PRODUCT MONOGRAPH

PRFORTOVASE® ROCHE®
(saquinavir)

Soft Gelatin Capsules - 200 mg

HIV Protease Inhibitor / Antiretroviral Agent

Hoffmann-La Roche Limited
2455 Meadowpine Boulevard
Mississauga, Ontario
L5N 6L7

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PHARMACOLOGIC / THERAPEUTIC CLASSIFICATION

HIV Protease Inhibitor / Antiretroviral Agent

ACTION AND CLINICAL PHARMACOLOGY

Action: Saquinavir is a selective inhibitor of the human immunodeficiency virus (HIV) protease (IC_{50} 1 to 30 nM). This enzyme is required for cleavage of precursor molecules into the structural proteins of the mature virion core, and for activation of reverse transcriptase during the HIV growth cycle. Saquinavir therefore blocks these functions which are essential for the release of infectious virus.

No inhibition of human aspartyl or other proteases has been seen even at a concentration of 10μM, indicating high selectivity (at least 50,000 fold). Experiments in cell culture indicate that saquinavir produces an additive to synergistic effect against HIV in double and triple combination with various reverse transcriptase inhibitors (including zidovudine [ZDV], didanosine [ddI], zalcitabine [ddC], lamivudine [3TC], stavudine [d4T], and nevirapine), without enhanced cytotoxicity.

Two key mutations have been identified in the protease gene which contribute to genotypic saquinavir resistance (G48V and L90M). This is the same pattern of resistance which was previously reported in patients treated with INVIRASE (saquinavir mesylate, 600 mg TID). Varying degrees of cross-resistance among protease inhibitors have been observed.

Absorption: The absolute bioavailability of FORTOVASE (saquinavir) has not been assessed. However, following a single 600 mg dose, the relative bioavailability of this soft gelatin capsule (SGC) formulation was 331% (95% CI 207 to 530) of that for the same dose of saquinavir mesylate hard gelatin capsule (HGC; INVIRASE). Additionally, among HIV-infected patients receiving doses of saquinavir SGC from 400 to 1200 mg TID, a greater than proportional increase in plasma concentrations has been observed. As a result, 1200 mg TID dosing results in a steady-state area under the plasma concentration versus time curve (AUC) of 7249 ng·h/mL (following 3 weeks of treatment). This is over 8-fold higher than following multiple dosing with 600 mg TID of saquinavir HGC (866 ng·h/mL).

FORTOVASE must be taken anytime within 2 hours following a meal. Absorption and relative bioavailability are improved when the drug is taken after a high fat meal. Similarly, the presence of food increases the time required to achieve maximum concentration. The mean 12-hour AUC after a single 800 mg oral dose of FORTOVASE in healthy volunteers (n=12) was increased from 167 ng·h/mL (CV 45%), under fasting conditions, to 1120 ng·h/mL (CV 54%) when FORTOVASE was given following a standardized high fat breakfast (45g protein, 76g carbohydrate, 55g fat; 961 kcal). The mean 12-hour AUC after a single 1200 mg oral dose of FORTOVASE in healthy volunteers (n=12) was increased from 952 ng·h/mL, following a light meal (21g protein, 50g carbohydrate, 28g fat; 524 kcal), to 1388 ng·h/mL when FORTOVASE was given following a heavy breakfast (45g protein, 76g carbohydrate, 55g fat; 961 kcal).

HIV-infected patients administered 1200 mg FORTOVASE, with the instructions to take their doses after a meal or substantial snack, had AUC and maximum plasma concentration (C_{max}) values which were about twice those observed in healthy volunteers receiving the same treatment regimen (AUC=8839 vs. 4159 ng·h/mL; C_{max}=2477 vs. 1420 ng/mL).

Distribution: The mean steady-state volume of distribution following intravenous administration (n=8) of a 12 mg dose of saquinavir is 700L (CV 39%), indicating extensive partitioning into tissues. Saquinavir also shows a high degree of protein binding (~98%), over a concentration range of 15-700 ng/mL.

Metabolism and Elimination: Saquinavir is metabolized extensively via the hepatic route; renal excretion acounts for less than 4%. Hepatic metabolism is P450-mediated, primarily (>90%) by the CYP3A4 isozyme. Based on in vitro studies, saquinavir is rapidly metabolized to a range of mono- and di-hydroxylated inactive compounds. No pharmacokinetic investigations of FORTOVASE in patients with renal or hepatic insufficiency have been performed. 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).

Gender, Race and Age: The effect of gender was investigated in healthy volunteers receiving single 1200 mg doses of FORTOVASE (n=12 females; 18 males). No effect of gender was apparent on the pharmacokinetics of FORTOVASE. The influence of race on the pharmacokinetics of FORTOVASE has not been determined, and there is limited experience in both older patients (>60 years) and pediatric patients (<16 years) (see PRECAUTIONS-Effect of Gender and Race; Children and Elderly Patients).

INDICATIONS AND CLINICAL USE

FORTOVASE (saquinavir) is indicated in combination with other antiretroviral drugs for the treatment of HIV infection. This indication is based on studies of surrogate marker responses in patients who received FORTOVASE in combination with reverse transcriptase inhibitor (RTI) nucleoside analogues. It is also based on studies that showed increased saquinavir concentrations and improved antiviral activity for FORTOVASE 1200 mg TID compared to INVIRASE (saquinavir mesylate) 600 mg TID.

CONTRAINDICATIONS

FORTOVASE (saquinavir) is contraindicated in patients with clinically significant hypersensitivity to saquinavir or to any components contained in the capsule.

FORTOVASE, like other HIV protease inhibitors, increases plasma levels of terfenadine. FORTOVASE should not be administered with terfenadine, cisapride, astemizole, triazolam, midazolam, ergot derivatives, or pimozide (see PRECAUTIONS; *Drug Interactions*).

Rifampin significantly decreases the plasma concentrations of saquinavir which may lead to loss of virologic response. Therefore, FORTOVASE is contraindicated in patients receiving rifampin if FORTOVASE is used as the sole protease inhibitor. FORTOVASE/ritonavir should not be given together with rifampin, due to the risk of severe hepatocellular toxicity if the three drugs are taken together (see PRECAUTIONS; *Drug Interactions*).

FORTOVASE is contraindicated in patients with severe hepatic impairment.

FORTOVASE should not be administered concurrently with drugs listed in Table 1 (also see PRECAUTIONS; *Drug Interactions*; Table 4).

Table 1: Drugs that are Contraindicated with FORTOVASE

Drug Class	Drugs within Class that are Contraindicated with FORTOVASE
Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine
Antihistamines	Astemizole*, terfenadine*
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
Antimycobacterial Agents	Rifampin
GI Motility Agents	Cisapride*
Neuroleptics	Pimozide
Sedative/Hypnotics	Triazolam, midazolam

* No longer marketed in Canada.

WARNINGS

FORTOVASE (saquinavir) and INVIRASE (saquinavir mesylate) are not bioequivalent and cannot be used interchangeably without physician supervision.

Diabetes Mellitus and Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustment of insulin or oral hypoglycemic agents for 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.

Interaction with HMG-CoA Reductase Inhibitors

HMG-CoA reductase inhibitors (statins) may interact with protease inhibitors and increase the risk of myopathy including rhabdomyolysis. Concomitant use of protease inhibitors with lovastatin or simvastatin is not recommended. Other HMG-CoA reductase inhibitors (statins), may also interact with protease inhibitors. This warning is based on clinical reports, and on indirect evidence from studies on the cytochrome P-450 CYP3A4 metabolism pathway.

Interaction with Ritonavir

Plasma concentrations of saquinavir increase if co-administered with ritonavir (a potent inhibitor of CYP3A4). In some cases, co-administration of saquinavir and ritonavir has led to severe adverse events, mainly diabetic ketoacidosis and liver disorders, especially with pre-existing liver disease. Therefore, combination therapy of saquinavir and ritonavir should be used with caution (see PRECAUTIONS - *Drug Interactions*).

Interaction with Rifabutin and Efavirenz

If FORTOVASE is the sole protease inhibitor, it should not be administered concurrently with either rifabutin or efavirenz as co-administration results in significantly reduced plasma concentrations of saquinavir and may lead to loss of virologic response (see PRECAUTIONS: *Drug Interactions*).

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

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

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 (see PRECAUTIONS: *Drug Interactions*).

PRECAUTIONS

General

When FORTOVASE (saquinavir) is prescribed in combination with other antiretroviral therapies, physicians should refer to the appropriate Product Monographs for safety and prescribing information.

If a serious or severe toxicity occurs during treatment with FORTOVASE, treatment with the drug should be interrupted until the etiology of the event is identified or the toxicity resolves. At that time, resumption of treatment with full dose may be considered.

Considerations when Initiating FORTOVASE Therapy:

When initiating saquinavir therapy, FORTOVASE is recommended rather than INVIRASE (saquinavir mesylate; HGC) due to the greater bioavailability. For patients taking INVIRASE as the sole protease inhibitor with viral load below the limit of quantification, a switch to FORTOVASE may be considered. For patients taking INVIRASE who have not had an adequate response or who are failing therapy, a switch to FORTOVASE is not advised.

Hemophiliac Patients:

There have been reports of increased bleeding including spontaneous skin hematomas and hemarthrosis in patients with Hemophilia Type A and Type B treated with protease inhibitors. In some patients, additional Factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or re-introduced. There is no proven relationship between protease inhibitors and such bleeding, however, the frequency of bleeding episodes should be closely monitored in patients on saquinavir.

Fat Redistribution:

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

Children and Elderly Patients:

The safety and efficacy of saquinavir in HIV-infected children (younger than 16 years) has not been established. Only limited information is available in children treated with FORTOVASE and none for children treated with INVIRASE.

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

Effect of Gender and Race:

No effect of gender was observed on the pharmacokinetics of Fortovase 1200 mg in healthy volunteers. The influence of race on the pharmacokinetics of Fortovase has not been determined.

Patients with Renal or Hepatic Impairment:

Only 1% of saquinavir is excreted in the urine, so the impact of renal impairment on saquinavir elimination should be minimal. However, patients with severe renal impairment have not been studied and caution should be exercised. Caution should also be exercised when administering FORTOVASE to patients with hepatic insufficiency, since patients with baseline liver function tests >5 times the upper limit of normal were not included in clinical studies. In patients with underlying hepatitis B or C, cirrhosis, chronic alcoholism and/or other underlying liver abnormalities there have been reports of worsening liver disease and development of portal hypertension after starting saquinavir. Associated symptoms include jaundice, ascites, edema and, in some cases esophageal varices. Several of these patients died. A causal relationship between saquinavir therapy and development of portal hypertension has not been established. Increased monitoring for signs and symptoms of liver toxicity should be considered (see CONTRAINDICATIONS).

Drug Interactions:

Several drug interaction studies have been completed with FORTOVASE and INVIRASE (saquinavir mesylate hard gelatin capsules). Observations from drug interaction studies with INVIRASE may not be predictive for FORTOVASE.

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.

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

Drugs that are contraindicated or not recommended for co-administration with saquinavir are included in Table 4. Drugs with established and other potentially significant drug interactions 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.

Table 2: Effects of Saquinavir on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug	Saquinavir Dose	N	% Change for Coadministered Drug	
			AUC (95% CI)	C_{max} (95% CI)
FORTOVASE (saquinavir soft gelatin capsules):				
Nelfinavir 750 mg single dose	1200 mg tid x 4 days	14P	⇑ 18% (5-33%)	⇔
Ritonavir 400 mg bid x 14 days	400 mg bid x 14 days	8V	⇔	⇔
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%)
Ketoconazole 400 mg qd x 7 days	1200 mg tid x 7 days	12V	⇔	⇔
**Midazolam 7.5 mg single oral dose	1200 mg tid x 3-5 days	6V	⇑ 514%	⇑ 235%
Rifabutin 300 mg qd x 10 days	1200 mg tid x 10 days	14P	⇑ 44% (17-78%)	⇑ 45% (14-85%)
**Terfenadine#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 x 10 days	1200 mg q8h x 10 days	13V	⇓12%*	⇓13%*
Sildenafil 100 mg single dose	1200 mg tid steady state	27V	⇑ 210% (150-300%)	⇑ 140% (80-230%)
Enfuvirtide 90 mg SC q12h (bid) for 7 days	1000/100 mg (bid) FORTOVASE/ritonavir	12P	⇔	⇔
INVIRASE (saquinavir mesylate hard gelatin capsules):				
Zalcitabine (ddC) 0.75 mg tid x 7 days	600 mg tid x 7 days	27P	⇔	⇔
Zidovudine 200 mg tid x >7 days - zidovudine - zidovudine glucuronide metabolite	600 mg tid x >7 days	18P	 ⇔ ⇔	 ⇔ ⇔
Delavirdine 400 mg tid x 28 days	600 mg tid x 14 days	7V	⇓ 15%±16%	⇓5%
Nevirapine 200 mg bid x 21 days	600 mg tid x 7 days	23P	⇔	⇔
Ketoconazole 200 mg qd x 6 days	600 mg tid x 6 days	12V	⇔	⇓ 18% (7-28%)

⇔ Denotes no relevant change in exposure was observed
⇑ Denotes an average increase in exposure by percentage indicated
⇓ Denotes an average decrease in exposure by percentage indicated
* No confidence intervals
** FORTOVASE should not be coadministered (see **Contraindications**)
# No longer marketed in Canada
P Patient
V Healthy Volunteers

Table 3: Effect of Coadministered Drugs on Saquinavir Pharmacokinetics

Coadministered Drug	Saquinavir Dose	N	% Change for Saquinavir	
			AUC (95% CI)	C_{max} (95% CI)
FORTOVASE (saquinavir soft gelatin capsules):				
Garlic Capsules bid	1200mg tid x 3 days	9V	⇓51%	⇓54%
Grapefruit Juice quadruple strength single dose	600 mg single dose	12V	⇑54%	⇑18%
Indinavir 800 mg q8h x 2 days	800 mg single dose 1200 mg single dose	6V 6V	⇑ 620% (273-1288%) ⇑ 364% (190-644%)	⇑ 551% (320-908%) ⇑ 299% (138-568%)
Nelfinavir 750 mg tid x 4 days	1200 mg single dose	14P	⇑ 392% (271-553%)	⇑ 179% (105-280%)
Ritonavir: 200 mg bid x 14 days 300 mg bid x 14 days 400 mg bid x 14 days	800 mg bid x 14 days 800 mg bid x 14 days 800 mg bid x 14 days	8V 8V 8V	⇑ 1589% (862-2867%) ⇑ 1981% (1098-3513%) ⇑ 2158% (1193-3842%)	⇑ 757% (416-1325%) ⇑ 989% (562-1690%) ⇑ 857% (479-1481%)
Ritonavir 400 mg bid x 14 days	400 mg bid x 14 days	8V	⇑ 121% (7-359%)†	⇔†
Ritonavir 100 mg bid	1000 mg bid ◊	24P	⇑176%	⇑ 153%
Ketoconazole 400 mg qd x 7 days	1200 mg tid x 7 days	12V	⇑190% (90-343%)	⇑171% (62-356%)
Rifabutin 300 mg qd x 10 days	1200 mg tid x 10 days	14P	⇓ 47%	⇓ 31%
Rifampicin 600 mg od x 14 days	1200 mg tid x 14 days	14V	⇓70%	⇓65%
Sildenafil 100 mg single dose	1200 mg tid steady state	27V	⇔	⇔
Efavirenz 600 mg x 10 days	1200 mg q8h x 10 days	13V	⇓62%*	⇓50%*
Erythromycin 250 mg qid x 7 days	1200 mg tid x 7 days	22P	⇑ 99%	⇑ 106%
Clarithromycin 500 mg bid x 7 days	1200 mg tid x 7 days	12V	⇑ 177% (108-269%)	⇑ 187% (105-300%)
Lopinavir/ritonavir 400/100 mg bid, 15 days	800 mg bid, 10 days combo vs. 1200 mg tid, 5 days alone 800 mg bid, 10 days combo vs. 1200 mg bid, 5 days combo	14V	⇑ 9.62-fold (8.05, 11.49)° ⇑ 0.97 (0.73, 1.28)□	⇑ 6.34-fold (5.32, 7.55)° ⇑ 0.98 (0.74, 1.30)□
INVIRASE (saquinavir mesylate hard gelatin capsules):				
Zalcitabine (ddC) 0.75 mg tid x 7 days	600 mg tid x 7 days	27P	⇔	⇔
Zidovudine 200 mg tid x >7 days	600 mg tid x >7 days	20P	⇔	⇔
Indinavir 800 mg q8h	600 mg or 1200 mg single doses	6V	⇑ 6-fold	Not available
Ritonavir 400 mg bid steady state	400 mg bid steady state	7P	⇑ 1587% (808-3034%)‡	⇑ 1277% (577-2702%)‡
Delavirdine 400 mg tid x 14 days	600 mg tid x 21 days	13V	⇑ 448% (292-687%)	⇑417% (265-656%)
Nevirapine 200 mg bid x 21 days	600 mg tid x 7 days	23P	⇓ 24% (1-42%)	⇓ 28% (1-47%)
Ketoconazole 200 mg qd x 6 days	600 mg tid x 6 days	12V	⇑ 130% (58-235%)	⇑ 147% (53-298%)

Ranitidine 150 mg x two doses	600 mg single dose	12V	⇑ 67%§	⇑ 74% (16-161%)
Rifabutin 300 mg qd x 14 days	600 mg tid x 14 days	12P	⇓ 43% (29-53%)	⇓30%§
Rifabutin 150 mg every 3 days or 300 mg every 7 days	400 mg bid; 400 mg ritonavir bid	24P	⇑ 19%	⇑ 15%
Rifampicin 600 mg qd x 7 days	600 mg tid x 14 days	12V	⇓ 84% (79-88%)	⇓ 79% (68-86%)

⇔ Denotes no relevant change in exposure was observed
⇑ Denotes an average increase in exposure by percentage indicated
⇓ Denotes an average decrease in exposure by percentage indicated
* No confidence intervals
† % change for described regimen versus historical data for standard FORTOVASE 1200 mg tid regimen
‡ % change for described regimen versus historical data for standard INVIRASE 600 mg tid regimen
§ Did not reach statistical significance
P Patient
V Healthy Volunteers
♢ Compared to standard FORTOVASE 1200 mg tid regimen (n=33)
□ Ratios are for saquinavir 1200 bid + lopinavir/ritonavir vs. saquinavir 800 bid + lopinavir/ritonavir
⌀ 90% CI reported

Table 4: Drugs that are Contraindicated or not Recommended for Co-administration with Saquinavir

Drug Class: Specific Drugs	Clinical Comment
Antiarrhythmics: Amiodarone, bepridil, flecainide, propafenone, quinidine	CONTRAINDICATED due to potential for serious and/or life threatening reactions.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Not recommended due to potential for serious reactions such as risk of myopathy including rhabdomyolysis (see WARNINGS-Interaction with HMG-CoA Reductase Inhibitors).
Neuroleptic: pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as 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.
Sedatives/Hypnotics: triazolam, midazolam[a]	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Antihistamines: astemizole[b], terfenadine[a,b]	CONTRAINDICATED due to potential for serious and/or life-threatening cardiac arrhythmias
GI Motility Agent: cisapride[b]	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	Not recommended due to risk of decreased plasma concentrations of saquinavir which may lead to loss of virologic response and possible resistance to saquinavir or to the class of protease inhibitors (see WARNINGS).
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	WARNING: saquinavir should not be given as the sole protease inhibitor to patients taking efavirenz.
Antimycobacterial: Rifabutin[a] Rifampin[a]	WARNING: saquinavir should not be given as the sole protease inhibitor to patients taking rifabutin. CONTRAINDICATED if saquinavir is the sole protease inhibitor due to significantly decreased plasma concentrations of saquinavir. Rifampin should not be administered in patients taking FORTOVASE/ritonavir as part of an ART regimen due to risk of hepatocellular toxicity.
Garlic Capsules[a]	WARNING: garlic capsules should not be used when taking saquinavir as the sole protease inhibitor due to the risk of decreased saquinavir plasma concentrations.

[a] for magnitude of interactions see Tables 2 and 3.
[b] No longer marketed in Canada.

Table 5: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction[a]

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
HIV protease inhibitor: Indinavir[a]	↑ Saquinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
HIV protease inhibitor: Lopinavir/ritonavir (coformulated capsule)[a]	↑ Saquinavir	FORTOVASE 800 mg bid + KALETRA produces ↑ AUC, ↑ Cmax, and ↑ Cmin relative to FORTOVASE 1200 mg tid.
HIV protease inhibitor: Nelfinavir[a]	↑ Saquinavir ↑ Nelfinavir	Quadruple therapy, including FORTOVASE and nelfinavir in addition to two nucleoside reverse transcriptase inhibitors gave a more durable response than triple therapy with either single protease inhibitor. The regimens were generally well tolerated. However, concomitant administration of nelfinavir and FORTOVASE resulted in a moderate increase in the incidence of diarrhea.
HIV protease inhibitor: Ritonavir[a]	↑ Saquinavir	In some cases, co-administration of SQV and RTV has led to severe adverse events (see WARNINGS-Interactions with ritonavir.
Non-nucleoside reverse transcriptase inhibitor: Delavirdine[a]	↑ Saquinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established. In a small, preliminary study, hepatocellular enzyme elevations occurred in 13% of subjects during the first several weeks of treatment with the delavirdine and saquinavir combination (6% Grade 3 or 4). Hepatocellular changes should be monitored frequently if this combination is prescribed.

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
Other Agents		
Anticoagulant: Warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin	↓ Saquinavir	Use with caution, saquinavir may be less effective due to decreased saquinavir plasma concentrations in patients taking these agents concomitantly.
Antifungal: Ketoconazole[a] Itraconazole	↑ Saquinavir ↔ Ketoconazole	No dose adjustment is required when the two drugs are co-administered for a limited time at the doses studied.
Anti-infective: Clarithromycin[a]	↑ Saquinavir ↑ Clarithromycin	No dose adjustment is required when the two drugs are co-administered for a limited time at the doses studied.
Erythromycin[a]	↑ Saquinavir	When saquinavir is administered as the sole protease inhibitor, no dose adjustment is required when the two drugs are co-administered.
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, 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
Immunosuppressants: Cyclosporine, tacrolimus, rapamycin	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with FORTOVASE
PDE5 inhibitor (phosphodiesterase type 5 inhibitors): Sildenafil[a], vardenafil, tadalafil	↔ Saquinavir ↑ Sildenafil ↑ Vardenafil ↑ Tadalafil	When PDE5 inhibitors are administered concomitantly with saquinavir a reduced starting dose and increased monitoring of adverse events should be performed.

[a] For magnitude of interactions see Tables 2 and 3.

Drugs that are Mainly Metabolized by CYP3A4

Compounds that are substrates of CYP3A4 (e.g. alfentanyl, alprazolam, amiodarone, calcium channel blockers, clindamycin, carbamazepine, cyclosporine, dapsone, disopyramide, fentanyl, nefazodone, pimozide, quinidine, quinine, tacrolimus, warfarin) may have elevated plasma concentrations when coadministered with FORTOVASE; therefore, these combinations should be used with caution and patients should be monitored for toxicities associated with such drugs.

Substrates of P-gp

Concomitant use of FORTOVASE with drugs that are substrates of P-gp may lead to elevated plasma concentrations of the concomitant drugs. Monitoring for toxicity is therefore recommended. Compounds that are substrates of P-gp include cyclosporine, paclitaxel, and vinblastine.

Ritonavir-Boosted INVIRASE and Rifampin

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).

Information for Patients

Patients should be informed that any change from INVIRASE to FORTOVASE should be made only under the supervision of a physician.

Patients should be informed that FORTOVASE is not a cure for HIV infection and that they may continue to contract illnesses associated with advanced HIV infection, including opportunistic infections. They should be informed that FORTOVASE therapy has not been shown to reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

FORTOVASE 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 (see WARNINGS).

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 advised that FORTOVASE should be taken within 2 hours after a full meal (see ACTION AND CLINICAL PHARMACOLOGY: Absorption). 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.

Patients should be advised that no studies have been conducted on the ability to drive or operate machinery while taking FORTOVASE. There is no evidence that FORTOVASE may alter the patient's ability to drive and use machines, however, the adverse event profile of FORTOVASE should be taken into account (see ADVERSE REACTIONS).

Patients should be told that the long-term effects of FORTOVASE are unknown at this time.

Pregnancy and Lactation:

Reproduction studies with saquinavir in rats have shown no embryotoxicity or teratogenicity at plasma exposures (AUC values) approximately 50% of those achieved in humans at the recommended dose, or in rabbits at plasma exposures approximately 40% of those achieved at the recommended clinical dose. Distribution studies in these species showed that placental transfer of saquinavir is low (less than 5% of maternal plasma concentrations).

Studies in rats indicated that exposure to saquinavir from late pregnancy through lactation at plasma concentrations (AUC values) approximately 50% of those achieved in humans at the recommended dose had no effect on the survival, growth and development of offspring to weaning.

There are however, no adequate or well controlled studies of FORTOVASE in pregnant women. Because animal reproduction studies are not always predictive of human response, FORTOVASE should be used during pregnancy only if potential benefits are considered to outweigh the potential risks to the fetus.

It is not known whether saquinavir is excreted in human milk. Because many drugs are excreted in human milk, it is advisable to caution mothers against breast feeding while taking FORTOVASE. Additionally, current medical practice advises against breast-feeding by HIV-infected women, due to the possibility of post-natal transmission.

Antiretroviral Pregnancy Registry

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

ADVERSE REACTIONS

Clinical Adverse Reactions:

The safety of FORTOVASE (saquinavir) was studied in patients who received the drug either alone or in combination with other antiretroviral agents. The majority of adverse events were of mild intensity. The most frequently reported adverse events among patients receiving FORTOVASE were diarrhea, abdominal discomfort, nausea and dyspepsia. Table 6 lists all clinical adverse experiences which occurred in $\geq$2% of patients receiving FORTOVASE in combination with other antiretroviral agents.

FORTOVASE did not alter the pattern, frequency or severity of known major toxicities associated with the use of reverse transcriptase inhibitors. Physicians should refer to the complete product information for other antiretroviral agents (as appropriate) regarding drug-associated adverse reactions to these other agents.

Table 6: Percentage of Patients, by Study Arm, with Clinical Adverse Experiences Considered at Least Possibly Related to Study Drug or of Unknown Relationship and of Moderate, Severe or Life-Threatening Intensity, Occurring in ≥2% of Patients in NV15182 and NV15355

	NV15182 (48 weeks)	NV15355 (48 weeks) naive patients	
ADVERSE EVENT	**FORTOVASE + TOC* N=442**	**INVIRASE + 2 RTIs† N=81**	**FORTOVASE + 2 RTIs† N=90**
GASTROINTESTINAL			
Diarrhea	19.9	12.3	15.6
Nausea	10.6	13.6	13.3
Abdominal Discomfort	8.6	4.9	10.0
Dyspepsia	8.4	–	7.8
Flatulence	5.7	7.4	10.0
Vomiting	2.9	1.2	4.4
Abdominal Pain	2.3	1.2	4.4
Constipation	–	–	3.3
BODY AS A WHOLE			
Fatigue	4.8	6.2	8.9
Appetite Decreased	–	–	2.2
Chest Pain	–	–	2.2
CENTRAL AND PERIPHERAL NERVOUS SYSTEM			
Headaches	5.0	4.9	5.6
PSYCHIATRIC DISORDERS			
Depression	2.7	–	–
Insomnia	–	1.2	5.6
Anxiety	–	2.5	2.2
Libido Disorder	–	–	3.3
SPECIAL SENSES DISORDERS			
Taste Alteration	–	1.2	4.4
MUSCULOSKELETAL DISORDERS			
Pain	–	3.7	3.3
DERMATOLGICAL DISORDERS			
Eczema	–	2.5	–
Rash	–	2.5	–
Verruca	–	–	2.2

* Antiretroviral Treatment of Choice

† Reverse Transcriptase Inhibitor

The following clinical adverse events (possibly or probably related to study drug, all severities) occurred with a frequency of <2% in clinical studies with FORTOVASE; or were reported under controlled trials with INVIRASE (saquinavir mesylate, hard gelatin capsule):

Body as a whole: appetite decreased/disturbed, asthenia, fever, wasting syndome, allergic reaction, chest pain, body pain, weight decrease, shivering, night sweats, edema, malaise, anorexia;
Cardiovascular: hypertension, heart rate disorder;
Endocrine / Metabolic: hyperglycemia, dehydration, increased triglycerides;
Gastro-intestinal: abdominal colic, buccal mucosa ulceration, eructation, stomatitis, stomach upset, discoloured feces, glossitis, gingivitis, frequent bowel movements, gastralgia, gastritis, gastrointestinal inflammation, pancreatitis, tooth ache/disorder, pruritis ani, pyrosis, esophageal ulcer, gastrointestinal ulcer;
Hematologic / Bleeding Disorders: cerebral hemorrhage, neutropenia, thrombocytopenia, pancytopenia, dermal bleeding;
Musculoskeletal: stiffness, arthralgia, myalgia, musculoskeletal pain, back pain, muscle cramps, myopathy;
Neurological: ataxia, confusion, dry mouth, convulsions, dysesthesia, spasms hyperesthesia, light headed feeling, numbness in extremities, neuropathy, peripheral neuropathy, tremor, dizziness, fecal incontinence;
Psychological: euphoria, reduced intellectual ability, lethargy, irritability, agitation, hallucination, somnolence, excessive dreaming;
Reproductive Disorder: erectile impotence;
Resistance Mechanisms: staphylococcal infection, influenza, infectious diarrhea, parasitic infestation;
Respiratory: pharyngitis, dyspnea, laryngitis, rhinitis, cough, bronchial asthma;
Skin: increased sweating, hot flushes, skin pigment changes, acne, dermatitis, folliculitis, pruritus, psoriasis, erythema, skin disorder, xeroderma, photosensitivity reaction, alopecia, red face;
Special Senses: conjunctivitis, visual disturbances, unpleasant taste, olfactory disorder, xerophthalmia;
Urinary: micturition disorder, nocturia

The following clinical adverse events were reported with a frequency of >2% during clinical studies with either FORTOVASE or INVIRASE, and were all assessed as "remotely related" to study drug:

Body as a Whole: Intoxication, pelvic pain, retrosternal pain, trauma, generalized weakness; ***Cardiovascular/Cerebrovascular:*** Cyanosis, heart murmur, heart valve disorder, hypotension, stroke, syncope, vein distended; ***Nervous System:*** Dysarthria, hyperreflexia, hyporeflexia, myelopolyradiculoneuritis, numbness in face, pain (facial/jaw/leg), paresis, paresthesis, poliomyelitis, prickly sensation, progressive multifocal leukoencephalopathy, unconsciousness; ***Dermatological:*** Chalazion, dermatitis seborrheic, furunculosis, hair changes, nail disorder, papillomatosis, papular rash, external parasites, maculopapular rash, skin nodule, skin ulceration, urticaria, skin syndrome; ***Endocrine/Metabolic:*** Diabetes mellitus, hypothyroidism, weight increase, thirst, hypoglycemia; ***Gastrointestinal:*** Abdominal distention, oral canker sores, cheilitis, dysphagia, esophagitis, feces bloodstained, rectal hemorrhage, hemorrhoids, melena, painful defecation, parotid disorder, salivary gland disorder; ***Hematologic/Bleeding Disorders:*** Anemia, splenomegaly, microhemorrhages; ***Liver and Biliary:*** Sclerosing cholangitis, cholelithiasis, hepatitis, hepatomegaly, hepatosplenomegaly, jaundice, liver enzyme disorder, pancreatitis; ***Musculoskeletal:*** Arthritis, leg cramps, lumbago, musculoskeletal disorders, tissue changes; ***Neoplasm:*** Kaposi's sarcoma; ***Psychological:*** Amnesia, anxiety attack, overdose effect, psychic disorder, psychosis, speech disorder, behaviour disturbances; ***Reproductive System:*** menstrual disorder/irregularity, penis disorder, prostate enlarged, vaginal discharge; ***Resistance Mechanism:*** Abscess, angina tonsillaris, candidiasis, cellulitis, herpes simplex, herpes zoster, bacterial infection, mycotic infection, lymphadenopathy, moniliasis, tumor; ***Respiratory:*** Bronchitis, epistaxis, hemoptysis, pneumonia, pulmonary disease, respiratory disorder, sinusitis, upper respiratory tract infection, allergic atopic rhinitis; ***Special Senses:*** Blepharitis, cytomegalovirus retinitis, dry eye syndrome, earache, ear pressure, eye irritation, decreased hearing, otitis, tinnitus; ***Urinary System:*** Renal calculus, renal colic, urinary tract bleeding, urinary tract infection.

Occurrences of the following serious adverse events have also been reported during clinical trials and/or post-market experience with either FORTOVASE, or the original market formulation of saquinavir mesylate (INVIRASE). These events were all considered possibly related to the

use of saquinavir: confusion, ataxia and weakness; acute myeloblastic leukemia; hemolytic anemia; attempted suicide; Stevens-Johnson syndrome; seizures; bullous skin eruption and polyarthritis; 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 LFTs, jaundice, ascites and right/left upper quadrant abdominal pain; drug fever; pancreatitis leading to death; nephrolithiasis; thrombocytopenia and intracranial hemorrhage leading to death; peripheral vasoconstriction; intestinal obstruction; portal hypertension; acute renal insufficiency; increased bleeding, including spontaneous skin hematomas and hemarthroses, in hemophiliac patients type A and B treated with protease inhibitors (see PRECAUTIONS - *Hemophiliac Patients*).

Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS- *Fat Redistribution*).

Additional adverse events that have been observed during the post-marketing period are similar to those seen in clinical trials with INVIRASE and FORTOVASE.

Laboratory Values:

The table below shows the percentage of patients with marked laboratory abnormalities in study NV15182 and NV15355. Marked laboratory abnormalities are defined as a Grade 3 or 4 abnormality in a patient with a normal baseline value or a Grade 4 abnormality in a patient with a Grade 1 abnormality at baseline (ACTG Grading System). In the safety study (NV15182) there was a 27-33% incidence of greater than or equal to 1 grade shifts in ALT and AST during the 48 week study period. 46% of these were single abnormal values. 3-4% of patients had greater than or equal to 3 grade shifts in transaminase levels (see table below) and less than 0.5% of patients had to discontinue the study for increased liver function tests.

Table 7: Percentage of Patients, by Treatment Group, with Marked Laboratory Abnormalities* in NV15182 and NV15355

	NV15182 (48 weeks)	NV15355 (48 weeks) Naive Patients	
	FORTOVASE + TOC** N=442	INVIRASE + 2 RTIs† N=81	FORTOVASE + 2 RTIs† N=90
BIOCHEMISTRY			
Alkaline Phosphatase (high)	0.5	0.0	0.0
Calcium (high)	0.2	0.0	0.0
Creatine Kinase (high)	7.8	0.0	6.0
Gamma GT (high)	5.7	2.6	5.0
Glucose (low)	6.4	2.5	3.5
Glucose (high)	1.4	1.3	0.0
Phosphate (low)	0.5	0.0	1.0
Potassium (high)	2.7	0.0	3.5
Serum Amylase (high)	1.9	ND	ND
SGOT (AST) (high)	4.1	0.0	0.0
SGPT (ALT) (high)	5.7	1.3	1.0
Sodium (high)	0.7	0.0	0.0
Sodium (low)	0.0		1.0
Total Bilirubin (high)	1.6	0.0	0.0
Triglycerides (high)	0.0		2.0
HEMATOLOGY			
Hemoglobin (low)	0.7	0.0	1.0
Absolute Neutrophil Count (low)	2.9	2.9	1.0
Platelets (low)	0.9	2.5	0.0

* Defined as ≥3 grade shift from baseline

** Antiretroviral Treatment of Choice

† Reverse Transcriptase Inhibitor

ND Not done

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Two patients were previously reported with overdoses of saquinavir mesylate hard gelatin capsules (INVIRASE). No sequelae was noted in the first patient after ingesting 8 grams of saquinavir as a single dose. The patient was treated with induction of emesis within 2 to 4 hours after ingestion. The second patient ingested 2.4 grams of saquinavir in combination with 600 mg of ritonavir, and experienced pain in the throat that lasted for 6 hours and then resolved.

Two cases of FORTOVASE (saquinavir) overdosage have been received (one case with unknown amount of FORTOVASE, second case 3.6 to 4 g at once). No adverse events have been reported in both cases.

In cases of overdose, vital signs should be monitored, and symptoms treated as they arise. Patients may also benefit from treatment with activated charcoal.

DOSAGE AND ADMINISTRATION

Adults: The recommended dosage for FORTOVASE (saquinavir) is 1200 mg (6 x 200 mg capsules) taken three times daily (TID), anytime within 2 hours after a meal or substantial snack. Total daily dose is 3600 mg.

Patients should be advised that, as with all protease inhibitors, the optimal use of this drug is in combination with an active antiretroviral regimen. Optimal benefit has been observed when antiretroviral therapies to which the patient is naive are begun simultaneously. Concomitant therapy should therefore be based on a patient's prior drug exposure. Adherence to the prescribed regimen is strongly recommended.

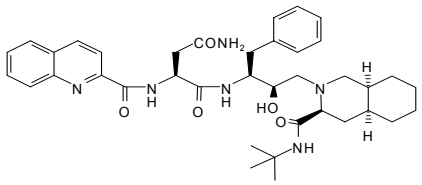
Monitoring of Patients: Clinical chemistry tests, viral load and CD_4 count should be performed prior to initiating therapy, and at appropriate intervals thereafter.

Dose Adjustments for Combination Therapy: For serious toxicities that may be associated with saquinavir, the drug should be interrupted. For recipients of combination therapy, dose adjustment of the other antiretroviral agents should be based on the known toxicity profile for those drugs. Physicians should refer to the Product Monographs of these drugs for comprehensive dose adjustment recommendations and drug-associated adverse reactions.

Plasma levels of saquinavir may be substantially increased when FORTOVASE is given in combination with other antiretroviral drugs. For combination treatment involving such compounds, dose reduction of FORTOVASE may be required. Please refer to the PRECAUTIONS (*Drug Interactions*) section for information concerning these combinations.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name	saquinavir (free base)
Chemical Name:	(S)-N-[(αS)-α-[(1R)-2-[(3S,4aS,8aS)-3-(*tert*Butylcarbamoyl)-octahydro-2(1H)-isoquinolyl]-1-hydroxyethyl]phenethyl]-2-quinaldamido succinamide
Structural Formula:	
Molecular Formula:	$C_{38}H_{50}N_6O_5$
Molecular Weight:	670.86
Description:	Saquinavir is a white to off-white powder
Melting Range:	123.3 - 124.6°C
Solubility:	Insoluble in aqueous medium at 25°C
pH:	Approximately 7 (since saquinavir is not water soluble)
pKa:	6.89±0.02
Partition Co-efficient:	log P=3.34; log D (pH 7.4)=2.75

Composition

Each beige opaque soft gelatin capsule contains 200 mg saquinavir. The non-medicinal ingredients are: dl-α-tocopherol, gelatin, glycerol, iron oxides, ascorbyl palmitate, lecithin, medium chain mono- and diglycerides, povidone K30, and titanium dioxide. Capsules are printed with `ROCHE 0246'. Printing ink contains as traces: aluminum chloride, carmine, hypromellose, propylene glycol, sodium hydroxide.

Stability and Storage Recommendations

Capsules should be refrigerated (2-8°C) in tightly closed bottles until dispensed. For patient use, refrigerated (2-8°C) capsules of FORTOVASE (saquinavir) remain stable until the expiration date printed on the label. Once brought to room temperature (at or below 25°C), capsules should be used within 3 months.

Availability of Dosage Forms

FORTOVASE (saquinavir) soft gelatin capsules are available in plastic (HDPE) bottles, each containing 180 capsules.

INFORMATION FOR THE PATIENT

You have been prescribed FORTOVASE (saquinavir) by your doctor. FORTOVASE belongs to a class of drugs used to fight the human immunodeficiency virus (HIV). FORTOVASE contains the active ingredient saquinavir, which fights the spread of HIV through your body. Please read this information carefully before you begin to take this medicine, since it will help you learn about FORTOVASE and how to make this drug work best for you. If you have any questions or concerns after reading this information, speak with your doctor or pharmacist.

What is HIV-Infection?

HIV is the virus that causes AIDS. As you may know, the immune system is the body's main defense against infection. The immune system includes special cells that recognize and destroy harmful bacteria and viruses. As HIV grows, it destroys these cells -- leaving fewer immune cells, and a greater risk of infection.

Over time, HIV disease usually "progresses" -- it gets more severe. With fewer immune cells, it is easier for you to get sick. Your doctor will watch you carefully to tell how you are doing. Your doctor may also do blood tests to measure the number of immune cells in your body (CD4 cell counts) and to measure how much virus is in your blood. All of this information can be used to help you and your doctor decide how best to manage your HIV disease.

What is FORTOVASE?

FORTOVASE is the brand name for saquinavir capsules. Saquinavir belongs to a class of drugs called protease inhibitors (pronounced PRO-tee-ase). It interferes with a different step in virus reproduction than some of the earliest drugs available to fight HIV. Although FORTOVASE contains the same active ingredient as INVIRASE, THESE TWO PRODUCTS CANNOT BE USED INTERCHANGEABLY. Therefore your doctor will provide directions on the switch from one medication to the other.

Each FORTOVASE capsule contains 200 mg of the active ingredient saquinavir. The capsules also contain additional (non-medical) ingredients, these are: medium chain mono- and diglycerides, dl-α-tocopherol, gelatin, glycerol, povidone K30, iron oxides, titanium dioxide, ascorbyl palmitate, and lecithin. Printing ink contains as traces: aluminum chloride, carmine,

hypromellose, propylene glycol, sodium hydroxide. IF YOU KNOW YOU HAVE AN ALLERGY OR HAVE HAD A SERIOUS REACTION TO ANY OF THE INGREDIENTS, YOU MUST NOT USE FORTOVASE.

How does FORTOVASE work?

FORTOVASE interferes with an important step in virus reproduction in cells. The first prescription drugs for the treatment of HIV disease all worked at the same place. These drugs, called nucleoside analogues, include Retrovir® [ZDV; zidovudine], Hivid® [ddC], Videx® [ddI], 3TC® [lamivudine], and Zerit® [d4T]. Now however, with the addition of FORTOVASE, we can fight the growth of HIV at *different* places in its life cycle.

FORTOVASE is not a cure for HIV and/or AIDS, though it may help to slow the progression of HIV disease in your body. While taking FORTOVASE however, you may continue to acquire illnesses associated with advanced HIV infection (i.e. opportunistic infections).

It is important to remember that there is NO evidence which suggests that FORTOVASE can prevent the transmission of HIV. FORTOVASE is NOT therefore a substitute for other measures which have been proven effective in this regard. To avoid transmission of HIV, you should not donate blood, share needles, or engage in unprotected sexual activity (i.e. without a condom).

How should FORTOVASE be taken?

Your doctor has prescribed FORTOVASE after carefully studying your case, because he/she believes that you may benefit from this medication. This may not be true for other patients with HIV infection, even those who exhibit symptoms similar to yours. AS WITH ANY PRESCRIPTION DRUG, FORTOVASE SHOULD ONLY BE TAKEN ON THE ADVICE OF A PHYSICIAN. DO NOT GIVE YOUR FORTOVASE TO ANY OTHER PERSON.

The recommended dose of FORTOVASE is 6 capsules, three times a day (for a total of 18 capsules each day), taken anytime within 2 hours of having eaten a meal or a substantial snack. For example, if you've eaten lunch at 1:00 PM, you can take your mid-day dose with that meal, or anytime between 1:00 and 3:00 PM. THE EFFECTIVENESS OF FORTOVASE MAY DEPEND ON TAKING IT WITH FOOD. Capsules should be swallowed unchewed, with water or some

other non-alcoholic drink. You should avoid excessive consumption of alcohol during your treatment with FORTOVASE. Your doctor may prescribe FORTOVASE in combination with other drugs which are used to control HIV infection. Your physician may adjust the recommended dose to suit your particular needs. FOLLOW THE ADVICE OF YOUR DOCTOR. DO NOT DISCONTINUE THERAPY OR ALTER YOUR DOSING WITHOUT CONSULTING YOUR DOCTOR.

What if you miss a dose of FORTOVASE?

The missed dose should be taken as soon as you remember, then just carry on with your regular dosing schedule. However, do not take 2 doses (12 capsules) at the same time. If you are unsure what to do, consult your doctor or pharmacist.

What should you tell your doctor before taking FORTOVASE?

Before beginning treatment with FORTOVASE, make sure your doctor knows if:

- you have ever had a bad reaction to saquinavir (INVIRASE or FORTOVASE), any component of the capsules, or any other brand of protease inhibitor;
- you have a problem with your liver or kidneys;
- you have any other illnesses besides HIV infection;
- you are currently, or plan to be taking ANY other drugs (including herbal preparations, especially St. John's Wort and garlic, drugs you purchase without prescriptions, and those not prescribed by your doctor); or
- you are pregnant, plan on becoming pregnant, or are breast-feeding a child.

This information will help you and your physician decide if the potential benefits of treating your condition with FORTOVASE outweigh the possible risks.

What are the possible unwanted effects of FORTOVASE?

As with any drug, the beneficial effects of FORTOVASE may be accompanied by unwanted effects (also known as side-effects or adverse events). It is often difficult to determine whether these adverse events are the result of taking FORTOVASE, an effect of your HIV-infection, or a side-effect from other drugs being used to treat the HIV-infection. IT IS VERY IMPORTANT HOWEVER, TO INFORM YOUR PHYSICIAN OF ANY CHANGE IN YOUR CONDITION.
The side effects which have been reported most often with FORTOVASE include diarrhea, nausea, abdominal pain or discomfort, headache, flatulence, fatigue, and vomiting.

Regular blood testing to detect any abnormalities with your liver, pancreas or blood is recommended as part of your FORTOVASE therapy. These abnormalities do not always cause side effects that you can detect yourself, so it is very important to adhere to the blood testing schedule recommended by your doctor.

In hemophiliacs, there have been reports of increased bleeding episodes among patients treated with FORTOVASE or other drugs of this class (protease inhibitors). If you suffer from hemophilia, remember to report all bleeding episodes to your doctor.

Changes in body fat have been seen in some patients taking antiretroviral therapy. 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, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

Side effects known to be associated with other drugs used to treat HIV may still occur when FORTOVASE is used in combination with these medicines. However, FORTOVASE does not appear to increase the frequency or severity of the unwanted effects. These side effects (associated with drugs such as ddC and zidovudine) include skin rash, inflammation or sores in the mouth and disturbances of the nerves (especially in the hands and feet). These disturbances may take the form of numbness, pins and needles, or shooting/burning pain in the hands and feet. If you are concerned about these or any other unexpected effects experienced while taking FORTOVASE, talk to your doctor or pharmacist.

How should FORTOVASE be stored?

For long-term storage, it is recommended that FORTOVASE be kept in the refrigerator, in its original package (tightly closed to protect from moisture). Once brought to room temperature (at or below 25°C), capsules should be used within 3 months (regardless of the expiry date printed on the label). KEEP THIS AND ANY OTHER DRUGS OUT OF SIGHT AND OUT OF REACH FROM CHILDREN. Do not use this medicine after the expiry date ("EXP") shown on the outside of the package.

Important notes to remember about your FORTOVASE therapy

- Your dosage of FORTOVASE: six capsules, three times a day
- FORTOVASE should be taken with food (anytime within 2 hours after eating a full meal or substantial snack)
- It is very important that you follow all of your doctor's instructions when taking FORTOVASE
- Contact your doctor if you are having trouble adjusting to your medication, or if you are experiencing any unexpected or bothersome symptoms.

This brochure does not contain all known information about FORTOVASE. If you have any further questions or concerns about your treatment with FORTOVASE, please contact your doctor or pharmacist.

VIROLOGY

The relationship between the *in vitro* susceptibility of HIV infection to saquinavir and the inhibition of HIV in humans or the clinical response to therapy has not been established.

Western blot analysis has shown that saquinavir can block viral protein cleavage in infected cells at concentrations as low as 3.0 nM. Its mode of action has been confirmed by direct observation of virus maturation by electron microscopy: mature virus particles are replaced by immature forms within 24 h of treatment of chronically-infected CEM cells with 10 nM saquinavir. Viral yields from such treated cultures proved, as predicted, non-infectious on further passage on to fresh cells in the absence of drug, although there may be some late breakthrough on continued culture.

Saquinavir has shown consistently potent antiviral activity in primary monocytes and monocytic lung cell lines, and in lymphocytes or lymphoblastoid cells. Unlike nucleoside analogues (zidovudine, etc., which act only in early infection), saquinavir acts directly on its viral target enzyme. As a consequence of this direct action and because it does not require metabolic activation, the antiviral potential of saquinavir is retained against resting (non-dividing), chronically infected cultures (as well as acutely infected cultures).

The antiviral activity of saquinavir has been demonstrated consistently at nM concentrations, irrespective of the assessment parameter (p24 or reverse transcriptase production, or syncytium formation) and has not been shown to be affected by multiplicity of infection or virus batch. For example, using the representative HIV-1 strain GB8 in JM or CEM-T4 lymphoblastoid cells, mean IC_{50}/IC_{90} values of 2.3/18 nM (JM) and 6.5/25 nM (CEM-T4) were obtained by syncytium reduction, and 3.1/15 nM (CEM-T4) by p24 ELISA; correspondingly, zidovudine (ZDV) treatment of HIV-1 GB8 infected CEM-T4 cells gave IC_{50}/IC_{90} values of 9.3/110 nM (syncytium formation) or 5.3/37 nM (p24 ELISA), but ZDV was essentially inactive (IC_{50}>1000 nM) in JM cells which cannot undertake the necessary metabolic activation.

From *in vitro* experiments, IC_{50} values were in the range of 1-30 nM.

In comparison with laboratory virus strains, clinical isolates of HIV-1 in primary PBMC cultures have shown similar or slightly reduced sensitivity ($IC_{50} \leq 30$ nM) to saquinavir, which performed comparably to or better than ZDV (IC_{50} 7-20 nM). Furthermore, saquinavir is fully active against ZDV-resistant virus; e.g. in primary PBL, using p24 production as an assay parameter, IC_{50} values (normal/ZDV-resistant virus) of 12/11 nM were obtained, in contrast to 7.1/$\geq$250 nM for ZDV.

Evidence of saquinavir cytotoxicity has been found only at µM concentrations (typically 5-100 µM), affording a high *in vitro* therapeutic index of >1000. This lack of cytotoxicity has allowed long-term administration of the compound without detriment to host cells, in consequence of which studies have indicated the disappearance of HIV-1 (infectivity and DNA) from infected MT-2 cell cultures after some 80 days of drug treatment at 100 nM , and without rebound infection after 35 days from drug removal; this has been explained by outgrowth of healthy cells following the progressive death of the infected component.

Experiments in cell culture indicate that saquinavir produces an additive to synergistic effect against HIV-1 in double and triple combination with various reverse transcriptase inhibitors (including zidovudine, zalcitabine, didanosine, 3TC, d4T, and nevirapine) without enhanced cytotoxicity.

Potential for Resistance and Cross-Resistance to Saquinavir:

In vitro, reduced sensitivity to saquinavir does not seem to arise readily. During prolonged *in vitro* passage with saquinavir, two key mutations at amino acid residues 48 and 90 (glycine 48 to valine [G48V] and leucine 90 to methionine [L90M]) have arisen consistently in the proteinase gene. Each of these contributes moderately to saquinavir resistance.

These two key viral protease mutations (L90M and/or G48V) were found in virus from treated, but not untreated, patients. Other amino acid changes from baseline were observed less frequently at amino acid positions 10, 63 and 71. However, these accessory changes did not contribute to a decrease in sensitivity to saquinavir.

In a study of 47 patients who had received FORTOVASE in combination with two nucleoside analogues for a period of 48 weeks, ten patients were found with plasma viral load >400 copies/mL. Sequence analysis of HIV protease in these patients indicated 90M was present in one patient after 16 and 24 weeks, without phenotypic alteration of susceptibility to saquinavir. Plasma from another patient showed a mixture of wild-type G48 present with the 48V substitution after 24 weeks, which resolved to the 48V substitution only, with secondary mutations at residues 54 and 82 after 48 weeks. This 48V substituted protease was found to give rise to phenotypic reduction of susceptibility to saquinavir in recombinant virus. Phenotypic reduction of susceptibility to saquinavir was not observed in any of the remaining samples analysed. The incidence of resistance mutations was too low to infer a link to clinical response.

Viruses with resistance substitutions including 48V and 90M that have been selected during long-term therapy with INVIRASE have been found to show modest reductions in susceptibility to saquinavir. In one study, 24 clinical isolates of virus containing 48V and/or 90M after therapy with INVIRASE showed a geometric mean reduction of susceptibility (increase in IC_{50}) of 7.3-fold relative to baseline virus (range 1.2- to 97-fold). Furthermore, in a study of 76 infected subjects after a median of 112 weeks of therapy with Invirase (ACTG 333), 71 of 76 subjects were found with IC_{50} <50 nM, despite the presence of 52 subjects carrying virus with the L90M and/or G48V substitutions.

Analysis of thirteen saquinavir-resistant isolates from patients following prolonged (24-147 weeks) therapy with INVIRASE (saquinavir mesylate; HGC) showed that 5 of 13 (38%) had cross-resistance to at least one of four other protease inhibitors (indinavir, nelfinavir, ritonavir, or experimental compound amprenavir). However, the majority (11 of 13; 85%) remained sensitive to at least one other protease inhibitor.

To date, therapy with saquinavir has demonstrated a distinctive and consistent pattern of mutations (L90M and/or G48V).

Cross-Resistance to other Antiretrovirals:

As a result of their different enzyme targets, no cross-resistance occurs between saquinavir and reverse-transcriptase inhibitors. HIV isolates resistant to zidovudine are sensitive to saquinavir, and conversely, HIV isolates resistant to saquinavir are sensitive to zidovudine.

In a study of viral susceptibility to the protease inhibitors saquinavir, indinavir, ritonavir, nelfinavir and amprenavir, 41 viral isolates from 37 patients 20 to 147 weeks post therapy with INVIRASE with or without nucleoside analogue RT inhibitors were examined. Twenty-two of 41 (54%) isolates showed resistance to saquinavir. Of these, 6/22 (27%) did not show cross-resistance with the other inhibitors, while 4/22 (18%) showed broad cross-resistance. The remaining 12/22 (55%) retained activity against at least one other protease inhibitor.

Cross-resistance with lopinavir is as yet undetermined in clinical isolates, although laboratory strains with substitutions at residues 10, 84 and 90 or 10, 48, 82 and 90 did not show significant reductions in susceptibility to lopinavir.

Therapy with saquinavir has demonstrated a distinctive and consistent pattern of mutations.

Cross-Resistance to Saquinavir from Resistance Mutations Selected by other Protease Inhibitors:

Subjects with high level resistance to other protease inhibitors do not necessarily show cross-resistance to saquinavir. In one study, isolates from 19 of 20 subjects who developed resistance to indinavir retained IC_{95} levels <1000 nM against saquinavir. Similarly, limited studies of molecular clones containing resistance mutations associated with ritonavir, nelfinavir or amprenavir showed significant resistance to these individual protease inhibitors, but not to saquinavir. However, extensive treatment of subjects with protease inhibitors after failure can lead to broad cross-resistance in a complex, dynamic process.

Hypersusceptibility to Mutant Virus:

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

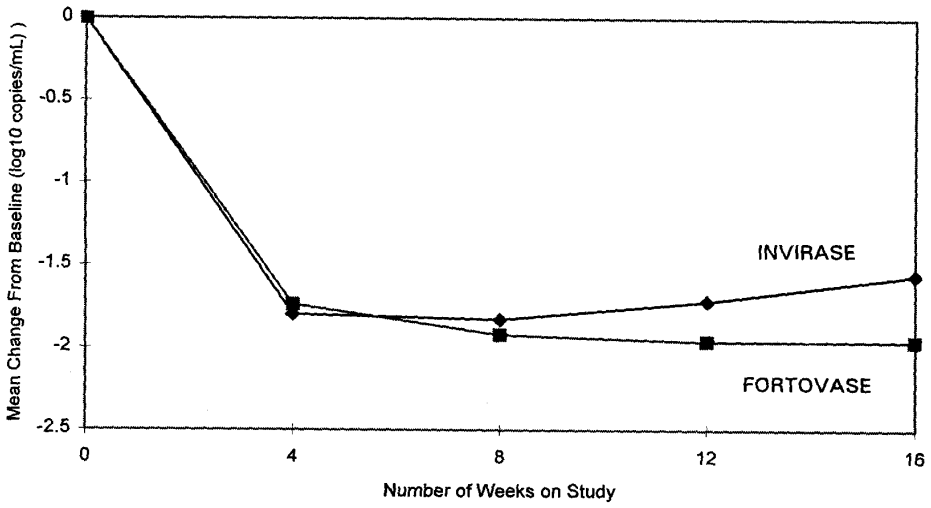
PHARMACOLOGY

Clinical Studies:

Study NV15355: FORTOVASE + 2 RTIs versus INVIRASE + 2 RTIs

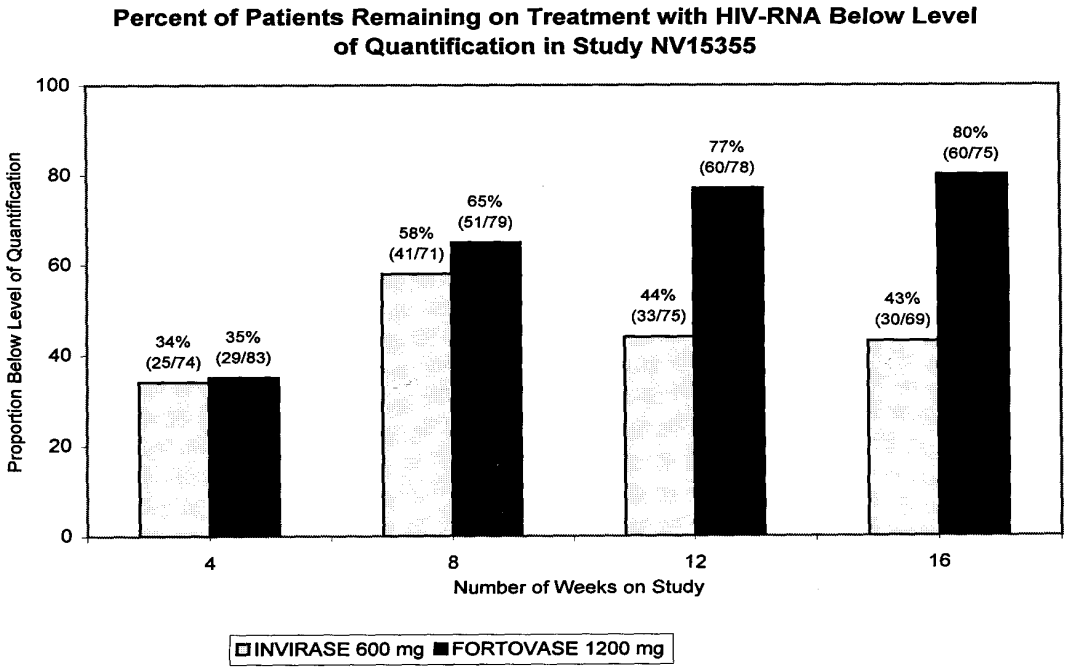
Study NV15355 is an open-label, randomized, parallel study of FORTOVASE (saquinavir) and INVIRASE (saquinavir mesylate hard gelatin capsules) in combination with two nucleoside antiretroviral drugs in treatment-naive patients. Of the 171 patients evaluated, 90 (53%) received FORTOVASE (mean baseline CD_4 = 448 cells/mm^3 and HIV-RNA = 4.8 $\log_{10}$ copies/mL) and 81 (47%) received INVIRASE (mean baseline CD_4 = 408 cells/mm^3 and HIV-RNA = 4.8 $\log_{10}$ copies/mL). After 16 weeks of treatment, there was a mean viral load suppression of -2.0 log and an increase in CD_4 of 97 cells in the FORTOVASE containing arm compared to -1.6 log mean viral load suppression and 115 cell increase observed in the INVIRASE containing arm (see figure below). These differences were not statistically significant.

Mean Change *from* Baseline
in Plasma HIV-RNA Levels in Study NV15355



Number of Patients					
Week	0	4	8	12	16
INVIRASE	81	74	71	75	69
FORTOVASE	90	83	79	78	75

Of patients still on treatment after 16 weeks, a total of 80% (60/75) on FORTOVASE and 43% (30/69) on INVIRASE had viral loads below the limit of quantification (BLQ <400 copies/mL) using the Amplicor HIV-1 Monitor™ Test (Roche Molecular Systems) at 16 weeks (see figure below). This result was statistically significant (p=0.001). By 16 weeks of therapy, 15 patients receiving FORTOVASE and 7 receiving INVIRASE had discontinued study treatment; 5 patients on INVIRASE had missing data at week 16.



* Amplicor HIV-1 Monitor™ Test. Limit of Qunatification = 400 copies/mL

Note: See Figure 2 for number of patients with HIV-RNA data at each time point

NV15182: FORTOVASE plus other antiretroviral agents (uncontrolled)

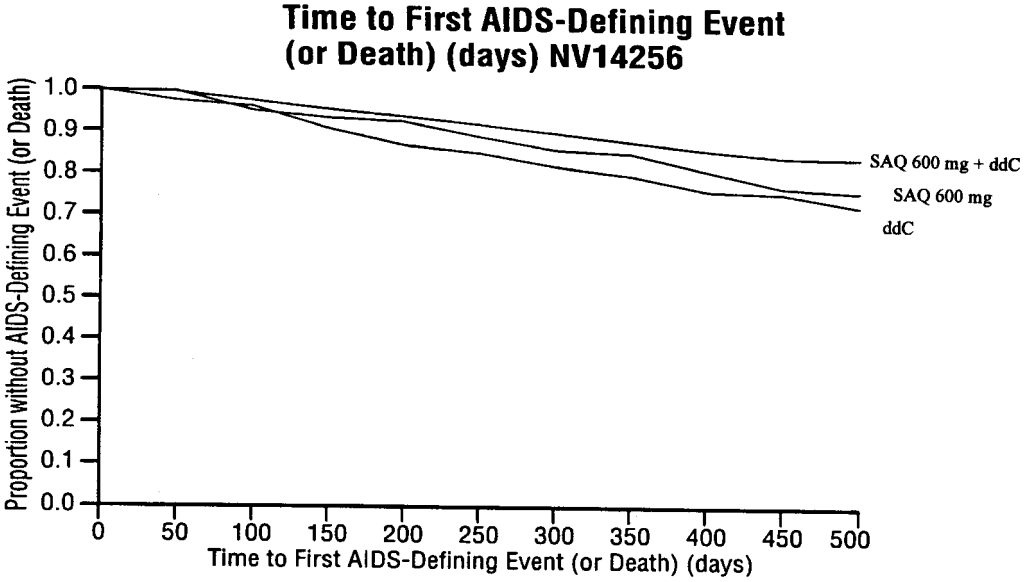
Study NV15182 was an open-label study designed primarily to evaluate the safety of FORTOVASE in combination with other antiretroviral agents in 442 patients (mean baseline CD_4 was 227 cells/mm^3 and HIV-RNA was 4.14 $\log_{10}$ copies/mL). Median duration of treatment was 52 weeks. Of the 442 patients enrolled, 96% (424) received prior antiretroviral therapy. The safety results from this study are displayed in the ADVERSE REACTIONS section.

Study NV14256: INVIRASE + ddC versus either monotherapy

Study NV14256 was a randomized, double-blind study comparing the combination of INVIRASE (saquinavir mesylate) 600 mg tid + zalcitabine (ddC) to ddC monotherapy and INVIRASE monotherapy. The study accrued 970 patients, with median baseline CD_4 cell count at study

entry of 170 cells/mm^3. Median duration of prior ZDV treatment was 17 months. Median duration of follow-up was 17 months. There were 88 first AIDS-defining events or deaths in the ddC monotherapy group, 84 in the INVIRASE monotherapy group and 51 in the combination group. For survival there were 30 deaths in the ddC group, 40 in the INVIRASE group and 11 deaths in the combination group.

The analysis of clinical endpoints from this study showed that the 18-month cumulative incidence of clinical disease progression to AIDS-defining event or death was 17.7% for patients randomized to INVIRASE +ddC compared to 30.7% for patients randomized to ddC monotherapy and 28.3% for patients randomized to INVIRASE monotherapy. The reduction in the number of clinical events for the combination regimen relative to both monotherapy regimens was statistically significant (see figure below for Kaplan-Meier estimates of time to disease progression).

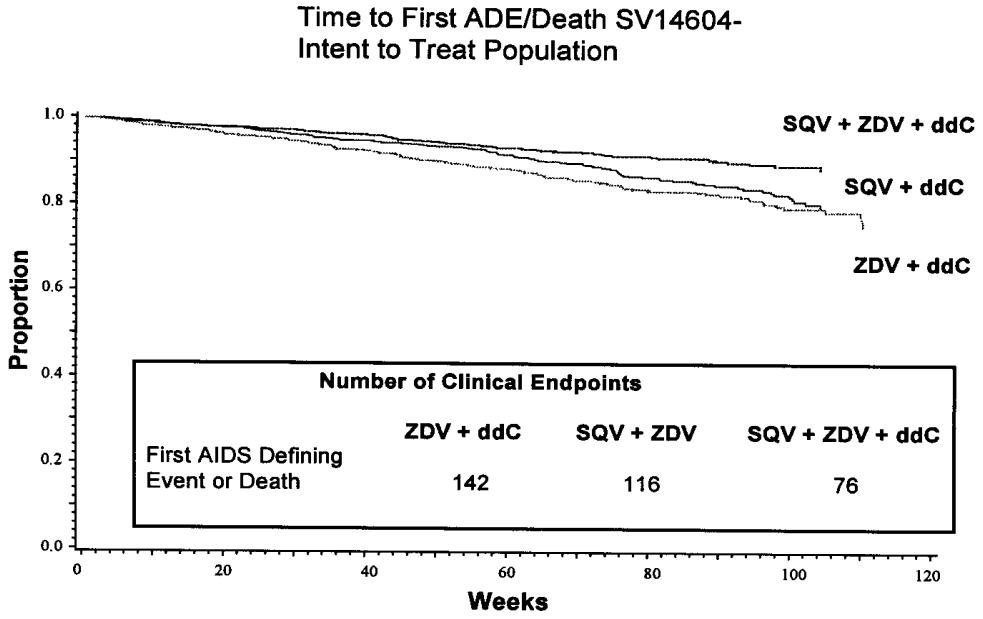


The 18-month cumulative mortality was 4% for patients randomized to INVIRASE + ddC, 8.9% for patients randomized to ddC monotherapy and 12.6% for patients randomized to INVIRASE monotherapy. The reduction in the number of deaths for the combination regimen relative to both monotherapy regimens was statistically significant.

Study SV14604: Triple therapy including INVIRASE vs. double antiretroviral therapy

SV14604 was a randomized, double-blind study comparing triple combination with INVIRASE (saquinavir mesylate) + zalcitabine (ddC) + zidovudine (ZDV), to double combinations of either ddC + ZDV or INVIRASE + ZDV. An initial monotherapy ZDV arm was discontinued early on, and these patients were switched (in a blinded manner) to triple therapy. The study accrued 3485 HIV-infected patients with $\leq$16 weeks prior therapy with ZDV. Median baseline CD_4 cell counts ranged from 195 to 204 cells/mm^3, and median baseline HIV-RNA were between 5.0 and 5.1 $\log_{10}$ copies/mL in each of the four original treatment groups. Median duration of treatment was approximately 14 months, and median duration of follow-up was approximately 17 months. There were 76 reports of AIDS-defining events or death in the triple combination arm, versus 116 in the INVIRASE + ZDV arm, and 142 in the ZDV + ddC arm.

Therefore, the inclusion of INVIRASE in a regimen with two nucleoside analogues reduced the time of progression to first AIDS-defining event or death (relative risk ratio of 0.502, 95% CI 0.38 to 0.66; p=0.0001). See figure below for Kaplan-Meier estimates of time to first AIDS-defining events or death in the intent-to-treat population of protocol SV14604.



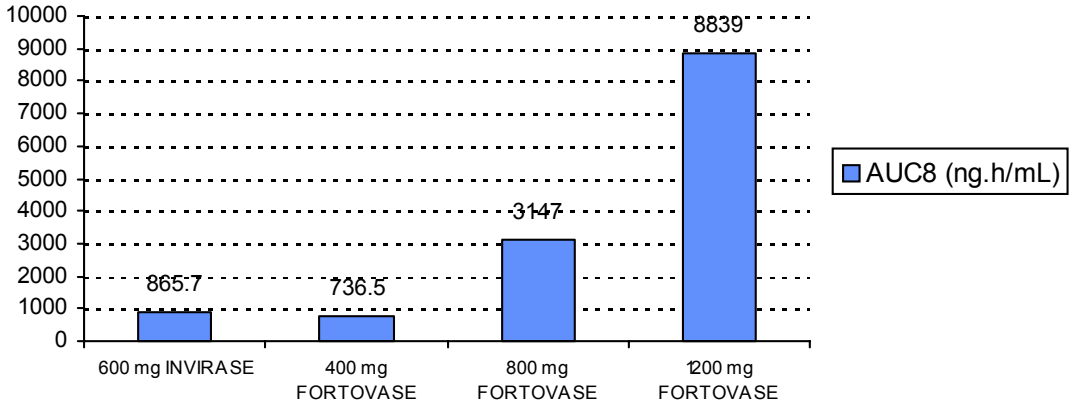
Based on emerging results from other clinical studies, the SV14604 data safety monitoring board recommended that all patients who had been receiving ZDV monotherapy under this protocol be switched to triple therapy with INVIRASE + ddC + ZDV (since monotherapy treatment of HIV with current agents was now recognized as suboptimal). This gives us the ability to examine the effect of immediate versus delayed triple therapy, since these patients were treated for a median of 225 days with monotherapy ZDV prior to receiving triple therapy. In an exploratory retrospective analysis in the group which started on monotherapy, 116 of 653 patients (17.8%) reported an AIDS-defining event or death, versus 76 of 955 (8.0%) in the group which had immediately received triple therapy from the outset (p=0.0001).

Human Pharmacokinetics:

The pharmacokinetic properties of FORTOVASE have been evaluated in healthy volunteers (n=162) and HIV-infected patients (n=77) after single oral doses of 300, 600, 800, 900 and 1200 mg and multiple oral doses of 400, 800 and 1200 mg TID. The disposition properties of saquinavir have been studied in healthy volunteers after intravenous doses of 6, 12, 36 or 72 mg (n=21).

The absolute bioavailability of FORTOVASE has not been assessed. However, following a single 600 mg dose, the relative bioavailability of this soft gelatin capsule (SGC) formulation was 331% (95% CI 207 to 530) of that for the same dose of saquinavir mesylate HGC (INVIRASE).

In healthy volunteers receiving single doses of saquinavir SGC (300-1200 mg) and in HIV infected patients receiving multiple doses of saquinavir SGC (400-1200 mg tid) a greater than dose-proportional increase in saquinavir plasma concentrations has been observed. Following multiple dosing with FORTOVASE in HIV-infected patients (1200 mg TID; n=33), the steady-state (Week 1) area under the plasma concentration versus time curve (AUC) was 8839 ng·h/mL. This was over 10 fold higher than following multiple dosing with 600 mg TID of saquinavir HGC (866 ng·h/mL; n=11; see figure below).



FORTOVASE (saquinavir) must be taken anytime within 2 hours following a meal. The mean 12-hour AUC after a single 800 mg oral dose of FORTOVASE in healthy volunteers (n=12) was increased from 167 ng·h/mL (CV 45%), under fasting conditions, to 1120 ng·h/mL (CV 54%) when FORTOVASE was given following a standardized high fat breakfast (45g protein, 76g carbohydrate, 55g fat; 961 kcal). The mean 12-hour AUC after a single 1200 mg oral dose of FORTOVASE in healthy volunteers (n=12) was increased from 952 ng·h/mL, following a light meal (21g protein, 50g carbohydrate, 28g fat; 524 kcal), to 1388 ng·h/mL when FORTOVASE was given following a heavy breakfast (45g protein, 76g carbohydrate, 55g fat; 961 kcal). The effect of food on saquinavir was shown to persist for up to 2 hours.

Following multiple dosing with FORTOVASE in healthy volunteers (1200 mg TID; n=18), the steady-state AUC was 80% (95% CI 22%-176%) higher than that observed after a single 1200 mg dose (n=30).

HIV-infected patients administered 1200 mg FORTOVASE, with the instructions to take their doses after a meal or substantial snack, had AUC and maximum plasma concentration (C_{max}) values which were about twice those observed in healthy volunteers receiving the same treatment regimen.

Administration of a single 600 mg dose of FORTOVASE with quadruple-strength grapefruit juice increased the bioavailability of saquinavir by 54% compared to the same dose administered with water. This effect is significantly less than that seen previously with the hard gelatin capsule formulation of saquinavir mesylate (INVIRASE).

Saquinavir partitions extensively into the tissues. A large steady-state volume of distribution (700 L) was observed following intravenous administration of 12 mg saquinavir; and saquinavir shows a high degree of protein binding (approximately 98%), which is independent of concentration over the range of 15 to 700 ng/mL. Concentrations of saquinavir in the CSF are very low compared to plasma. Based on animal data however, concentrations in brain tissue are expected to be several-fold higher than those in CSF.

Saquinavir is metabolized extensively via the hepatic route. In vitro work has established that the metabolism of saquinavir is P450 mediated with one isozyme (CYP3A4) responsible for more than 90% of the hepatic metabolism. Renal excretion of saquinavir is minor (<4%). The metabolic profile of saquinavir has been investigated in bile, plasma and microsomes in rats and in microsomes from other species, including man. Saquinavir is rapidly metabolized to a range of mono- and di-hydroxylated inactive compounds.

In a mass balance study using 600 mg ^{14}C-saquinavir (HGC; n=8), 88% and 1% of the orally administered radioactivity, was recovered in feces and urine, respectively, within 4 days of dosing. In an additional 4 subjects administered 10.5 mg ^{14}C-saquinavir i.v., 81% and 3% of the intravenously administered radioactivity was recovered in feces and urine, respectively, within 4 days of dosing.

Also 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).

The effect of gender was investigated in healthy volunteers receiving single 1200 mg doses of FORTOVASE (n=12 females; 18 males). No effect of gender was apparent on the pharmacokinetics of FORTOVASE in this study. The influence of race on the pharmacokinetics of FORTOVASE has not been determined, and there is limited experience in older patients (>60 years) and pediatric patients (<16 years).

General Animal Pharmacology:

Saquinavir produced only minor effects in general pharmacology studies when administered orally at a dose level of 30 mg/kg either as a single dose or daily for five days. No pharmacodynamic effects were seen in the test models used when a single intravenous dose of the drug was given at a dose level of 1 mg/kg.

A transient reduction in response to a painful stimulus, and an acute anti-convulsant effect to leptazol were observed in mice after oral administration of saquinavir. These effects however, were not confirmed in either the same models following IV dosing, or after oral dosing in other models used to investigate neuropharmacological or analgesic properties of the drug.

A stimulation of respiration was seen in two of four anesthetized cats following intraduodenal administration of saquinavir. However, this effect was seen neither in anesthetized cats when the drug was given IV, nor in conscious cats following either IV or oral administration of saquinavir. Furthermore, no gross changes in respiration were seen during preclinical toxicity testing of saquinavir.

Table 8: Single-Dose General Pharmacology

Test Model	Species #/sex/dose	Route Dose	Observations
gross behaviour	mouse 6 males cat: 4/sex	IV: 1 mg/kg IV: 1 mg/kg	no effects on gross behaviour or rectal temperature were seen no effects on gross behaviour were seen
leptazol-induced convulsions	mouse 10 females/dose	oral: 30 mg/kg IV: 1 mg/kg	anti-convulsant activity against tonic/ clonic convulsions (oral dosing only)
electroshock-induced convulsions	mouse 10 females/dose	oral: 30 mg/kg IV: 1 mg/kg	no anti-convulsant effect was seen
acetylcholine-induced writhing	mouse 10 males/dose	oral: 30 mg/kg IV: 1 mg/kg	no analgesic effect was seen
autonomic response	anesthetized cat 2/sex/dose	i.d.: 30 mg/kg IV: 1 mg/kg	small incr. in respiration rate in response to acetylcholine administration; no effect on autonomic response was seen
interaction on ouabain arrhythmias	mouse 10 females/dose	oral: 30 mg/kg IV: 1 mg/kg	no anti-arrhythmic effect was seen
cardiovascular and respiratory effects	anesthetized cat 2/sex/dose	i.d.: 30 mg/kg IV: 1 mg/kg	slight incr. in respiration rate and minute volume with decr. pCO_2; no effects on cardiovascular or respiratory parameters
blood pressure, heart rate & respiratory rate	conscious cat 4/sex	IV: 1 mg/kg	no effects on systolic blood pressure, heart rate or respiration rate
urine excretion	rat 8 males	IV: 1 mg/kg	no effect was seen on diuresis
gut motility	mouse 15/sex	IV: 1 mg/kg	no effect on GI motility was seen
sheep red blood cell antibody test	rat 10 males	IV: 1 mg/kg	no effect was seen on antibody formation
platelet aggregation (in vitro)	human plasma (2 M; 3 F)	concentration in plasma of $\leq$60 µM	no effect was observed on aggregation: alone or on aden. diphos.-induced aggregation

Table 9: Five-Day Multiple Dose General Pharmacology

Test Model	Species #/sex/dose	Route Daily Dose	Observations
gross behaviour	mouse 6 males cat 4/sex	oral: 30 mg/kg oral: 30 mg/kg	transient depression of pain response was seen Days 1 & 5; transient reduction in body temp. recorded on Day 5; no effects on gross behaviour were seen
leptazol-induced convulsions	mouse 10 females	oral: 30 mg/kg	no anti-convulsant activity was seen
electroshock-induced convulsions	mouse 10 females	oral: 30 mg/kg	no anti-convulsant effect was seen
acetylcholine-induced writhing	mouse 10 males	oral: 30 mg/kg	no analgesic effect was seen
interaction on ouabain arrhythmias	mouse 10 females	oral: 30 mg/kg	no anti-arrhythmic effect was seen
blood pressure, heart rate & respiratory rate	conscious cat 4/sex	oral: 30 mg/kg	no effects on systolic blood pressure, heart rate or respiration rate
urine excretion	rat 8 males	oral: 30 mg/kg	marginal incr. in sodium excretion on Day 5
gut motility	mouse 30 females	oral: 30 mg/kg	no effect on GI motility was seen
sheep red blood cell antibody test	mouse 10 males	oral: 30 mg/kg	no effect on antibody formation was seen
effects on developing adjuvant arthritis	rat 5 females	oral: 30 mg/kg	no effects on adjuvant arthritis, secondary response, edema secondary lesions, or joint mobility were observed

TOXICOLOGY

Oral toxicity and toxicokinetic studies in the rat and marmoset of up to six months duration have demonstrated excellent tolerance to high plasma levels of saquinavir. Increased susceptibility to saquinavir,as a result of gastrointestinal irritancy, was seen in neonatal rats. After weaning, juvenile animals tolerated the drug with no indications of toxicity. No reproductive, teratogenic, developmental or mutagenic effects have been seen with saquinavir.

A four-week oral combination study of saquinavir and zidovudine was conducted in mice; no toxic or toxicokinetic interactions were observed between these two drugs. A small toxicity and toxicokinetic program was also conducted to evaluate the intravenous use of saquinavir. Administration to rats and marmosets for up to four weeks produced mild to severe effects at the injection site. Only minor systemic findings were observed that were considered related to treatment with saquinavir.

A combination study of saquinavir soft gelatin capsules and ritonavir conducted in dogs demonstrated a significant pharmacokinetic interaction between these two protease inhibitors. Ritonavir increased plasma exposure to saquinavir approximately 10-fold, but this did not result in systemic toxicological sequelae.

Intentionally degraded FORTOVASE (saquinavir) soft gelatin capsules (with abnormally high levels of impurities) were administered orally to dogs for 13 weeks; the level of degradation products was estimated at up to 13 times the maximum human exposure. Degraded capsules did not appear to cause either an increase in toxicity, or the emergence of new toxicities compared to non-degraded capsules.

Table 10: Acute Toxicity

Species Strain	Route #/sex/dose	Dose (mg/kg) Observation	Results
Mouse Crl:CD-1	oral 2/sex/dose oral 7/sex/dose	500-5000 mg/kg 14 days 5000 mg/kg 15 days	maximum non-lethal dose > 5000 mg/kg
Mouse Crl:CD-1	IV 2/sex/dose IV 7/sex/dose	5-20 mg/kg 14 days 20 mg/kg 15 days	maximum non-lethal dose > 20 mg/kg
Rat Sprague-Dawley	oral 2/sex/dose oral 7/sex/dose	1000-5000 mg/kg 14 days 5000 mg/kg 14 days	maximum non-lethal dose > 5000 mg/kg
Marmoset C. jacchus	oral 1/sex/dose	1680 mg/kg 14 days	maximum non-lethal dose > 1680 mg/kg
Rat Sprague-Dawley	subcutaneous 4 males/dose	125 mg/kg base or salt 1 day	mild to moderate intolerance at injection sites with both free base and mesylate salt base: C_{max}=179 ng/mL AUC=2220 ng h/mL salt:: C_{max}=231 ng/mL AUC=3070 ng h/mL

Table 11: Multiple-Dose Toxicity

Species/Strain Duration	Route #/sex/dose	Dose (mg/kg/day)	Observations
Mouse Crl:CD-1 3 weeks	oral (admix) 10/sex/dose	0,150, 500, 1500, 5000	No dose-related toxicological findings at any dose level
Mouse Crl:CD-1 13 weeks	oral (admix) 21/sex/dose	0, 500, 1500, 2500, 5000	slight decr. in female body-weight gain (2500 & 5000 mg) slightly incr. ALP in females (5000 mg)
Mouse Crl:CD-1 4 weeks / with 30 days recovery (combination with zidovudine)	oral (gavage) 16/sex (control) 22/sex/dose	SAQ + ZDV 0 + 0 (I) 0 + 1000 (II) 2000 + 0 (III) 2000 + 1000 (IV) (BID dosing)	No tox. findings for saquinavir alone Reversible macrocytic anemia, leukopenia, lymphopenia, neutropenia, thrombocytosis, thymic atrophy and splenic hemopoiesis in all zidovudine-treated groups; irreversible splenic hemopoiesis in ZDV-alone males
Mouse Crl:CD-1 2 weeks	oral (gavage) 12/sex (control) 20/sex/dose	0, 1000, 2000 (BID dosing)	marginal incr. in glucose (1000 mg) minimal incr. in glucose and decr. in female erythrocyte parameters (2000 mg)
Mouse Crl:CD-1 2 or 4 weeks (palatability study)	oral (admix) 6/sex/dose	g/kg of diet* 1, 3, 10, 50 (14 days) 0, 30 (29 days)	marginal transient decr. in weight gain (30 g) no weight gain in males (50 g)
Rat Sprague Dawley 3 weeks	oral (admix) 10/sex/dose	0, 150, 500, 1000, 2000	no dose-related toxicological findings at any dose level
Rat Wistar 4 weeks/ with 26 days recovery	oral (gavage) 12/sex/dose	0, 30, 90, 300	mild reversible anemia and minimal incr. in leukocyte count (all doses) slight reversible incr. in triglycerides, small decr. in A/G ratio, minimal reversible decr. in adrenal weight (90 & 300 mg)
Rat Sprague Dawley 13 weeks	oral (admix) 20/sex/dose	0, 400, 1000, 2500	slight decr. in female weight gain & food intake, decr. male water consumption, slight incr. in male AST & ALT (all doses) minimal decr. in weight gain (1000 mg) slight decr. in male weight gain and incr. in female relative thyroid weight (2500 mg)

* equivalent to approximately 0, 220, 700, 2100, 5500 and 10000 mg/kg/day

Table 11 (continued): Multiple-Dose Toxicity

Species/Strain Duration	Route #/sex/dose	Dose (mg/kg/day)	Observations
Rat Sprague Dawley 6 month	oral (gavage) 30/sex/dose	0, 50, 150, 600	slight reversible decr. in female leukocytes, lymphocytes & neutrophils (all doses) marginal incr. in AST & ALT; slight incr. in relative liver weight at wk. 13 but not wk. 27 (600 mg)
Rat Wistar 2 weeks	IV 10 males/dose	0, 1, 3, 10→5 high dose reduced to 5 mg on Day 5	mild to severe intolerance at injection site (dose dependant; 60% of mid- and 100% of high-dose rats were sacrificed prematurely) slight anemia, leukocytosis, neutrophilia, incr. fibrinogen & bilirubin, slight decr. in A/G ratio, incr. splenic hemopoiesis (3 mg) incr. splenic hemopoiesis (10 mg); no clinical pathology was performed
Rat Sprague Dawley 4 weeks/ with 36 days recovery	IV 10/sex/dose	0, 1, 2, 5	no toxicological findings (1 mg) mild transient intol. at inj. site, reversible iatrogenic pulmonary inflam. changes, slight incr. in relative weight of spleen & lung (2 mg) mild to severe reversible intol. at inj. site, mild reversible anemia, moderate leukocytosis, lymphocytosis & neutrophilia, minimal decr. in triglycerides, reversible iatrogenic pulmonary inflam. changes, slight incr. in relative weight of spleen & lung (5 mg)
Rat Sprague Dawley 4 weeks	IV 10 males/dose	0, 1, 5	mild to moder. intol. at inj. site (dose depend.) mild anemia, marginal leukocytosis & lymphocytosis, slight incr. in relative weight of spleen (5 mg)
Rat (neonatal/juvenile) Sprague Dawley 9 week	oral (gavage) 10/sex/dose(Day 4 to 22, post-partum) 10/sex/dose (Day 4 post-part. to wk.9)	0, 125, 375, 1200	all tox. findings seen prior to weaning only dose-related soft-yellow excreta, perianal staining, inflam. of recto-anal junction & vagina (all doses) transient decr. in weight gain (375 mg) morbidity/mortality, transient decr. in weight gain (1200 mg)

Table 11 (continued): Multiple-Dose Toxicity

Species/Strain Duration	Route #/sex/dose	Dose (mg/kg/day)	Observations
Rat Sprague Dawley 7 days	oral (gavage) 7/sex/dose	200, 600 (BID dosing)	no toxicological findings
Rat Sprague Dawley 10 days	oral (gavage) 3/sex	50 (Day 1 & 2) 125 (Day 3 & 4) 300 (Day 5 & 7) 1000 (Day 8 & 10)	marginal incr. in relative weight of liver & thymus
Rat Sprague Dawley 2 or 4 weeks (palatability study)	oral (admix) 6/sex/dose	g/kg of diet* 1, 3, 10, 50 (14 days) 0, 30 (29 days)	slight transient decr. in weight gain & food consumption, slight decr. in relative weight of spleen & thymus in males (30 & 50 g)
Rat Sprague Dawley 7 days	IV 3/sex/dose	0, 10	slight incr. in relative weight of lung, pulmonary inflam. changes (10 mg)
Rat Sprague Dawley 2 weeks	IV (continuous infusion) 3/sex/dose	0, 100, 300, 600, 1000	no histological target-organ toxicity (all doses) mortality due to severe local effects at infusion site; distended abdomen, ascites, peritoneal cysts, peritonitis, anemia; increased platelets, leukocytes, neutrophils, AST, ALT, ALP, CK & Phos.; decr. Na & Cl (100, 300 & 600 mg) early mortality, thickening/discolor. of infusion site, ascites, extensive hemorrhage in lungs and other tissues; frank hematuria, anemia; incr. in AST, ALP & CK; decr. in Na & Cl (1000 mg)
Dog Beagle 7 days	IV (continuous infusion) 3 males/dose	0, 4	slight incr. in adrenal weight
Marmoset C. jacchus 4 weeks	oral (gavage) 5/sex/dose	0, 30, 120, 500	no effects at any dose level
Marmoset C. jacchus 4 weeks	oral (gavage) 6/sex (control) 8/sex (3000 mg)	0, 3000 (BID dosing)	minimal decrease in body weight
Marmoset C. jacchus 6 month	oral (gavage) 8/sex (control) 10/sex/dose	0, 50, 200, 750 (750 increased to 1000 from wk. 10)	slight decr. in weight gain, minimal post-dose emesis & diarrhea (1000 mg only)

* equivalent to approximately 0, 85. 230, 815, 2200 and 3600 mg/kg/day

Table 11 (continued): Multiple-Dose Toxicity

Species/Strain Duration	Route #/sex/dose	Dose (mg/kg/day)	Observations
Marmoset C. jacchus 4 weeks	IV 4 males/dose	0, 1, 3, 10	slight transient decr. in A/G ratio (3 & 10 mg) mild intol. at inj. site (10 mg only)
Marmoset C. jacchus 10 days	oral (gavage) 1/sex	50 (Day 1 & 2) 125 (Day 3 & 4) 300 (Day 5 & 7) 1000 (Day 8 & 9) 500 (Day 10)	no toxicological findings
Marmoset C. jacchus 7 days	IV 1/sex/dose	10	mild intol. at inj. site, slight incr. in AST among females (10 mg)

Toxicology of Degraded Soft Gelatin Capsules (FORTOVASE)

Dog Marshall Beagle 13 weeks	oral (capsule) 3/sex/dose	0 (placebo) 0 (empty capsule) 40 (degraded) 100 (degraded) 300 (degraded) 300 (non-degraded)	Toxicity findings were minor and limited to emesis, occasional diarrhea, and (300 mg/kg only) slight elevations in ALP, ALT and AST. Degradation of capsules was not associated with increases in toxicity or emergence of new toxicity.

Table 12: Dermal Toxicity

Species/Strain Study	Route #/sex/dose	Dose	Observations
Rabbit/New Zealand white; Acute irritation/ corrosion	epidermal 3 females/dose	0.5 mg/site (4 hours under semi-occlusive dressing)	Observation period: 1, 24, 48 and 72 hours after dose; no skin irritancy or corrosion seen
Guinea pig/ himalayan; contact hyper-sensitivity study	<u>induction</u> intradermal & epidermal <u>challenge</u> epidermal 10 female (control) 20 female (dose)	<u>induction</u> 0.3% (ID) and 10% (epiderm.) <u>challenge</u> 10% (epiderm.)	Observation period: 24 and 48 hours after both induction and challenge applications; no skin reactions observed

Table 13: Teratology and Reproductive Toxicity

Title	Species Strain	Route #/sex/dose	Dose (mg/kg/day)	Dosing Duration	Observations
fertility and general reprod. performance	Rat Sp. Dawley	oral (gavage) 30 (F0 gener.) 15 (F1 gener.)	0, 125, 375, 1200	M: 60 days before to day 23 after mating F: 14 days before mating until day 20 of preg. or day 21 post-part.	no toxicological findings in any generation
embryotoxicity and teratogenicity	Rat Wistar	oral (gavage) 26 mated females/dose	0, 200, 600, 1600	day 6 to 15 of gestation	no toxicological findings observed
embryotoxicity and teratogenicity	Rabbit Swiss Hare	oral (gavage) 18 mated females/dose	0, 100, 300, 1000	day 7 to 18 of gestation	no toxicological findings observed
peri- and post-natal toxicity	Rat Sp. Dawley	oral (gavage) 20 mated females/dose	0,200, 600, 1600	from day 15 of gestation to lactation & day 20 post-part.	no toxicological findings observed
toxicokinetic study in pregnant female	Rat Wistar	oral (gavage) 12 mated females/dose	600, 1600	day 7 to 16 of gestation	no toxicological findings observed
embryotoxicity and teratogenicity	Rat Wistar	oral (gavage) 10 mated females/dose	0, 500, 2000	day 6 to 15 of gestation	no toxicological findings observed
embryotoxicity and teratogenicity	Rabbit Swiss hare	oral (gavage) 7 mated females/dose	0, 200, 600, 2000 (BID dosing)	day 7 to 18 of gestation	slight decr. in maternal weight gain (all doses) no embryotox. or teratogenicity seen

Table 14: Mutagenicity and Genotoxicity

Title	Strain/Concentration	Exposure	Observations
bacterial cell gene mutation test (Ames test)	*S. typhimurium* (strains TA1535, 1537, 1538, 97. 98, 100 & 102) 33 to 333 µg/plate	48 hours	no mutagenic activity observed with or without metabolic activation cytotoxic at 333 µg/plate or above (with our without activation)
mammalian cell gene mutation (V79/HPRT assay)	Chinese hamster lung cell (V79) 5 to 30 µg/mL (no activ.) 5 to 100 µg/mL (activ.)	16 hrs (without activation) 5 hrs(with activation)	no mutagenic activity observed with or without metabolic activation cytotoxic at 30 µg/mL (without activation) and at 80 µg/mL (with activation)
chromosome aberration (*in vitro*)	human peripheral blood lymphocytes 10 to 50 µg/mL (no activ.) 25 to 100 µg/mL (activ.)	3,24,48 hrs (without activation) 3 hrs (with activation)	no clastogenic or aneuploidogenic effects observed with or without metabolic activation cytotoxic at 50 µg/mL (without activation) and at 75 µg/mL (with activation)
DNA damage/ repair (UDS Assay)	freshly isolated rat hepatocytes 1 to 15 µg/mL	18 hours	no unscheduled DNA synthesis was seen cytotoxic at 12.5 µg/mL and above
chromosome aberration (*in vivo*)	Mouse micronucleus test strain: Fu-moro oral: 2500, 5000 mg/kg	post-dose: 24 hours (2500 mg) 24, 48, 72 hours (5000 mg)	no chromosome breakage, spindle disturbances or anti-proliferative effects observed mortality: 4/7 females at 2500 mg; 8/20 females and 1/18 males at 5000 mg

Mutagenicity of Degraded Soft Gelatin Capsules (FORTOVASE)

bacterial cell gene mutation test (Ames test)	*S. typhimurium* (strains TA1535, 1537, 1538, 97. 98, 100 & 102) 10 to 500 µg/plate	48 hours	Neither degraded FORTOVASE nor the capmul excipient were found to be mutagenic in the described experimental conditions
chromosome aberration (*in vitro*)	human peripheral blood lymphocytes 13 to 200 µg/mL (no activ.) 50 to 200 µg/mL (activ.)	3 or 24 hours (without activation) 3 hours (with activation)	no clastogenic or aneuploidogenic effects observed with or without metabolic activation cytotoxic at 400 µg/mL after 3 hours; after 24 hours 50 µg/mL reduced mitotic index by >50%

SELECTED BIBLIOGRAPHY

1. Cameron DW, Japour AJ, Xu Y, et al. Ritonavir and saquinavir combination therapy for the treatment of HIV infection. AIDS 1999;13(2):213-24.

2. Cohen Stuart JW, Schuurman R, Burger DM, et al. Randomized trial comparing saquinavir soft gelatin capsules versus indinavir as part of triple therapy (CHEESE study). AIDS 1999;13(7):F53-8.

3. Collier AC, Coombs RW, Schoenfeld DA, et al. Treatment of Human Immunodeficiency Virus Infection with Saquinavir, Zidovudine, and Zalcitabine. N Engl J Med 1996;334(16):1011-1018

4. Craig JC, Duncan IB, Hockley D et al. Antiviral properties of Ro 31-8959, an inhibitor of human immunodeficiency virus (HIV) proteinase. Antiviral Res 1991;16:295-305.

5. Gill MJ on behalf of the NV15182 Study Team. Safety profile of soft gelatin formulation of saquinavir in combination with nucleosides in a broad patient population. AIDS 1998; 12: 1400-2.

6. Hsu A, Granneman GR, Cao G, et al. Pharmacokinetic interactions between two human immunodeficiency virus protease inhibitors, ritonavir and saquinavir. Clin Pharmacol Therapeutics 1998;63(4):453-464.

7. Kline MW, Brundage RC, Fletcher CV, et al. Combination therapy with saquinavir soft gelatin capsules in children with human immunodeficiency virus infection. Ped Infect Dis J 2001;20(7):666-671.

8. Lalezari, Jay; On behalf of the NV15107 Study Group. Selecting the Optimum Dose for a New Soft Gelatin Capsule Formulation of Saquinavir. JAIDS 1998;19(2):195-197.

9. Mitsuyasu RT, Skolnik PR, Cohen SR et al on behalf of the NV15355 Study Team. Activity of the soft gelatin formulation of saquinavir in combination therapy in antiretroviral-naïve patients. AIDS 1998;12:F103-9.

10. Moyle G. Saquinavir: a review of its development, pharmacological properties and clinical use. Exp Opin Invest Drugs 1996;5(2):1-13.

11. Moyle G, Pozniak A, Opravil M, et al. The SPICE study: 48-week activity of combinations of saquinavir soft gelatin and nelfinavir with and without nucleoside analogues. Study of Protease Inhibitor Combinations in Europe. JAIDS 2000;23(2):128-37.

12. Muirhead GJ, Shaw TM Williams PEO, et al. Pharmacokinetics of the HIV proteinase inhibitor, Ro 31-8959, after single and multiple oral doses in healthy volunteers. Br J Clin Pharmacol 1992;34(2):170P-1P.

13. Muirhead GJ, Williams PEO, Shaw TM et al. Investigations of the effect of food on the phamacokinetics of the HIV proteinase inhibitor Ro 31-8959 in healthy volunteers. AIDS 1992;6:P74.

14. Paredes R, Puig T, Arno A, et al. High-Dose Saquinavir Plus Ritonavir: Long-Term Efficacy in HIV-Positive Protease Inhibitor-Experienced Patients and Predictors of Virologic Response. JAIDS 1999;22(2):132.

15. Perry CM, Noble S. Saquinavir soft-gel capsule formulation. A review of its use in patients with HIV infection. Drugs 1998;55:461-486

16. Roberts NA, Craig JC, Sheldon J. Resistance and cross-resistance with saquinavir and other HIV protease inhibitors: theory and practice. AIDS 1998;12:453-460.

17. Roberts NA, Redshaw S. Discovery and development of the HIV proteinase inhibitor Ro 31-8959. In: Adams J and Merluzzi J, eds. The Search for Antiviral Drugs. Boston, Basel, Berlin. Birkhauser 1993:129-151.

18. Schapiro JM, Winters MA, Stewart F, et al. The effect of high-dose saquinavir on viral load and CD4+ T-cell counts in HIV-infected patients. Ann Intern Med 1996; 124:1039-50.

19. Vella S. Clinical experience with saquinavir. AIDS 1995; 9(suppl 2):S21-S25.

20. Vella S, Butto S, Franco M et al. Viral load and CD4 responses during combination therapy with zidovudine and saquinavir: correlation with the emergence of viral isolates with reduced sensitivity. J AIDS & Human Retrov 1995;10(suppl 3):S21.

21. Viora M, Di Genova G, Quarant MG, et al. Lack of Immunotoxicity of Saquinavir (Ro 31-8959) Used Alone or in Double or Triple Combination with AZT and ddC. J Clin Immunol 1998;18(5):346-354.