrointestinal disorders (such as diarrhea). Similar bioavailability was demonstrated and no clinically significant differences in

saquinavir exposures were seen. Thus, similar safety profiles are expected between the two INVIRASE formulations.

In a study investigating the drug-drug interaction of rifampin 600 mg/day daily and INVIRASE 1000 mg/ritonavir 100 mg twice daily (ritonavir-boosted INVIRASE) involving 28 healthy volunteers, 11 of 17 healthy volunteers (65%) exposed concomitantly to rifampin and ritonavir-boosted INVIRASE developed severe hepatocellular toxicity presented as increased hepatic transaminases. In some subjects, transaminases increased up to >20-fold the upper limit of normal and were associated with gastrointestinal symptoms including abdominal pain, gastritis, nausea, and vomiting. Following discontinuation of all three drugs, clinical symptoms abated and the increased hepatic transaminases normalized (see **CONTRAINDICATIONS**).

Experience from Clinical Trials with FORTOVASE

The safety of FORTOVASE was studied in more than 500 patients who received the drug either alone or in combination with other antiretroviral agents. The most frequently reported adverse events among patients receiving FORTOVASE in combination with other antiretroviral agents were diarrhea, nausea, abdominal discomfort, and dyspepsia. Clinical adverse events of at least moderate intensity, which occurred in ≥2% of patients in 2 studies with FORTOVASE, which are not listed above, are listed below by body system.

Gastrointestinal Disorders: constipation, flatulence, vomiting

Body as a Whole: appetite decreased, chest pain, fatigue

Psychological: depression, insomnia, anxiety, libido disorder

Special Senses: taste alteration

Skin and Appendages: verruca, eczema

Laboratory Abnormalities with INVIRASE

Grade 3 and 4 lab abnormalities have been observed with FORTOVASE in combination with ritonavir. At 48 weeks, lab abnormalities included increased ALT, anemia, increased AST, increased GGT, hyperglycemia, hypertriglyceridemia, increased TSH, neutropenia, raised amylase, raised LDH, and thrombocytopenia.

INVIRASE may be used only if it is combined with ritonavir, which significantly inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal to those achieved with FORTOVASE.

In studies NV14255/ACTG 229 and NV14256, the following grade 3 or grade 4 abnormalities in laboratory tests were reported among patients receiving INVIRASE 600 mg tid alone or in combination with ZDV and/or HIVID:

Biochemistry

- Incidence between <1% and 4%-hypoglycemia, hyper- or hypocalcemia, hypophosphatemia, hyper- or hypokalemia, hyper- or hyponatremia, raised serum amylase grade 3 or 4 elevations in transaminases (SGOT [AST] SGPT [ALT]), hyperbilirubinemia
- Incidence of ≤5%: hyperglycemia. Incidence of between 7% and 12%: elevated creatine phosphokinase.

Hematology

- Incidence of ≤2%: thrombocytopenia and anemia. Incidence of between 1% and 8%: leucopenia.

Additional marked lab abnormalities have been observed with FORTOVASE. These include: alkaline phosphatase (high), gamma GT (high), and triglycerides (high).

Monotherapy and Combination Studies

Other clinical adverse experiences of any intensity, at least remotely related to INVIRASE, including those in <2% of patients on arms containing INVIRASE in studies NV14255/ACTG229 and NV14256, and those in smaller clinical trials, are listed below by body system.

Body as a Whole: allergic reaction, anorexia, chest pain, edema, fatigue, fever, intoxication, parasites external, retrosternal pain, shivering, wasting syndrome, weakness generalized, weight decrease, redistribution/accumulation of body fat (see **PRECAUTIONS: Fat Redistribution**)

Cardiovascular: cyanosis, heart murmur, heart valve disorder, hypertension, hypotension, syncope, vein distended

Endocrine/Metabolic: dehydration, diabetes mellitus, dry eye syndrome, hyperglycemia, weight increase, xerophthalmia

Gastrointestinal: cheilitis, colic abdominal, constipation, dyspepsia, dysphagia, esophagitis, eructation, feces bloodstained, feces discolored, flatulence, gastralgia, gastritis, gastrointestinal inflammation, gingivitis, glossitis, hemorrhage rectum, hemorrhoids, hepatitis, hepatomegaly, hepatosplenomegaly, infectious diarrhea, jaundice, liver enzyme disorder, melena, pain pelvic, painful defecation, pancreatitis, parotid disorder, salivary glands disorder, stomach upset, stomatitis, toothache, tooth disorder, vomiting

Hematologic: anemia, bleeding dermal, microhemorrhages, neutropenia, pancytopenia, splenomegaly, thrombocytopenia

Musculoskeletal: arthralgia, arthritis, back pain, cramps leg, cramps muscle, creatine phosphokinase increased, musculoskeletal disorders, stiffness, tissue changes, trauma

Neurological: ataxia, bowel movements frequent, confusion, convulsions, dysarthria, dysesthesia, heart rate disorder, hyperesthesia, hyperreflexia, hyporeflexia, light-headed feeling, mouth dry, myelopolyradiculoneuritis, numbness face, pain facial, paresis, poliomyelitis, prickly sensation, progressive multifocal leukoencephalopathy, spasms, tremor, unconsciousness

Psychological: agitation, amnesia, anxiety, anxiety attack, depression, dreaming excessive, euphoria, hallucination, insomnia, intellectual ability reduced, irritability, lethargy, libido disorder, overdose effect, psychic disorder, psychosis, somnolence, speech disorder, suicide attempt

Reproductive System: impotence, prostate enlarged, vaginal discharge

Resistance Mechanism: abscess, angina tonsillaris, candidiasis, cellulitis, herpes simplex, herpes zoster, infection bacterial, infection mycotic, infection staphylococcal, influenza, lymphadenopathy, moniliasis, tumor

Respiratory: bronchitis, cough, dyspnea, epistaxis, hemoptysis, laryngitis, pharyngitis, pneumonia, pulmonary disease, respiratory disorder, rhinitis, sinusitis, upper respiratory tract infection

Skin and Appendages: acne, alopecia, chalazion, dermatitis, dermatitis seborrheic, eczema, erythema, folliculitis, furunculosis, hair changes, hot flushes, nail disorder, night sweats, papillomatosis, photosensitivity reaction, pigment changes skin, rash maculopapular, skin disorder, skin nodule, skin ulceration, sweating increased, urticaria, verruca, xeroderma

Special Senses: blepharitis, earache, ear pressure, eye irritation, hearing decreased, otitis, taste alteration, tinnitus, visual disturbance

Urinary System: micturition disorder, renal calculus, urinary tract bleeding, urinary tract infection

Postmarketing Experience with INVIRASE and FORTOVASE

Additional adverse events that have been observed during the postmarketing period are similar to those seen in clinical trials with INVIRASE and FORTOVASE and administration of INVIRASE and FORTOVASE in combination with ritonavir.

OVERDOSAGE

No acute toxicities or sequelae were noted in 1 patient who ingested 8 grams of INVIRASE as a single dose. The patient was treated with induction of emesis within 2 to 4 hours after ingestion. A second patient ingested 2.4 grams of INVIRASE in combination with 600 mg of ritonavir and experienced pain in the throat that lasted for 6 hours and then resolved. In an exploratory Phase II study of oral dosing with INVIRASE at 7200 mg/day (1200 mg q4h), there were no serious toxicities reported through the first 25 weeks of treatment.

DOSAGE AND ADMINISTRATION

INVIRASE (saquinavir mesylate) capsules and FORTOVASE (saquinavir) soft gelatin capsules are not bioequivalent and cannot be used interchangeably. INVIRASE may be used only if it is combined with ritonavir, because it significantly inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal to those achieved with FORTOVASE at the recommended dose of 1200 mg tid. When using saquinavir as the sole protease inhibitor in an antiretroviral regimen, FORTOVASE is the recommended formulation (see CLINICAL PHARMACOLOGY: Drug Interactions).

Adults (Over the Age of 16 Years)

- INVIRASE 1000-mg bid (5 x 200-mg capsules or 2 x 500-mg tablets) in combination with ritonavir 100-mg bid.
- Ritonavir should be taken at the same time as INVIRASE.
- INVIRASE and ritonavir should be taken within 2 hours after a meal.

Concomitant Therapy: INVIRASE with Lopinavir/Ritonavir

When administered with lopinavir/ritonavir 400/100 mg bid, the appropriate dose of INVIRASE is 1000 mg bid (with no additional ritonavir).

Monitoring of Patients

Clinical chemistry tests, viral load, and CD_4 count should be performed prior to initiating INVIRASE therapy and at appropriate intervals thereafter. For comprehensive patient monitoring recommendations for other nucleoside analogues, physicians should refer to the complete product information for these drugs.

Dose Adjustment for Combination Therapy with INVIRASE

For serious toxicities that may be associated with INVIRASE, the drug should be interrupted. INVIRASE at doses less than 1000 mg with 100 mg ritonavir bid are not recommended since lower doses have not shown antiviral activity. For recipients of combination therapy with INVIRASE and ritonavir, dose adjustments may be necessary. These adjustments should be based on the known toxicity profile of the individual agent and the pharmacokinetic interaction between saquinavir and the coadministered drug (see **PRECAUTIONS: Drug Interactions**). Physicians should refer to the complete product information for these drugs for comprehensive dose adjustment recommendations and drug-associated adverse reactions of nucleoside analogues.

HOW SUPPLIED

INVIRASE 200-mg capsules are light brown and green opaque capsules with ROCHE and 0245 imprinted on the capsule shell — bottles of 270 (NDC 0004-0245-15).

INVIRASE 500-mg film coated tablets are light orange to greyish- or brownish-orange, oval cylindrical, biconvex tablets with ROCHE and SQV 500 imprinted on the tablet face—bottles of 120 (NDC 0004-0244-51).

The capsules and tablets should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature] in tightly closed bottles.

HIVID, FORTOVASE and VERSED are registered trademarks of Hoffmann-La Roche Inc.

KALETRA is a registered trademark of Abbott Laboratories.

Capsules Manufactured by:

F. Hoffmann-La Roche Ltd., Basel, Switzerland

Tablets Manufactured by:

Roche Farma, S.A., Leganes, Spain

Distributed by:

Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

XXXXXXXX

XXXXXXXX

Revised: Month/Year

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-785 / S-002
20-828 / S-020, 019
20-628 / S-023

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20828/20628/21785	Submission Date(s): 07MAR2005
Brand Name	Invirase
Generic Name	Saquinavir
Reviewer	Kimberly L. Bergman, Pharm.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
OCPB Division	DPE III
OND Division	DAVDP
Applicant	Roche
Relevant IND(s)	41099
Submission Type; Code	Labeling Supplement/SLR 001
Formulation; Strength(s)	Invirase (saquinavir) 200 mg capsules and 500 mg film-coated tablets
Indication	Treatment HIV infection

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

Per post-marketing commitment, the Sponsor conducted clinical study BP18180 to document the effects of multiple-dose co-administration of the CYP3A4 inducer rifampicin on saquinavir/ritonavir pharmacokinetics, as well as the effect of the combination on rifampicin. In this labeling supplement, the Sponsor submitted the results of the clinical study BP18180 in healthy volunteers given rifampin 600 mg QD concomitantly with saquinavir/ritonavir (SQV/r) 1000/100 mg BID. Eleven subjects enrolled in this study developed significant elevations of liver transaminase enzymes, indicating drug induced hepatotoxicity. These findings demonstrate a potential for treatment emergent hepatotoxicity in SQV/r treated HIV infected patients receiving concomitant treatment with rifampin. This supplement provides the available data from Study 18180 and proposed labeling changes for updating the INVIRASE package insert to include results from this study, specifically to add rifampin to the CONTRAINDICATIONS section, to add the interaction with rifampin to the WARNINGS section, to expand text and describe the clinical pharmacology results for rifampin in the

DRUG INTERACTIONS section, and to describe the hepatotoxicity findings in ADVERSE REACTIONS section of the label.

In addition, due to the seriousness of this observation, the Sponsor issued a warning letter contraindicating the concomitant use of rifampin, ritonavir and saquinavir to the prescribing community by means of a Dear Health Care Provider letter dated February 7, 2005. This information has also been communicated to other Health Authorities, AIDS organizations, the World Health Organization and the manufacturers of rifampin (Sanofi-Aventis) and ritonavir (Abbott).

1.1. Recommendation

The Clinical Pharmacology and Biopharmaceutics information provided in this labeling supplement supports the Applicant's proposed labeling revisions and the conclusion that an immediate contraindication of rifampin treatment in patients receiving SQV/r as part of combination antiretroviral therapy (ART) is warranted.

1.2. Phase IV Commitments

Not applicable.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Study BP18180 is a single-center, open-label, randomized, two-arm, one-sequence, two-period crossover, multiple-dose study in 28 healthy male subjects designed to investigate the effect of multiple dose rifampin on the steady-state pharmacokinetics of film-coated saquinavir tablets combined with low dose ritonavir and vice versa. Subjects were randomized to receive study medication in one of the following two sequences as follows:

- Arm 1: Saquinavir 1000 mg/ritonavir 100 mg BID (SQV/r) for 14 days followed by SQV/r with rifampin 600 mg QD for 14 days
- Arm 2: Rifampin alone for 14 days followed by rifampin with SQV/r for 14 days

This study was discontinued prematurely on January 25th, 2005 for safety reasons (significant elevations of transaminases indicating drug induced hepatotoxicity). Seventeen (17) subjects discontinued on or after Day 15, 11 of which were due to hepatic enzyme abnormalities (2 subjects in Arm 1, 9 subjects in Arm 2).

Blood (plasma) samples were collected for the analyses of concentrations of saquinavir, ritonavir, rifampicin and desacetyl-rifampicin, but due to premature discontinuation of this study for safety reasons, full multiple-dose pharmacokinetic profiles following saquinavir, ritonavir and rifampicin planned for study Day 28 could not be characterized. Only sparse pharmacokinetic samples could be obtained after triple combination when treatment was stopped (1 to 3 sample(s) per subject).

The following is a summary of important Clinical Pharmacology findings from Study 18180:

- Following 2-week treatment with rifampicin 600 mg QD, Arm 2 subjects presented plasma concentrations of rifampicin and its main metabolite that were within the expected ranges, based on historical comparison.

- In Arm 2 subjects, sparse rifampicin plasma concentrations during triple combination were generally comparable to those seen with rifampicin alone, except in two subjects; for Subjects 11 and 4, rifampicin concentrations were approximately 2-fold and 10-fold higher, respectively, when SQV/r was added to rifampicin. A possible trend towards increased plasma concentrations of the desacetyl metabolite of rifampicin was noted.
- Subjects in Arm 1 who received 1 to 5 rifampicin doses concomitantly with saquinavir/ritonavir displayed rifampicin and desacetyl-rifampicin plasma concentrations comparable to or higher than those seen after 2-week treatment with rifampicin alone in Arm 2. For one subject (subject 17), the rifampicin concentration was substantially higher (approximately 10-fold higher compared to average 10-hour value after rifampicin alone).
- Following 2-week treatment with SQV/r 1000/100 mg BID, Arm 1 subjects presented plasma concentrations of saquinavir and ritonavir that were within expected ranges based on historical comparison and anticipated accumulation.
- Following multiple dose SQV/r to which 1 to 5 doses of rifampicin were added (Arm 1), the plasma concentrations of saquinavir and ritonavir were similar to those following SQV/r alone.
- Following multiple dose rifampicin to which 1 to 3 doses of SQV/r were added (Arm 2), plasma concentrations of both saquinavir and ritonavir were substantially lower compared to those after SQV/r alone. This is consistent with the induction of CYP3A4 by 2-week treatment with rifampicin.

In summary, SQV/r plasma concentrations are substantially decreased when SQV/r is co-administered with steady-state rifampicin, a finding consistent with CYP3A4 induction by rifampicin. Based on the limited data from Study BP18180, an increase in exposure to rifampicin and its main metabolite was observed during combination treatment with SQV/r. Data from Study BP18180 suggests that concomitant administration of rifampin with SQV/r 1000/100 mg BID can induce acute hepatotoxicity. Given the vulnerable status of the patient population likely to receive this combination of therapies, the Sponsor appropriately advised contraindication of the use of rifampin in patients taking SQV/r until more data can be obtained to provide information on dose adjustment.

2. LABELING RECOMMENDATIONS

The following changes reflect Clinical Pharmacology Reviewer recommendations to the proposed labeling.

CLINICAL PHARMACOLOGY

Labeling changes in the CLINICAL PHARMACOLOGY section proposed by the Sponsor are acceptable.

CONTRAINDICATIONS

Proposed by Sponsor:
INVIRASE/ritonavir should not be given together with rifampin, due to the risk of severe hepatocellular toxicity if the three drugs are given together (see PRECAUTIONS: Drug Interactions).

Reviewer Recommendations (in bold italics):

WARNINGS

Labeling changes in the WARNINGS section proposed by the Sponsor are acceptable.

PRECAUTIONS

Drug Interactions

Table 5 Drugs that Should Not Be Coadministered With INVIRASE/Ritonavir

Proposed by Sponsor:

Drug Class: Drug Name	Clinical comment
Antimycobacterial Agents: rifampin	CONTRAINDICATED since the coadministration of this product with saquinavir in an antiretroviral regimen reduces the plasma concentrations of saquinavir. Rifampin should not be administered in patients taking ritonavir-boosted INVIRASE as part of an ART regimen due to the risk of severe hepatocellular toxicity.

Reviewer Recommendations (in bold italics):

Drug Class: Drug Name	Clinical comment
[redacted]	[redacted]

ADVERSE REACTIONS

Labeling changes in the ADVERSE REACTIONS section proposed by the Sponsor are acceptable.

3. APPENDICES

3.1. Individual Study Reviews

3.1.1. Study BP18180

Study: BP18180

Objectives:

- Primary: to investigate the effect of co-administration of ritonavir boosted saquinavir and rifampicin on the pharmacokinetics of saquinavir, rifampicin and ritonavir at steady state and the safety and tolerability of the triple combination of saquinavir, ritonavir and rifampicin.

Study Design:

This was a single-center, open-label, randomized, two-arm, one-sequence, two-period crossover, multiple-dose study in 28 healthy male subjects. Subjects were randomized to receive study medication in one of the following two sequences as follows:

- Arm 1: Saquinavir 1000 mg/ritonavir 100 mg BID (SQV/r) for 14 days followed by SQV/r with rifampin 600 mg QD for 14 days
- Arm 2: Rifampin alone for 14 days followed by rifampin with SQV/r for 14 days

This study was discontinued prematurely on January 25, 2005 for safety reasons (significant elevations of transaminases indicating drug induced hepatotoxicity).

Formulations:

Saquinavir was administered as 2×500 mg Invirase® FCT (Roche), ritonavir as 100 mg Norvir® capsules (Abbott) and rifampicin as 2×300 mg Rifadin® capsules (Aventis).

Pharmacokinetic Measurements:

Blood (plasma) samples were collected at the following specified times for the analyses of concentrations of saquinavir, ritonavir, rifampicin and desacetyl-rifampicin:

- Arm 1: Samples for both saquinavir and ritonavir were taken at pre-dose on days 11, 12, and 13, at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14 and 24 hours post saquinavir/ritonavir dose on Day 14.
- Arm 2: Samples for rifampicin and desacetyl-rifampicin were taken at pre-dose on days 11, 12, and 13, at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 hours post rifampicin dose on Day 14.

Due to premature discontinuation of this study for safety reasons, full pharmacokinetic profiles following saquinavir, ritonavir and rifampicin planned for study Day 28 could not be characterized. Only sparse pharmacokinetic samples could be obtained after triple combination when treatment was stopped (1 to 3 sample(s) per subject).

Pharmacokinetic/Statistical Analysis:

Pharmacokinetic parameters were estimated using standard noncompartmental methods on Day 14 for saquinavir and ritonavir in Arm 1 and for rifampicin and desacetyl-rifampicin in Arm 2. Pharmacokinetic parameters were calculated using scheduled times. For the unscheduled additional pharmacokinetic samples the actual relative time was derived. Sparse plasma concentrations of saquinavir, ritonavir, rifampicin and desacetylrifampicin obtained after discontinuation of study treatment are graphically reported versus time.

In order to calculate the fold increase of rifampicin and its metabolite desacetyl-rifampicin after the triple combination compared to rifampicin alone the following was done:

- Arm 1: Individual concentration following triple combination (Arm 1) divided by the arithmetic mean concentration after rifampicin alone (Arm 2) at the same time point. Concentrations which were below limit of quantitation were set to the limit of quantitation of the respective analyte.
- Arm 2: Individual concentration following triple combination (Arm 2) divided by individual concentration after rifampicin alone (Arm 2) at the same time point. Concentrations which were below limit of quantitation were set to the limit of quantitation of the respective analyte.

Study Population Results:
Twenty-eight (28) subjects were enrolled and received at least one dose of study drug (14 subjects assigned to each arm). All subjects were male.

Eleven (11) subjects discontinued prior to Day 14:
- Subjects 006 and 016 withdrew on Days 1 and 2, respectively, due to personal reasons.
- Subject 020 withdrew on Day 3 due to malaise.
- Subjects 022, 024, 026, and 028 in Arm 1 and 021, 023, 025, and 027 in Arm 2 withdrew prior to starting triple combination therapy when the study itself was discontinued.

Seventeen (17) subjects discontinued on or after Day 15, 11 of which were due to hepatic enzyme abnormalities:
- Subjects 002, 004, 005, 008, 010, 011, 014, 018, and 019 in Arm 2 withdrew due to elevated transaminase values.
- Subjects 001 and 003 in Arm 1 withdrew from study following the transaminase rise in other subjects. Of note, these subjects had mild tranaminase elevations at the time of withdrawal.
- Subjects 007, 009, 012, 013, 015, and 017 in Arm 1 withdrew following study discontinuation.

Pharmacokinetic Results:

Rifampicin and Desacetyl-Rifampicin
Mean plasma concentration-time profiles for rifampicin and desacetyl-rifampicin following oral administration of 600 mg QD alone for 14 days (Arm 2) are presented in Figure 1. Plasma pharmacokinetic parameters for rifampicin and desacetyl-rifampicin following oral administration of 600 mg QD for 14 days (Arm 2) are summarized in Table 1. Rifampicin and desacetyl-rifampicin plasma concentrations from sparse sampling following addition of SQV/r to steady-state rifampicin (Arm 2) and following addition of rifampicin to steady-state SQV/r (Arm 1) are presented with full individual profiles in Figures 2 and 3, respectively.

Figure 1 Mean (SD) Concentrations of Rifampicin and Desacetyl-Rifampicin in Plasma Following Administration of 600 mg QD for 14 Days in Healthy Subjects.

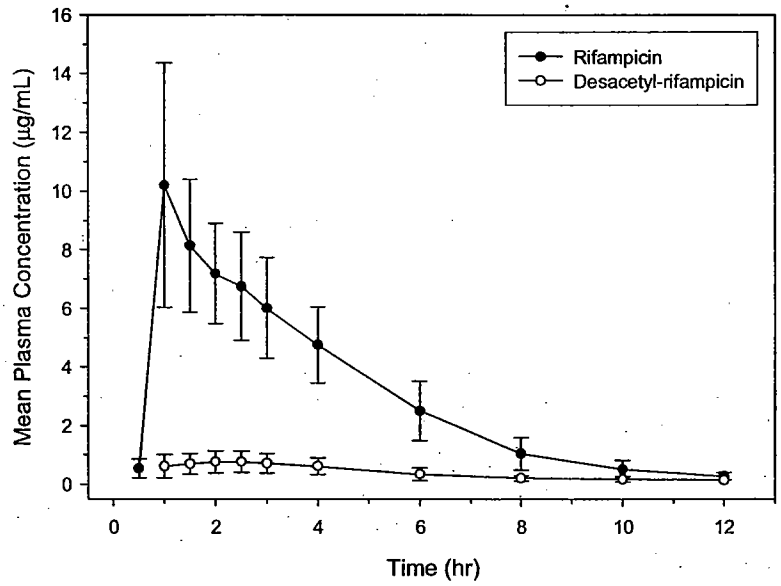
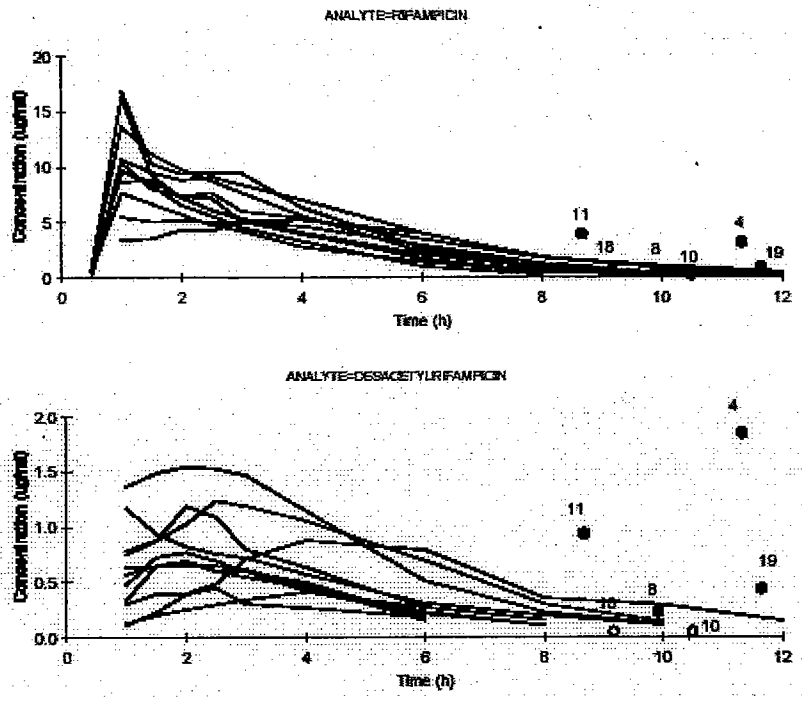


Table 1 Summary of Rifampicin and Desacetyl-Rifampicin Plasma Pharmacokinetic Parameters Following Administration of 600 mg QD for 14 Days in Healthy Subjects.

Parameter	Rifampicin	Desacetyl-Rifampicin
Cmax (µg/mL)	9.76 (40.0)	0.814 (44.5)
AUC(TAU) (µg•h/mL)	37.2 (23.2)	4.26 (40.5)
Tmax[a] (hr)	1.00 (1.00 – 4.00)	2.00 (1.00 – 4.00)
t½β (hr)	1.59 (22.0)	2.22 (39.1)

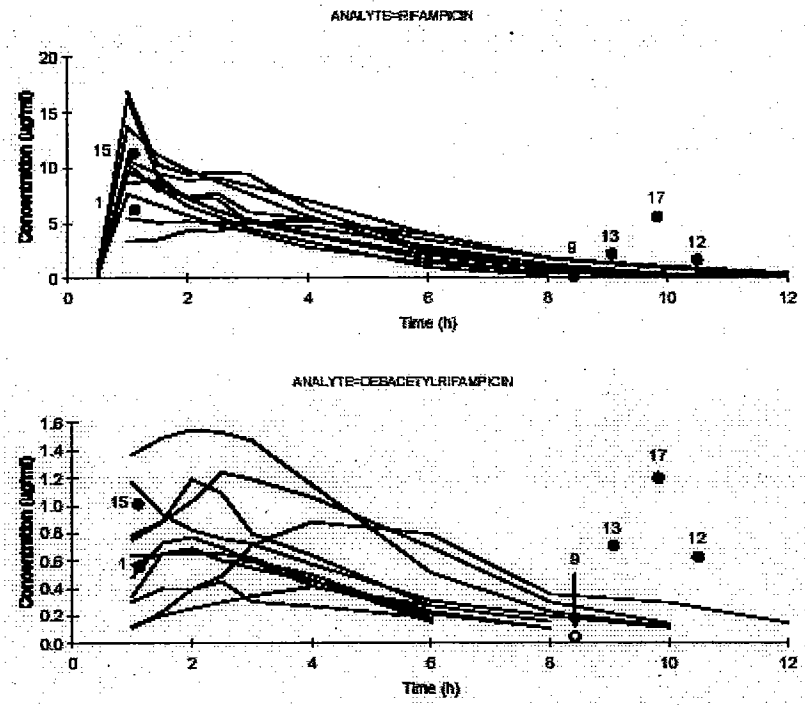
Data presented as geometric mean (CV%) unless otherwise specified.
[a] Data presented as median (minimum, maximum).

Figure 3 Sparse Rifampicin and Desacetyl-Rifampicin Plasma Concentrations (Rifampicin + SQV/r) Compared to Full Rifampicin PK Profiles (Rifampicin Alone) – Arm 2



Lines represent full PK profiles following rifampicin only.
Dots represent individual sparse sampling concentrations following rifampicin + SQV/r.
Numbers represent subject numbers.

Figure 4 Sparse Rifampicin and Desacetyl-Rifampicin Plasma Concentrations (Rifampicin + SQV/r, Arm 1) Compared to Full Rifampicin PK Profiles (Rifampicin Alone) - Arm 2



Lines represent full PK profiles following rifampicin only.
Dots represent individual sparse sampling concentrations following rifampicin + SQV/r.
Numbers represent subject numbers.

Saquinavir and Ritonavir

Mean plasma concentration-time profiles for saquinavir and ritonavir following oral administration of SQV/r 1000/100 mg BID alone for 14 days (Arm 1) are presented in Figure 5. Plasma pharmacokinetic parameters for saquinavir and ritonavir following oral administration of SQV/r 1000/100 mg BID alone for 14 days (Arm 1) are summarized in Table 2. Saquinavir and ritonavir plasma concentrations from sparse sampling following addition of rifampicin to steady-state SQV/r (Arm 1) and following addition of SQV/r to steady-state rifampicin (Arm 2) are presented with full individual profiles in Figures 6 and 7, respectively.

Figure 5 Mean (SD) Concentrations of Saquinavir and Ritonavir Following Oral Administration of SQV/r 1000/100 mg BID for 14 Days in Healthy Subjects.

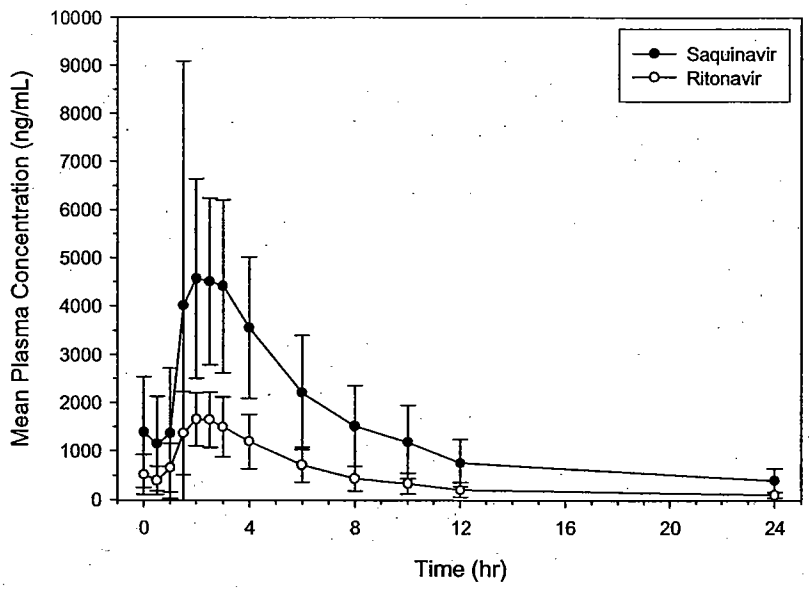
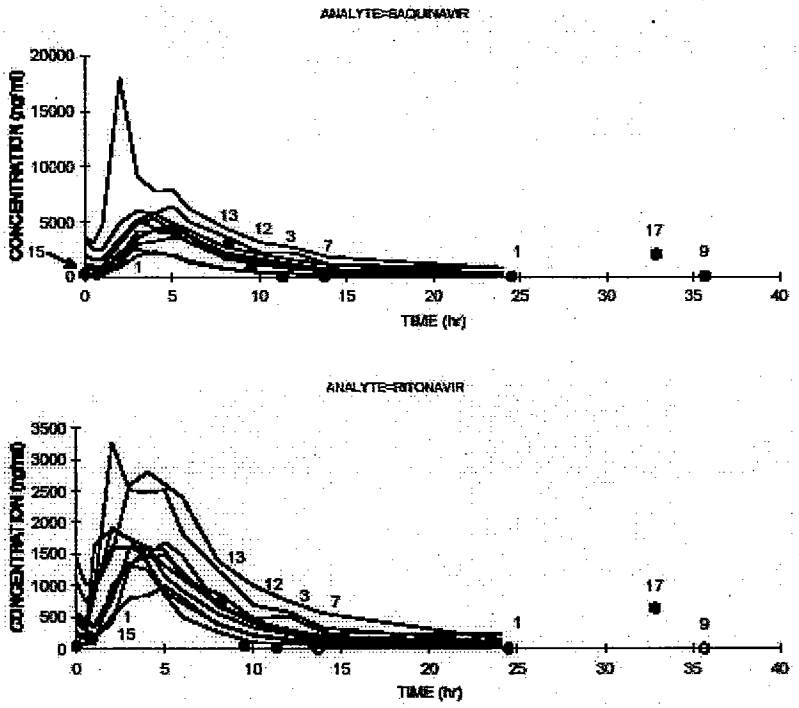


Table 2 Summary of Saquinavir and Ritonavir Plasma Pharmacokinetic Parameters Following Administration of SQV/r 1000/100 mg BID for 14 Days in Healthy Subjects.

Parameter	Saquinavir	Ritonavir
Cmax (ng/mL)	4560 (43.8)	1750 (35.6)
AUC(TAU) (ng•h/mL)	29000 (54.1)	10600 (42.1)
Tmax[a] (hr)	4.00 (3.00 – 6.00)	3.50 (2.00 – 5.00)
t½β (hr)	5.59 (17.3)	4.68 (31.1)

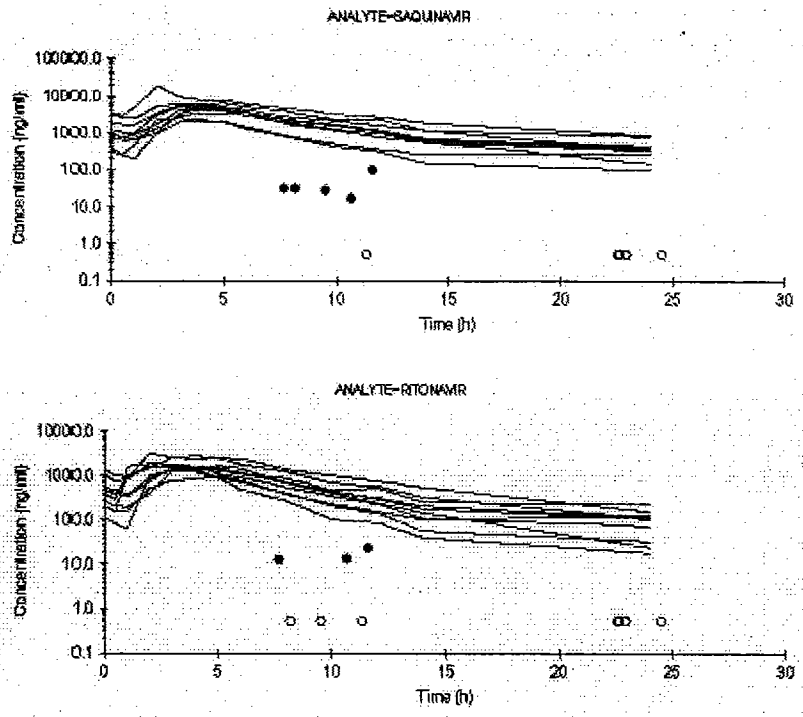
Data presented as geometric mean (CV%) unless otherwise specified.
[a] Data presented as median (minimum, maximum).

Figure 6 Sparse Saquinavir and Ritonavir Plasma Concentrations (Rifampicin + SQV/r) Compared to Full Saquinavir and Ritonavir PK Profiles (SQV/r Alone) – Arm 2



Lines represent full PK profiles for saquinavir and ritonavir, respectively.
Dots represent individual sparse sampling concentrations following rifampicin + SQV/r.
Numbers represent subject numbers.

Figure 7 Sparse Saquinavir and Ritonavir Plasma Concentrations (Rifampicin + SQV/r, Arm 1) Compared to Full Saquinavir and Ritonavir PK Profiles (SQV/r Alone) - Arm 2



Lines represent full PK profiles for saquinavir and ritonavir, respectively.
Dots represent individual sparse sampling concentrations following rifampicin + SQV/r.
Numbers represent subject numbers.

PK/Safety Correlation

Fold-change in steady-state plasma concentrations of rifampicin and desacetyl-rifampicin when co-administered with SQV/r and corresponding increases in ALT are presented in Table 3 below.

Table 3 Comparison of Increase in ALT and Fold-Change in Steady-State Plasma Concentrations of Rifampicin and Desacetyl-Rifampicin When Co-Administered with SQV/r in Healthy Subjects.

Subject	Maximum Increase in ALT (Fold × ULN)	Fold-Increase in Rifampicin Concentration	Fold-Increase in Desacetyl-Rifampicin Concentration
Arm 1			
001	5	NC	NC
003	8	NC	NC
007	1.8	NC	NC
009	0	0	NR
012	1.6	0	4
013	1.05	0	4
015	0	NC	NC
017	0	10	7
Arm 2			
002	11	NC	NC
004	70*	10	19
005	40	NC	NC
008	15	0	2
010	12*	0	BLQ
011	50	2	4
014	21	NC	NC
018	33	0	BLQ
019	67	0	3

NC Not calculable, due to no quantifiable data available within 12 hr post-dose
NR Not reported
* Lab value abnormal at the end of Day 14 (rifampicin alone)
Fold change obtained by comparing concentrations from full profiles on Day 14 versus concentrations obtained via sparse sampling following study drug discontinuation.

Assessment/Conclusion:

- Following 2-week treatment with rifampicin 600 mg QD, Arm 2 subjects presented plasma concentrations of rifampicin and its main metabolite that were within the expected ranges, based on historical comparison.
- In Arm 2 subjects, sparse rifampicin plasma concentrations during triple combination were generally comparable to those seen with rifampicin alone, except in two subjects; for Subjects 11 and 4, rifampicin concentrations were approximately 2-fold and 10-fold higher, respectively, when SQV/r was added to rifampicin. A possible trend towards increased plasma concentrations of the desacetyl metabolite of rifampicin was noted. Due to the variability in the data and limited number of quantifiable samples, these results should be interpreted with caution.
- Subjects in Arm 1 who received 1 to 5 rifampicin doses concomitantly with saquinavir/ritonavir displayed rifampicin and desacetyl-rifampicin plasma concentrations comparable to or higher than those seen after 2-week treatment with rifampicin alone in Arm 2. For one subject (subject 17), the rifampicin concentration was substantially higher (approximately 10-fold higher compared to average 10-hour value after rifampicin alone). The Sponsor theorizes this finding could be due to insufficient auto-induction with the limited number of rifampicin doses administered in Arm 1, or other metabolic mechanisms such as inhibition of rifampicin metabolism. As mentioned previously, due to the limited amount and variability of data, these results should be interpreted with caution.
- Following 2-week treatment with SQV/r 1000/100 mg BID, Arm 1 subjects presented plasma concentrations of saquinavir and ritonavir that were within expected ranges based on historical comparison and anticipated accumulation.
- Following multiple dose SQV/r to which 1 to 5 doses of rifampicin were added (Arm 1), the plasma concentrations of saquinavir and ritonavir were similar to those following SQV/r alone.
- Following multiple dose rifampicin to which 1 to 3 doses of SQV/r were added (Arm 2), plasma concentrations of both saquinavir and ritonavir were substantially lower compared to those after SQV/r alone. This is consistent with the induction of CYP3A4 by 2-week treatment with rifampicin.
- The Sponsor suggests that the limited data available suggests a possible correlation between the maximum increase in ALT and the increase in rifampicin and desacetyl-rifampicin exposure in Arm 2. The Sponsor states that in Arm 2 where subjects have been treated with rifampicin for 14 days before starting the triple combination, the increase in hepatic transaminase levels was more pronounced than in Arm 1 where subjects only received 1 to 5 rifampicin doses before the study was stopped. Although greater increases in ALT were observed in Arm 2 following 14 days of rifampin, a relationship between increased ALT and fold change in rifampin or desacetyl-rifampin plasma concentrations was not evident due to the limited amount of data available and small sample size. Fold change in rifampin and desacetyl-rifampin plasma concentrations was comparable between Arm 1 and Arm 2, whereas maximum increases in ALT were not. Due to the limited amount of data from this study, no conclusions can be drawn regarding a relationship between SQV/r or rifampin PK and hepatotoxicity.

- In summary, SQV/r plasma concentrations are substantially decreased when SQV/r is co-administered with steady-state rifampicin, a finding consistent with CYP3A4 induction by rifampicin. Based on the limited data from Study BP18180, an increase in exposure to rifampicin and its main metabolite was observed during combination treatment with SQV/r

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