INVIRASE®

(saquinavir mesylate)

CAPSULES and TABLETS

R_x only

WARNING

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, 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).

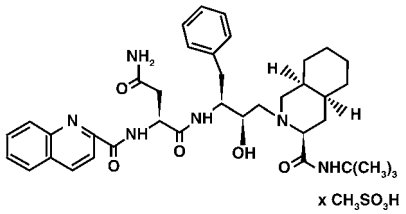
Product identification in this document includes: INVIRASE in reference to saquinavir mesylate; FORTOVASE in reference to saquinavir soft gel formulation, and saquinavir in reference to the active base.

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%
Rifampin 600 mg once daily	1200 mg tid x 14 days	14V	↓70%	↓65%
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				
400/100 mg bid, 15 days	800 mg bid, 10 day combo vs. 1200 mg tid, 5 days alone	14V	↑9.62-fold (8.05, 11.49)^	↑6.34-fold (5.32, 7.55)^
400/100 mg bid, 20 days	1200 mg bid, 10 day combo vs. 1200 mg tid, 5 days alone	10V	↑9.91-fold (8.28, 11.86)^	↑6.44 -fold (5.59, 7.41)^

Coadministered Drug	INVIRASE Dose	N	% Change for Saquinavir	
			AUC (95%CI)	C_{max} (95%CI)
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%

↑ 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.
* 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.
^ 90% CI reported
† 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.

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 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

*INVIRASE used as a sole protease inhibitor

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 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.
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.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	WARNING potential for serious reactions such as risk of myopathy including rhabdomyolysis.

Drug Class: Drug Name	Clinical Comment
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: Indinavir*	↑ Saquinavir Effect on indinavir is not well established **INVIRASE/ritonavir**	Appropriate doses of the combination of indinavir and INVIRASE/ritonavir with respect to safety and efficacy have not been established.

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
	Interaction has not been evaluated	
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 Effect on lopinavir is not well established	FORTOVASE (SQV) 800 mg bid + KALETRA produces ↑ AUC, ↑ C_{max}, and ↑ C_{min} relative to FORTOVASE 1200 mg tid (see **CLINICAL PHARMACOLOGY**, Table 3)
HIV fusion inhibitor: Enfuvirtide*	FORTOVASE Interaction has not been evaluated FORTOVASE/ritonavir ↔ enfuvirtide	No clinically significant 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

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
		(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: • 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	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

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
		mg tid). A similar increase in plasma concentrations of saquinavir could occur with itraconazole.
	INVIRASE/ritonavir Interaction has not been evaluated	
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.
Antimycobacterial Rifampin*	↓ Saquinavir ↑ Rifabutin **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 rifampin 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, amlodipine, nisoldipine, isradipine	↑ Calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	↓ Saquinavir	Use with caution, saquinavir may be less effective due to decreased saquinavir plasma concentrations in patients taking these agents concomitantly.

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
	INVIRASE/ritonavir Interaction has not been evaluated	
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 should be used when estrogen-based oral contraceptives and INVIRASE/ritonavir are coadministered.
PDE5 inhibitors (phosphodiesterase type 5 inhibitors):	↑ Sildenafil ↔ Saquinavir	Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
Sildenafil*, vardenafil, tadalafil	↑ Vardenafil ↑ Tadalafil	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.

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.

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.

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.

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Patient Information About INVIRASE (in-ver-ase)

INVIRASE®

(saquinavir mesylate) Capsules and Tablets

Generic Name: Saquinavir mesylate (sa-KWIN-a-veer mes-il-late)

Rx only

ALERT: Find out about medicines that should NOT be taken with INVIRASE. Please also read the section MEDICINES YOU SHOULD NOT TAKE WITH INVIRASE.

Please read this product information carefully before you start taking INVIRASE and each time you renew your prescription. There may be new information. Reading this information can help you take this medicine correctly. However, it is not a substitute for your doctor's advice about the safety and benefits of INVIRASE. You should talk to your doctor about INVIRASE as part of your long-term treatment plan for HIV before you start taking your medication and ask any questions you may have at regular checkups. Remember, you should remain under a doctor's care when using INVIRASE and should not change or stop your therapy without talking to your doctor first.

What is INVIRASE?

INVIRASE belongs to a class of anti-HIV medicines called protease (PRO-tee-ase) inhibitors. INVIRASE Capsules and Tablets in combination with other anti-HIV drugs are used for the treatment of HIV, the virus that causes AIDS (acquired immunodeficiency syndrome).

How does INVIRASE work?

INVIRASE fights HIV as it grows inside cells by blocking an enzyme (protease) that HIV needs to reproduce.

How is INVIRASE different from FORTOVASE ® (saquinavir)?

Both INVIRASE and FORTOVASE contain the same active ingredient—saquinavir. When INVIRASE or FORTOVASE are taken two times a day with ritonavir, a similar amount of saquinavir gets into the blood to fight HIV. However, FORTOVASE can be taken three times a day without ritonavir and the correct amount of saquinavir can get into the blood.

INVIRASE should never be taken without ritonavir. FORTOVASE may be taken without ritonavir if you are not able to tolerate even a small amount of ritonavir.

You should not substitute one for the other. If the medicine you receive does not look like the light brown and green capsule (INVIRASE) it is not the right drug. Talk to your doctor, nurse or pharmacist if you are not sure that you have the right medication.

Who should not take INVIRASE?

Anyone who has had a severe allergic reaction to INVIRASE or any of the ingredients in the capsule or tablet should not take it. The use of INVIRASE in patients under 16 years of age, over 65 years of age, or patients with severe liver problems has not been fully investigated.

How should INVIRASE/Norvir® (ritonavir) be taken?

- The recommended dosage of INVIRASE in combination with Norvir® (ritonavir) is INVIRASE 5 capsules or 2 tablets twice a day taken with 1 capsule of Norvir twice a day. In some combinations, your dose may change.
- INVIRASE must be taken along with Norvir (ritonavir).
- INVIRASE must be taken with meals or up to 2 hours after a meal—but it is easiest to remember if you take it with your meals. When INVIRASE is taken without food, the amount of INVIRASE in the blood is lower and may not fight HIV as well.
- When taking INVIRASE and other anti-HIV medicines, it is very important to follow the directions exactly and take your medication every day. If you skip doses—or take less than the prescribed dose—the medicine will not work as well, and your disease could get worse.
  - If you miss a dose, you should take the next dose as soon as possible. However, do not double the dose.

What results have been seen with INVIRASE?

INVIRASE with ritonavir has been shown to reduce the amount of virus in the blood ("viral load") and increase CD_4 (T) cells when taken with other HIV therapy.

What are the side effects of INVIRASE?

People treated with INVIRASE in combination with Norvir may have side effects. The majority of these have been described as mild. In clinical studies of patients who received saquinavir in combination with Norvir and other HIV drugs the side effects seen most often were: body fat change (5.4%), nausea (10.8%), vomiting (7.4%), diarrhea (6.8%), stomach pain (6.1%), tiredness (6.1%), and pneumonia (5.4%).

Diabetes (new onset or worsening) and increased blood sugar levels have been reported with the use of protease inhibitors. In addition, increased bleeding in patients with hemophilia has also been associated with these drugs.

When saquinavir is taken with ritonavir, some patients may experience large increases in triglyceride and lipid levels. The long-term chance of getting complications such as heart attack and stroke due to increases in triglyceride and cholesterol levels caused by protease inhibitors is not known at this time.

Changes in body fat have been seen in some patients taking anti-HIV medications. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breasts, and around the trunk. Loss of fat from the legs and arms may also happen. The cause and long-term health effects of these conditions are not known at this time.

These are not the only side effects that can occur with INVIRASE. Your doctor can discuss with you a more complete list of side effects and laboratory abnormalities that may accompany this medication.

If any side effects or unusual symptoms do occur, contact your doctor immediately. Do not stop or decrease your dose on your own. Lowering the dose may make INVIRASE less effective in fighting HIV.

Are there other medications that I should not take with INVIRASE/Norvir (ritonavir)?

There are some drugs that should not be taken with INVIRASE. Before starting therapy with INVIRASE, be sure to tell your doctor all of the medicines—prescription medications, as well as over-the-counter drugs and nutritional supplements—that you are now taking or plan to take.

MEDICINES YOU SHOULD NOT TAKE WITH INVIRASE

Drug Class	Drugs Within Class Not to Be Taken with INVIRASE/Norvir (ritonavir)
Antiarrhythmics	Pacerone® (amiodarone), Tambocor® (flecainide), Rhythmol® (propafenone), bepridil, quinidine
Antihistamines	Seldane® (terfenadine)*, Hismanal® (astemizole)*
Antimigraines	Ergot medications (eg, Wigraine® and Cafergot®)
GI motility agents	Propulsid® (cisapride)*
Sedatives, hypnotics	Versed® (midazolam), Halcion® (triazolam)
Antimycobacterial agents	Rifampin
Neuroleptics	Pimozide

* No longer sold in the US.

INVIRASE causes increased blood levels of these compounds. This can lead to serious or life-threatening reactions such as irregular heartbeat or prolonged sedation.

Taking INVIRASE with St. John’s wort (hypericum perforatum), an herbal product sold as a dietary supplement, or products containing St. John’s wort is not recommended. Talk with your doctor if you are taking or are planning to take St. John’s wort. Taking St. John’s wort may decrease INVIRASE levels and lead to increased viral load and possible resistance to INVIRASE or cross-resistance to other antiretroviral drugs.

Garlic capsules should not be used while taking FORTOVASE as the sole protease inhibitor due to the risk of decreased saquinavir in the blood. No data are available for the coadministration of FORTOVASE and Norvir with garlic capsules or INVIRASE and Norvir with garlic capsules.

Your doctor may want to change your medicine if you are taking rifampin (known as Rifadin®, Rifamate®, Rifater® or Rimactane®) or Mycobutin® (rifabutin); these drugs substantially reduce the level of INVIRASE in the blood.

The following drugs increase blood levels of INVIRASE: Norvir® (ritonavir)‡, Viracept® (nelfinavir)§, Rescriptor® (delavirdine)§‖, Nizoral® (ketoconazole), Crixivan® (indinavir)§ and Biaxin® (clarithromycin).

Talk to your doctor if you are taking lipid (cholesterol) lowering drugs and Viagra® (sildenafil citrate), Levitra® (vardenafil), and Cialis® (tadalafil).

Does INVIRASE cure HIV/AIDS?

INVIRASE does not cure AIDS, and it does not prevent you from getting other illnesses that result from advanced HIV infection. In addition, INVIRASE has not been shown to reduce the risk that you may transmit HIV to others through sexual contact or infected blood. You must continue to follow all of your doctor's recommendations for managing your illness.

What else should I discuss with my doctor?

Inform your doctor:

- If you are pregnant or become pregnant while taking INVIRASE. The effects of INVIRASE on pregnant women or unborn babies are not yet fully known. In addition, experts advise against breast-feeding if you are HIV positive, to reduce the risk of passing the virus to your baby.
- If you are taking anti-HIV medications. Your doctor may want to change one or more of your anti-HIV drugs in order to achieve the best results when you start treatment with INVIRASE.
- If you have diabetes or a family history of diabetes, or if you have hemophilia, hepatitis or other liver disease, your doctor should decide if INVIRASE is right for you.
- If you have ever taken FORTOVASE, discuss with your doctor whether INVIRASE is right for you.

How is INVIRASE supplied?

INVIRASE is available as light brown and green capsules in a 200-mg strength. INVIRASE comes in bottles of 270 capsules.

INVIRASE is also available as light orange to greyish- or brownish-orange tablets in a 500-mg strength. INVIRASE comes in bottles of 120 tablets.

How should I store INVIRASE?

INVIRASE capsules and tablets should be stored at room temperature. The bottles should be kept tightly closed.

INVIRASE has been prescribed specifically for you, and only for a particular condition. Do not use it for anything else. Do not give it to anyone else. If you think you have taken more than your prescribed dose, seek medical attention.

Keep this medication and all other medications out of the reach of children. Do not keep medicine that is out of date or that you no longer need. Be sure that if you throw any medicine away, it is out of the reach of children.

This provides only a brief summary of product information about INVIRASE. If you have any questions about INVIRASE or HIV, talk to your doctor.

† Below the amount that could be found using a standard test.

‡ Dosages greater than 100 mg twice a day of ritonavir when taken in combination with saquinavir were associated with an increase in side effects.

§ The safety and efficacy of INVIRASE in combination with these drugs has not been established. Dosage adjustments may be required.

‖ Use of this combination should be accompanied by close monitoring of liver enzymes.

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If you have any questions about INVIRASE, call toll free at 1-800-910-4687.

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