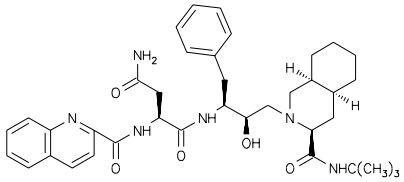
FORTOVASE® (saquinavir) PI

FORTOVASE®
(saquinavir)
SOFT GELATIN CAPSULES

DESCRIPTION: FORTOVASE brand of saquinavir is an inhibitor of the human immunodeficiency virus (HIV) protease. FORTOVASE is available as beige, opaque, soft gelatin capsules for oral administration in a 200-mg strength (as saquinavir free base). Each capsule also contains the inactive ingredients medium chain mono- and diglycerides, povidone and dl-alpha tocopherol. Each capsule shell contains gelatin and glycerol 85% with the following colorants: red iron oxide, yellow iron oxide and titanium dioxide. The chemical name for saquinavir is N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide which has a molecular formula $C_{38}H_{50}N_6O_5$ and a molecular weight of 670.86. Saquinavir has the following structural formula:



Saquinavir is a white to off-white powder and is insoluble in aqueous medium at 25°C.

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

Antiviral Activity In Vitro: In vitro antiviral activity of saquinavir was assessed in lymphoblastoid and monocytic cell lines and in peripheral blood lymphocytes. Saquinavir inhibited HIV activity in both acutely and chronically infected cells. IC_{50} and IC_{90} values (50% and 90% inhibitory concentrations) were in the range of 1 to 30 nM and 5 to 80 nM, respectively; however, these concentrations may be altered in the presence of human plasma due to protein binding of saquinavir. In cell culture saquinavir demonstrated additive to synergistic effects against HIV in double- and triple-combination regimens with reverse transcriptase inhibitors zidovudine, zalcitabine, didanosine, lamivudine, stavudine and nevirapine, without enhanced cytotoxicity. The relationship between in vitro susceptibility of HIV to saquinavir and inhibition of HIV replication in humans has not been established.

Drug Resistance: HIV isolates with reduced susceptibility to saquinavir (4-fold or greater increase in IC_{50} from baseline; ie, phenotypic resistance) have been selected in vitro. Genotypic analyses of these HIV isolates showed several mutations in the HIV-protease gene but only those at codons 48 (Gly→Val) and/or 90 (Leu→Met) were consistently associated with saquinavir resistance.

Isolates from selected patients with loss of antiviral activity and prolonged (range: 24 to 147 weeks) therapy with INVIRASE® (saquinavir mesylate) (alone or in combination with nucleoside analogues) showed reduced susceptibility to saquinavir. Genotypic analysis of these isolates showed that mutations at amino acid positions 48 and/or 90 of the HIV-protease gene were most consistently associated with saquinavir resistance. Other mutations in the protease gene were also observed. Mutations at codons 48 and 90 have not been detected in isolates from protease inhibitor naive patients.

In a study (NV15107) of treatment-experienced patients receiving FORTOVASE monotherapy (1200 mg tid) for 8 weeks followed by antiretroviral combination therapy for a period of 4 to 48 weeks (median 32 weeks), 10 of 32 patients showed genotypic changes associated with reduced susceptibility to saquinavir. However, for resistance evaluation virus could not be recovered from 11 of 32 patients.

In a study (NV15355) of treatment-naive patients receiving FORTOVASE in combination with two nucleoside analogues for a period of 16 weeks, 1 of 28 patient isolates showed genotypic changes at codon 71 and 90 in the HIV-protease gene.

Cross-resistance: Among protease inhibitors variable cross-resistance has been recognized. Analysis of saquinavir-resistant isolates from patients following prolonged (24 to 147 weeks) therapy with INVIRASE showed that a majority of patients had resistance to at least one of four other protease inhibitors (indinavir, nelfinavir, ritonavir, 141W94).

CLINICAL PHARMACOLOGY: ***Pharmacokinetics:*** The pharmacokinetic properties of saquinavir when administered as FORTOVASE have been evaluated in healthy volunteers (n=207) and HIV-infected patients (n=91) after single-oral doses (range: 300 mg to 1200 mg) and multiple-oral doses (range: 400 mg to 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).

ABSORPTION AND BIOAVAILABILITY IN ADULTS: Following multiple dosing of FORTOVASE (1200 mg tid) in HIV-infected patients in study NV15107, the mean steady-state area under the plasma concentration versus time curve (AUC) at week 3 was 7249 ng·h/mL (n=31) compared to 866 ng·h/mL (n=10) following multiple dosing with 600 mg tid of INVIRASE (Table 1). Preliminary results from a pharmacokinetic substudy of NV15182 showed a mean saquinavir AUC of 3485 (CV 66%) ng·h/mL (n=11) in patients sampled between weeks 61 to 69 of therapy (see PRECAUTIONS: *General*). While this mean AUC value was lower than that of the week 3 steady-state value for FORTOVASE (1200 mg tid) from study NV15107, it remained higher than the mean AUC value for INVIRASE in study NV15107.

Table 1. Mean AUC_8 in Patients Treated With FORTOVASE and INVIRASE (Week 3)

Treatment	n	AUC_8 ng·h/mL	± SD
FORTOVASE			
1200 mg tid	31	7249	± 6174
INVIRASE			
600 mg tid	10	866	± 533

The absolute bioavailability of saquinavir administered as FORTOVASE has not been assessed. However, following single 600-mg doses, the relative bioavailability of saquinavir as FORTOVASE compared to saquinavir administered as INVIRASE was estimated as 331% (95% CI 207% to 530%). The absolute bioavailability of saquinavir administered as INVIRASE averaged 4% (CV 73%, range: 1% to 9%) in 8 healthy volunteers who received a single 600-mg dose of INVIRASE following a high-fat breakfast (48 g protein, 60 g carbohydrate, 57 g fat; 1006 kcal). In healthy volunteers receiving single doses of FORTOVASE (300 mg to 1200 mg) and in HIV-infected patients receiving multiple doses of FORTOVASE (400 mg to 1200 mg tid), a greater than dose-proportional increase in saquinavir plasma concentrations has been observed.

Comparison of pharmacokinetic parameters between single- and multiple-dose studies shows that following multiple dosing of FORTOVASE (1200 mg tid) in healthy male volunteers (n=18), the steady-state AUC was 80% (95% CI 22% to 176%) higher than that observed after a single 1200-mg dose (n=30).

HIV-infected patients administered FORTOVASE (1200 mg tid) had AUC and maximum plasma concentration (C_{max}) values approximately twice those observed in healthy volunteers receiving the same treatment regimen. The mean AUC values at week 1 were 4159 (CV 88%) and 8839 (CV 82%) ng·h/mL, and C_{max} values were 1420 (CV 81%) and 2477 (CV 76%) ng/mL for healthy volunteers and HIV-infected patients, respectively.

FOOD EFFECT: The mean 12-hour AUC after a single 800-mg oral dose of saquinavir 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 with breakfast (48 g protein, 60 g carbohydrate, 57 g fat; 1006 kcal).

DISTRIBUTION IN ADULTS: The mean steady-state volume of distribution following intravenous administration of a 12-mg dose of saquinavir (n=8) was 700 L (CV 39%), suggesting saquinavir partitions into tissues. It has been shown that saquinavir, up to 30 µg/mL is approximately 97% bound to plasma proteins.

METABOLISM AND ELIMINATION IN ADULTS: In vitro studies using human liver microsomes have shown that the metabolism of saquinavir is cytochrome P450 mediated with the specific isoenzyme, CYP3A4, responsible for more than 90% of the hepatic metabolism. Based on in vitro studies, saquinavir is rapidly metabolized to a range of mono- and di-

hydroxylated inactive compounds. In a mass balance study using 600 mg ^{14}C-saquinavir mesylate (n=8), 88% and 1% of the orally administered radioactivity was recovered in feces and urine, respectively, within 5 days of dosing. In an additional 4 subjects administered 10.5 mg ^{14}C-saquinavir intravenously, 81% and 3% of the intravenously administered radioactivity was recovered in feces and urine, respectively, within 5 days of dosing. In mass balance studies, 13% of circulating radioactivity in plasma was attributed to unchanged drug after oral administration and the remainder attributed to saquinavir metabolites. Following intravenous administration, 66% of circulating radioactivity was attributed to unchanged drug and the remainder attributed to saquinavir metabolites, suggesting that saquinavir undergoes extensive first-pass metabolism.

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

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

Gender, Race and Age: 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 saquinavir in this study.

The effect of race on the pharmacokinetics of saquinavir when administered as FORTOVASE is unknown.

The pharmacokinetics of saquinavir when administered as FORTOVASE has not been investigated in patients >65 years of age or in pediatric patients (<16 years of age).

DRUG INTERACTIONS (see PRECAUTIONS: *Drug Interactions*): Several drug interaction studies have been completed with both INVIRASE and FORTOVASE. Results from studies conducted with INVIRASE may not be applicable to FORTOVASE. Table 2 summarizes the effect of FORTOVASE on the geometric mean AUC and C_{max} of coadministered drugs. Table 3 summarizes the effect of coadministered drugs on the geometric mean AUC and C_{max} of saquinavir.

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Table 2. Effect of FORTOVASE on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug	FORTOVASE Dose	N	% Change for Coadministered Drug	
			AUC (95%CI)	C_{max} (95%CI)
Clarithromycin 500 mg bid x 7 days Clarithromycin 14-OH clarithromycin metabolite	1200 mg tid x 7days	12V	 ↑45% (17-81%) ↓24% (5-40%)	 ↑39% (10-76%) ↓34% (14-50%)
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	↔	↔
Sildenafil 100-mg single dose	1200 mg tid x 8 days	27V	↑210% (150-300%)	↑140% (80-230%)
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%)

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

Table 3. Effect of Coadministered Drugs on FORTOVASE and INVIRASE Pharmacokinetics

Coadministered rug	FORTOVASE Dose	N	% Change for Saquinavir	
			AUC (95%CI)	C_{max} (95%CI)
Clarithromycin 500 mg bid x 7 days	1200 mg tid x 7days	12V	↑177% (108-269%)	↑187% (105-300%)
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 x 4 days	1200-mg single dose	14P	↑392% (271-553%)	↑179% (105-280%)
Ritonavir 400 mg bid x 14 days*	400 mg bid x 14 days†	8V	↑121% (7-359%)	↑64%§

Coadministered Drug	INVIRASE Dose	N	% Change for Saquinavir	
			AUC (95%CI)	C_{max} (95%CI)
Delavirdine 400 mg tid x 14 days	600 mg tid x 21 days	13V	↑5-fold	Not available
Ketoconazole 200 mg qd x 6 days	600 mg tid x 6 days	12V	↑130% (58-235%)	↑147% (53-298%)
Nevirapine 200 mg bid x 21 days	600 mg tid x 7 days	23P	↓24% (1-42%)	↓28% (1-47%)
Ranitidine 150 mg x 2 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%§
Rifampin 600 mg qd x 7 days	600 mg tid x 14 days	12V	↓84% (79-88%)	↓79% (68-86%)
Ritonavir 400 mg bid steady state*	400 mg bid steady state‡	7P	↑1587% (808-3034%)	↑1277% (577-2702%)
Zalcitabine (ddC) 0.75 mg tid x 7 days	600 mg tid x 7 days	27P	↔	↔
Zidovudine (ZDV) 200 mg tid x > 7 days	600 mg tid x > 7 days	20P	↔	↔

↑ Denotes an average increase in exposure by the percentage indicated.
↓ Denotes an average decrease in exposure by the percentage indicated.
↔ Denotes no statistically significant change in exposure was observed.
* When ritonavir was combined with the same dose of either INVIRASE or FORTOVASE, actual mean plasma exposures (AUC_{12}, 18.2 µg·h/mL, 20.0 µg·h/mL, respectively) were not significantly different.
† Compared to standard FORTOVASE 1200 mg tid regimen (n=33).
‡ Compared to standard INVIRASE 600 mg tid regimen (n=114).
§ Did not reach statistical significance.
P Patient
V Healthy Volunteers

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

INDICATIONS AND USAGE: FORTOVASE is indicated for use in combination with other antiretroviral agents for the treatment of HIV infection. This indication is based on a study that showed a reduction in both mortality and AIDS-defining clinical events for patients who received INVIRASE in combination with HIVID® (zalcitabine) compared to patients who received either HIVID or INVIRASE alone. This indication is also based on studies that showed increased saquinavir concentrations and improved antiviral activity for FORTOVASE 1200 mg tid compared to INVIRASE 600 mg tid.

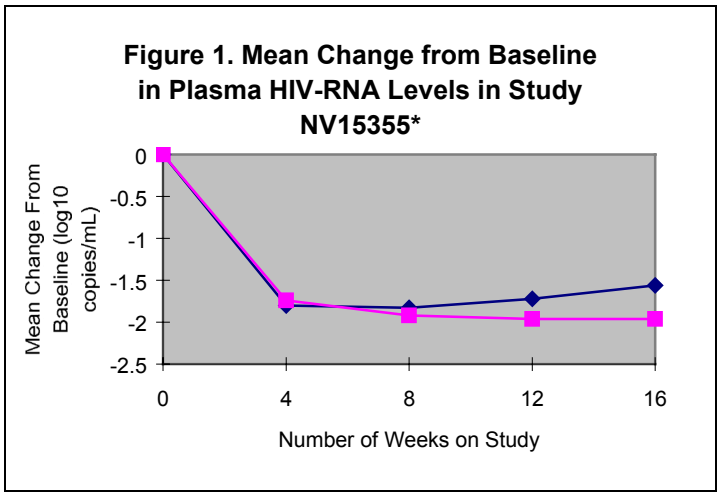
Description of Clinical Studies: *STUDIES WITH FORTOVASE (saquinavir):*

Study NV15355: Efficacy Study

Study NV15355 is an ongoing, open-label, randomized, parallel study comparing FORTOVASE (n=90) and INVIRASE (n=81) in combination with two nucleoside reverse transcriptase inhibitors of choice in treatment-naive patients. The median age was 35 (range: 18 to 63), 92% of patients were male, and 68% were Caucasian. Mean baseline CD_4 cell count was 429 cells/mm^3, and mean baseline plasma HIV-RNA was 4.8 $\log_{10}$ copies/mL.

At week 16, 60 patients on the FORTOVASE arm compared to 30 patients on the INVIRASE arm had plasma HIV RNA levels below the limit of assay quantification (<400 copies/mL, Amplicor HIV-1 Monitor™ Test).

At week 16, mean changes from baseline in CD_4 cell counts and plasma HIV-RNA levels between the two treatment arms were statistically indistinguishable. The mean change in CD_4 cell count was 97 cells/mm^3 for the FORTOVASE arm and 115 cells/mm^3 for the INVIRASE arm. The mean changes in plasma HIV-RNA levels are summarized in Figure 1.



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

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

† 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.

Study NV15182: Safety Study

Study NV15182 was an open-label safety study of FORTOVASE in combination with other antiretroviral agents in 442 patients (median age 39 [range: 15 to 71], 90% male and 73% Caucasian). The mean baseline CD_4 cell count was 227 cells/mm^3 and mean baseline HIV-RNA was 4.14 $\log_{10}$ copies/mL. The safety results from this study are displayed in the ADVERSE REACTIONS section.

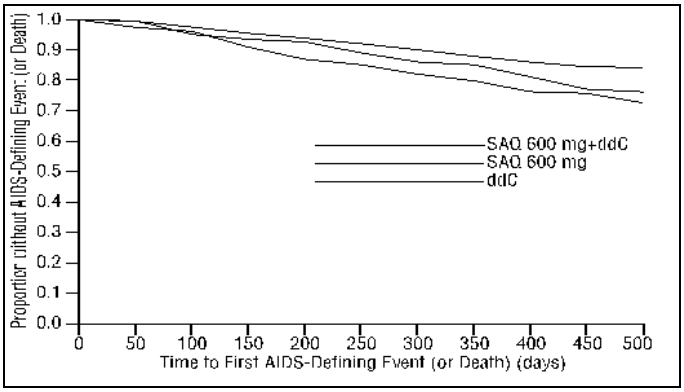
STUDIES WITH INVIRASE (saquinavir mesylate):

Study NV14256: INVIRASE + HIVID Versus Either Monotherapy

Study NV14256 (North America) was a randomized, double-blind study comparing the combination of INVIRASE 600 mg tid + HIVID to HIVID 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 HIVID monotherapy group, 84 in the INVIRASE monotherapy group and 51 in the combination group. For survival there were 30 deaths in the HIVID group, 40 in the INVIRASE group and 11 deaths in the combination group.

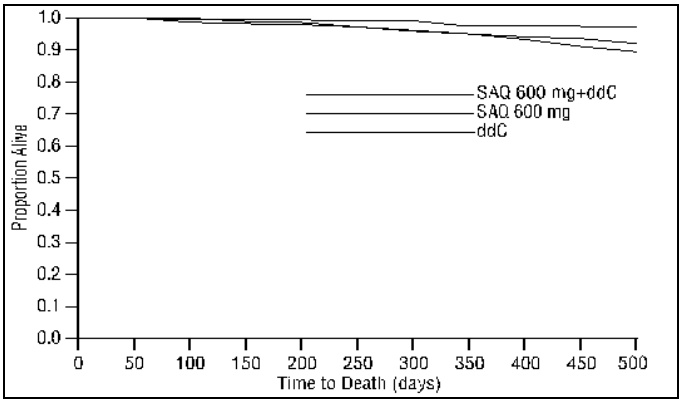
The analysis of clinical endpoints from this study showed that the 18-month cumulative incidence of clinical disease progression to AIDS-defining event or death was 17.7% for patients randomized to INVIRASE + HIVID compared to 30.7% for patients randomized to HIVID monotherapy and 28.3% for patients 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 2 for Kaplan-Meier estimates of time to disease progression).

Figure 2. Time to First AIDS-Defining Event (or Death) (days) NV14256



The 18-month cumulative mortality was 4% for patients randomized to INVIRASE + HIVID, 8.9% for patients randomized to HIVID 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 (see Figure 3 for Kaplan-Meier estimates of time to death).

Figure 3. Time to Death (days) NV14256



CONTRAINDICATIONS: FORTOVASE is contraindicated in patients with clinically significant hypersensitivity to saquinavir or to any of the components contained in the capsule.

FORTOVASE should not be administered concurrently with terfenadine, cisapride, astemizole, triazolam, midazolam or ergot derivatives, because competition for CYP3A by saquinavir could result in inhibition of the metabolism of these drugs and create the potential for serious and/or life-threatening reactions such as cardiac arrhythmias or prolonged sedation (see PRECAUTIONS: *Drug Interactions*).

WARNINGS:

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

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

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

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.

PRECAUTIONS: ***General:*** FORTOVASE (saquinavir) soft gelatin capsules and INVIRASE (saquinavir mesylate) capsules are not bioequivalent and cannot be used interchangeably. Only FORTOVASE should be used for the initiation of saquinavir therapy (see DOSAGE AND ADMINISTRATION) since FORTOVASE soft gelatin capsules provide greater bioavailability and efficacy than INVIRASE capsules. For patients taking INVIRASE capsules with a viral load below the limit of quantification, a switch to FORTOVASE is recommended to maintain a virologic response. For patients taking INVIRASE capsules who have not had an adequate response or are failing therapy, if saquinavir resistance is clinically suspected, then FORTOVASE should not be used. If resistance to saquinavir is not clinically suspected, a switch to FORTOVASE may be considered.

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

Preliminary results from a pharmacokinetic substudy of NV15182 from patients sampled between weeks 61 to 69 of treatment showed that the mean saquinavir AUC was lower than the week 3 mean AUC from study NV15107. However, the mean AUC of saquinavir at week 61 to 69 remained higher than the mean AUC of INVIRASE in study NV15107 (see CLINICAL PHARMACOLOGY: *Pharmacokinetics*). The clinical significance of this finding is unknown.

Hepatic Insufficiency: Saquinavir is principally metabolized by the liver. Therefore, caution should 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. Although a causal relationship has not been established, there have been reports of exacerbation of chronic liver dysfunction, including portal hypertension, in patients with underlying hepatitis B or C, cirrhosis or other underlying liver abnormalities.

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

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

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

Information for Patients: A statement to patients and health care providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with FORTOVASE.** A Patient Package Insert (PPI) for FORTOVASE is available for patient information.

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.

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 CLINICAL PHARMACOLOGY: *Pharmacokinetics*). 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 told that the long-term effects of FORTOVASE are unknown at this time.

Patients should be informed that refrigerated (36° to 46°F, 2° to 8°C) capsules of FORTOVASE remain stable until the expiration date printed on the label. Once brought to room temperature [at or below 77°F (25°C)], capsules should be used within 3 months.

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

Drug Interactions: **Several drug interaction studies have been completed with both INVIRASE and FORTOVASE. Observations from drug interaction studies with INVIRASE may not be predictive for FORTOVASE.**

Drugs That Should Not Be Coadministered With FORTOVASE	
Antihistamines	Astemizole, Terfenadine
Antimigraine	Ergot Derivatives
GI Motility Agents	Cisapride
Sedatives/Hypnotics	Midazolam, Triazolam

Clinically Significant Drug Interactions Which Decrease Saquinavir Plasma Concentrations	
HIV Non-nucleoside Reverse Transcriptase Inhibitors	Nevirapine*
Antimycobacterial Agents	Rifabutin*, Rifampin*

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Clinically Significant Drug Interactions Which Increase Saquinavir Plasma Concentrations	
Antibiotics	Clarithromycin†
HIV Protease Inhibitors	Indinavir†, Ritonavir*†, Nelfinavir†
HIV Non-nucleoside Reverse Transcriptase Inhibitors	Delavirdine*
Antifungal Agents	Ketoconazole*
Other Potential Drug Interactions‡	
Anticonvulsants: Carbamazepine, Phenobarbital, Phenytoin	May decrease saquinavir plasma concentrations
Corticosteroids: Dexamethasone	May decrease saquinavir plasma concentrations

* Studied with INVIRASE.
† Studied with FORTOVASE.
‡ This table is not all inclusive.

ANTIBIOTICS:

Clarithromycin: Coadministration of clarithromycin with FORTOVASE resulted in a 177% increase in saquinavir plasma AUC, a 45% increase in clarithromycin AUC and a 24% decrease in clarithromycin 14-OH metabolite AUC.

ANTIHISTAMINES:

Terfenadine: Coadministration of terfenadine with FORTOVASE resulted in increased terfenadine plasma levels; therefore, FORTOVASE should not be administered concurrently with terfenadine because of the potential for serious and/or life-threatening cardiac arrhythmias.

Astemizole: Because a similar interaction to that seen with terfenadine is likely from the coadministration of FORTOVASE and astemizole, FORTOVASE should not be administered concurrently with astemizole.

ERECTILE DYSFUNCTION AGENTS:

Sildenafil: In a study performed in healthy male volunteers, coadministration of saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg tid) with sildenafil (100 mg single dose) resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics. When sildenafil is administered concomitantly with saquinavir a starting dose of 25 mg of sildenafil should be considered.

HIV PROTEASE INHIBITORS:

Indinavir: Coadministration of indinavir with FORTOVASE (1200-mg single dose) resulted in a 364% increase in saquinavir plasma AUC. Currently, there are no safety and efficacy data available from the use of this combination.

Nelfinavir: Coadministration of nelfinavir with FORTOVASE resulted in an 18% increase in nelfinavir plasma AUC and a 392% increase in saquinavir plasma AUC. Currently, there are no safety and efficacy data available from the use of this combination.

Ritonavir: Following approximately 4 weeks of a combination regimen of saquinavir (400 mg or 600 mg bid) and ritonavir (400 mg or 600 mg bid) in HIV-infected patients, saquinavir AUC values were at least 17-fold greater than historical AUC values from patients who received saquinavir 600 mg tid without ritonavir. When used in combination therapy for up to 24 weeks, doses greater than 400 mg bid of either ritonavir or saquinavir were associated with an increase in adverse events. Plasma exposures achieved with INVIRASE (400 mg bid) and ritonavir (400 mg bid) are similar to those achieved with FORTOVASE (400 mg bid) and ritonavir (400 mg bid).

HIV REVERSE TRANSCRIPTASE INHIBITORS:

Based on known metabolic pathways and routes of elimination for nucleoside reverse transcriptase inhibitors, no interaction with saquinavir is expected.

HIV NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS:

Delavirdine: Coadministration of delavirdine with INVIRASE resulted in a 5-fold increase in saquinavir plasma AUC. Currently there are limited safety and no efficacy data available from the use of this combination. In a small, preliminary study, hepatocellular enzyme elevations occurred in 13% of subjects during the first several weeks of the delavirdine and saquinavir combination (6% Grade 3 or 4). Hepatocellular changes should be monitored frequently if this combination is prescribed.

Nevirapine: Coadministration of nevirapine with INVIRASE resulted in a 24% decrease in saquinavir plasma AUC. Currently, there are no safety and efficacy data available from the use of this combination.

ANTIFUNGAL AGENTS:

Ketoconazole: Coadministration of ketoconazole with INVIRASE resulted in a 130% increase in saquinavir plasma AUC.

ANTIMYCOBACTERIAL AGENTS:

Rifabutin: Coadministration of rifabutin with INVIRASE resulted in a 43% decrease in saquinavir plasma AUC. Physicians should consider using an alternative to rifabutin when a patient is taking FORTOVASE.

Rifampin: Coadministration of rifampin with INVIRASE resulted in an 84% decrease in saquinavir plasma AUC. Physicians should consider using an alternative to rifampin when a patient is taking FORTOVASE.

H_2 ANTAGONISTS:

Ranitidine: Little or no change in the pharmacokinetics of INVIRASE was observed when coadministered with ranitidine. No significant interaction would be expected between FORTOVASE and ranitidine.

GI MOTILITY AGENTS:

Cisapride: Although no interaction study has been conducted, cisapride should not be administered concurrently with FORTOVASE because of the potential for serious and/or life-threatening cardiac arrhythmias.

Carcinogenesis, Mutagenesis and Impairment of Fertility: *Carcinogenesis:* Carcinogenicity studies in rats and mice have not yet been completed.

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

Impairment of Fertility: Fertility and reproductive performance were not affected in rats at plasma exposures (AUC values) approximately 50% of those achieved in humans at the recommended dose.

Pregnancy: *Teratogenic Effects:* Category B. Reproduction studies conducted 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 of FORTOVASE. 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 of FORTOVASE had no effect on the survival, growth and development of offspring to weaning. Because animal reproduction studies are not always predictive of human response, FORTOVASE should only be used during pregnancy after taking into account the importance of the drug to the mother. Presently, there are no reports of women receiving FORTOVASE in clinical trials who became pregnant.

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

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

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

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

ADVERSE REACTIONS (see PRECAUTIONS)**:** The safety of FORTOVASE was studied in more than 500 patients who received the drug either alone or in combination with other antiretroviral agents. The majority of treatment-related adverse events were of mild intensity. The most frequently reported treatment-emergent adverse events among patients receiving FORTOVASE in combination with other antiretroviral agents were diarrhea, nausea, abdominal discomfort and dyspepsia.

Clinical adverse events of at least moderate intensity which occurred in ≥2% of patients in studies NV15182 and NV15355 are summarized in Table 4. The median duration of treatment in studies NV15182 and NV15355 were 52 and 18 weeks, respectively. In NV15182, more than 300 patients were on treatment for approximately 1 year.

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

Rare occurrences of the following serious adverse experiences have been reported during clinical trials of FORTOVASE and/or INVIRASE and were considered at least possibly related to use of study drugs: confusion, ataxia and weakness; seizures; headache; acute myelobastic leukemia; hemolytic anemia; thrombocytopenia; thrombocytopenia and intracranial hemorrhage leading to death; attempted suicide; Stevens-Johnson syndrome; bullous skin eruption and polyarthritis; severe cutaneous reaction associated with increased liver function tests; isolated elevation of transaminases; exacerbation of chronic liver disease with Grade 4 elevated liver function tests,

jaundice, ascites, and right and left upper quadrant abdominal pain; pancreatitis leading to death; intestinal obstruction; portal hypertension; thrombophlebitis; peripheral vasoconstriction; drug fever; nephrolithiasis; and acute renal insufficiency.

Table 5 summarizes the percentage of patients with marked laboratory abnormalities in study NV15182 and NV15355 (median duration of treatment was 52 and 18 weeks, respectively). In study NV15182, by 48 weeks <1% of patients discontinued treatment due to laboratory abnormalities.

FORTOVASE® (saquinavir) PI

Table 4. Percentage of Patients With Treatment-Emergent Adverse Events* of at Least Moderate Intensity, Occurring in ≥2% of Patients

	NV15182 (48 weeks)	NV15355 (16 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	17.8
Abdominal Discomfort	8.6	4.9	13.3
Dyspepsia	8.4	–	8.9
Flatulence	5.7	7.4	12.2
Vomiting	2.9	1.2	4.4
Abdominal Pain	2.3	1.2	7.8
Constipation	–	–	3.3
BODY AS A WHOLE			
Fatigue	4.8	6.2	6.7
CENTRAL AND PERIPHERAL NERVOUS SYSTEM			
Headaches	5.0	4.9	8.9
PSYCHIATRIC DISORDERS			
Depression	2.7	–	–
Insomnia	–	1.2	5.6
Anxiety	–	2.5	2.2
Libido Disorder	–	–	2.2
SPECIAL SENSES DISORDERS			
Taste Alteration	–	1.2	4.4
MUSCULOSKELETAL DISORDERS			
Pain	–	3.7	3.3
DERMATOLOGICAL DISORDERS			
Eczema	–	2.5	–
Rash	–	2.5	–
Verruca	–	–	2.2

* Includes adverse events at least possibly related to study drug or of unknown intensity and/or relationship to treatment (corresponding to ACTG Grade 3 and 4).

† Antiretroviral Treatment of Choice.

‡ Reverse Transcriptase Inhibitor.

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Table 5. Percentage of Patients With Marked Laboratory Abnormalities*

		NV15182 (48 weeks)	NV15355 (16 weeks) Naive Patients	
		FORTOVASE + TOC† N=442	INVIRASE + 2 RTIs‡ N=81	FORTOVASE + 2 RTIs‡ N=90
BIOCHEMISTRY	**Limit**			
Alkaline Phosphatase	>5 x ULN§	0.5	0.0	0.0
Calcium (high)	>12.5 mg/dL	0.2	0.0	0.0
Creatine Kinase	>4 x ULN§	7.8	0.0	4.8
Gamma GT	>5 x ULN§	5.7	2.6	7.1
Glucose (low)	<40 mg/dL	6.4	2.5	3.5
Glucose (high)	>250 mg/dL	1.4	1.3	1.2
Phosphate	<1.5 mg/dL	0.5	0.0	0.0
Potassium (high)	>6.5 mEq/L	2.7	0.0	1.2
Serum Amylase	>2 x ULN§	1.9	ND	ND
SGOT (AST)	>5 x ULN§	4.1	0.0	1.2
SGPT (ALT)	>5 x ULN§	5.7	1.3	2.3
Sodium (high)	>157 mEq/L	0.7	0.0	0.0
Total Bilirubin	>2.5 x ULN§	1.6	0.0	0.0
HEMATOLOGY				
Hemoglobin	<7.0 gm/dL	0.7	0.0	1.2
Absolute Neutrophil Count	<750 mm^3	2.9	2.9	1.2
Platelets	<50,000 mm^3	0.9	2.5	0.0

* ACTG Grade 3 or above.

† Antiretroviral Treatment of Choice.

‡ Reverse Transcriptase Inhibitor.

§ ULN = Upper limit of normal range.

ND Not done.

Additional marked lab abnormalities have been observed with INVIRASE. These include: calcium (low), phosphate (low), potassium (low), sodium (low).

Monotherapy and Combination Studies: Other clinical adverse experiences of any intensity, at least remotely related to FORTOVASE and INVIRASE, including those in <2% of patients, are listed below by body system.

Autonomic Nervous System: Mouth dry, night sweats, sweating increased

Body as a Whole: Allergic reaction, anorexia, appetite decreased, appetite disturbances, asthenia,

chest pain, edema, fever, intoxication, malaise, olfactory disorder, pain body, pain pelvic, retrosternal pain, shivering, trauma, wasting syndrome, weakness generalized, weight decrease, redistribution/accumulation of body fat (see PRECAUTIONS: *Fat Redistribution*)

Cardiovascular/Cerebrovascular: Cyanosis, heart murmur, heart rate disorder, heart valve disorder, hypertension, hypotension, stroke, syncope, vein distended

Central and Peripheral Nervous System: Ataxia, cerebral hemorrhage, confusion, convulsions, dizziness, dysarthria, dysesthesia, hyperesthesia, hyperreflexia, hyporeflexia, light-headed feeling, myelopolyradiculoneuritis, neuropathy, numbness extremities, numbness face, paresis, paresthesis, peripheral neuropathy, poliomyelitis, prickly sensation, progressive multifocal leukoencephalopathy, spasms, tremor, unconsciousness

Dermatological: Acne, alopecia, chalazion, dermatitis, dermatitis seborrheic, erythema, folliculitis, furunculosis, hair changes, hot flushes, nail disorder, papillomatosis, papular rash, photosensitivity reaction, pigment changes skin, parasites external, pruritus, psoriasis, rash maculopapular, rash pruritic, red face, skin disorder, skin nodule, skin syndrome, skin ulceration, urticaria, verruca, xeroderma

Endocrine/Metabolic: Dehydration, diabetes mellitus, hyperglycemia, hypoglycemia, hypothyroidism, thirst, triglyceride increase, weight increase

Gastrointestinal: Abdominal distention, bowel movements frequent, buccal mucosa ulceration, canker sores oral, cheilitis, colic abdominal, dysphagia, esophageal ulceration, esophagitis, eructation, fecal incontinence, feces bloodstained, feces discolored, gastralgia, gastritis, gastroesophageal reflux, gastrointestinal inflammation, gingivitis, glossitis, hemorrhage rectum, hemorrhoids, infectious diarrhea, melena, painful defecation, parotid disorder, pruritus ani, pyrosis, salivary glands disorder, stomach upset, stomatitis, taste unpleasant, toothache, tooth disorder, ulcer gastrointestinal

Hematologic: Anemia, neutropenia, pancytopenia, splenomegaly

Liver and Biliary: Cholangitis sclerosing, cholelithiasis, hepatitis, hepatomegaly, hepatosplenomegaly, jaundice, liver enzyme disorder, pancreatitis

Musculoskeletal: Arthralgia, arthritis, back pain, cramps leg, cramps muscle, lumbago, musculoskeletal disorders, myalgia, myopathy, pain facial, pain jaw, pain leg, pain musculoskeletal, stiffness, tissue changes

Neoplasm: Kaposi's sarcoma, tumor

Platelet, Bleeding, Clotting: Bleeding dermal, hemorrhage, microhemorrhages, thrombocytopenia

Psychiatric: Agitation, amnesia, anxiety attack, behavior disturbances, dreaming excessive, euphoria, hallucination, intellectual ability reduced, irritability, lethargy, overdose effect, psychic

disorder, psychosis, somnolence, speech disorder

Reproductive System: Epididymitis, erectile impotence, impotence, menstrual disorder, menstrual irregularity, penis disorder, prostate enlarged, vaginal discharge

Resistance Mechanism: Abscess, angina tonsillaris, candidiasis, cellulitis, herpes simplex, herpes zoster, infection bacterial, infection mycotic, infection staphylococcal, infestation parasitic, influenza, lymphadenopathy, molluscum contagiosum, moniliasis

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

Special Senses: Blepharitis, conjunctivitis, cytomegalovirus retinitis, dry eye syndrome, earache, ear pressure, eye irritation, hearing decreased, otitis, taste unpleasant, tinnitus, visual disturbance, xerophthalmia

Urinary System: Micturition disorder, nocturia, renal calculus, renal colic, urinary tract bleeding, urinary tract infection

OVERDOSAGE: Overdosage with FORTOVASE has not been reported. There were 2 patients who had overdoses with INVIRASE. No sequelae were noted in the first patient after ingesting 8 grams of INVIRASE 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 INVIRASE in combination with 600 mg of ritonavir and experienced pain in the throat that lasted for 6 hours and then resolved.

DOSAGE AND ADMINISTRATION: FORTOVASE (saquinavir) soft gelatin capsules and INVIRASE (saquinavir mesylate) capsules are not bioequivalent and cannot be used interchangeably. When using saquinavir as part of an antiviral regimen FORTOVASE is the recommended formulation. In rare circumstances, INVIRASE may be considered if it is to be combined with antiretrovirals that significantly inhibit saquinavir's metabolism (see CLINICAL PHARMACOLOGY: *DRUG INTERACTIONS*).

The recommended dose of FORTOVASE is six 200-mg capsules orally, three times a day (1200 mg tid). FORTOVASE should be taken with a meal or up to 2 hours after a meal. When used in combination with nucleoside analogues, the dosage of FORTOVASE should not be reduced as this will lead to greater than dose proportional decreases in saquinavir plasma levels.

Patients should be advised that FORTOVASE, like other protease inhibitors, is recommended for use in combination with active antiretroviral therapy. Greater activity has been observed when new antiretroviral therapies are begun at the same time as FORTOVASE. As with all protease inhibitors, adherence to the prescribed regimen is strongly recommended. Concomitant therapy should be based on a patient’s prior drug exposure.

Monitoring of Patients: Clinical chemistry tests should be performed prior to initiating FORTOVASE therapy and at appropriate intervals thereafter. For comprehensive patient monitoring recommendations for other antiretroviral therapies, physicians should refer to the complete product information for these drugs.

Dose Adjustment for Combination Therapy With FORTOVASE: For toxicities that may be associated with FORTOVASE, the drug should be interrupted. For recipients of combination therapy with FORTOVASE and other antiretroviral agents, dose adjustment of the other antiretroviral agents should be based on the known toxicity profile of the individual drug. Physicians should refer to the complete product information for these drugs for comprehensive dose adjustment recommendations and drug-associated adverse reactions.

HOW SUPPLIED: FORTOVASE 200-mg capsules are beige, opaque, soft gelatin capsules with ROCHE and 0246 imprinted on the capsule shell — bottles of 180 (NDC 0004-0246-48).

The capsules should be refrigerated at 36° to 46°F (2° to 8°C) in tightly closed bottles until dispensed.

For patient use, refrigerated (36° to 46°F, 2° to 8°C) capsules of FORTOVASE remain stable until the expiration date printed on the label. Once brought to room temperature [at or below 77°F (25°C)], capsules should be used within 3 months.

Rx only

Manufactured by:
F. Hoffmann-La Roche Ltd., Basel, Switzerland

Distributed by:

Roche Pharmaceuticals

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

XXXXXXXX-XXXX

Revised: XXXXX 2001
Printed in USA

FORTOVASE® (saquinavir) PPI

Patient Information About FORTOVASE (FOR-toe-vase)

FORTOVASE®
(saquinavir) Soft Gel Capsules

Generic Name: Saquinavir (sa-KWIN-a-veer)

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

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

What is FORTOVASE?

FORTOVASE is one of a class of drugs called HIV protease (PRO-tee-ase) inhibitors. FORTOVASE Soft Gel Capsules in combination with other anti-HIV drugs are used for the treatment of HIV, the virus that causes AIDS (acquired immunodeficiency syndrome).

How does FORTOVASE work?

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

How is FORTOVASE different from INVIRASE® (saquinavir mesylate)?

Both FORTOVASE and INVIRASE contain the same active ingredient—saquinavir. However, FORTOVASE gets more of the saquinavir into the blood to fight HIV. While you may be taking twice as many capsules (six instead of three capsules, three times a day), you will be getting higher levels of saquinavir into your bloodstream.* Because FORTOVASE produces higher blood levels of saquinavir than INVIRASE, you should not substitute one for the other. If the medicine you receive does not look like the beige soft gel capsules in this patient information, it is not FORTOVASE. Talk to your doctor, nurse or pharmacist if you are not sure that you have the right medication.

FORTOVASE® (saquinavir) PPI

Who should not take FORTOVASE?

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

How should FORTOVASE be taken?

- The recommended dosage of FORTOVASE in combination with nucleoside analogues is six capsules three times a day. In some combinations, your dose may change. Your doctor will tell you the dose of FORTOVASE that is right for you.

- FORTOVASE must be taken with meals or up to 2 hours after a meal—but it is easiest to remember if you take it with your meals. When FORTOVASE is taken without food, the amount of FORTOVASE in the blood is lower and may not fight HIV as well.

- When taking FORTOVASE and other anti-HIV medicines, it is very important to follow the directions exactly and take your medication every day. If you skip doses—or take less than the prescribed dose—the medicine will not work as well, and your disease could get worse.

  – If you miss a dose, you should take the next dose as soon as possible. However, do not double the dose.

What results have been seen with FORTOVASE?

FORTOVASE has been shown to reduce the amount of virus in the blood ("viral load") and increase CD_4 (T) cells when taken with other HIV therapy. In a study of patients who had never been treated before, a higher number of patients taking FORTOVASE with two nucleoside analogues had undetectable viral load† at 4 months, compared to those receiving INVIRASE with two nucleoside analogues.

What are the side effects of FORTOVASE?

People treated with FORTOVASE may have side effects. The majority of these have been described as mild. In clinical studies of patients who received FORTOVASE in combination with other HIV drugs the side effects seen most often were: diarrhea (16% to 20%), nausea (11% to 18%), abdominal discomfort (9% to 13%) and heartburn (8% to 9%).

Other side effects seen in more than 2% of patients in clinical studies were abdominal pain, gas, vomiting, fatigue, headache, body aches, anxiety, depression, warts, change in sexual appetite, taste changes, constipation and sleeplessness.

Side effects occurring in 0.5% to 2% of patients in clinical studies included weight gain, gum

disease, numbness or tingling, fever, convulsions, itching and rash, shortness of breath, fungal infection, hepatitis, night sweats, blurred vision and difficult urination. Side effects occurring rarely, in less than 0.5% of patients, and also considered serious, included dizziness, coughing blood, bleeding in the brain, ulcers, inflamed pancreas and rapid heart rate.

Significant increases in liver function tests have been reported in 1.2% to 5.7% of patients taking FORTOVASE. Worsening of liver problems has also been reported in people with pre-existing liver disease.

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

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

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

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

Are there other medications that I should not take with FORTOVASE?

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

MEDICINES YOU SHOULD NOT TAKE WITH FORTOVASE

Drug Class	Drugs Within Class Not to Be Coadministered With FORTOVASE
Antihistamines	Seldane® (terfenadine), Hismanal® (astemizole)
Antimigraines	Ergot medications (eg, Wigraine® and Cafergot®)
GI motility agents	Propulsid® (cisapride)
Sedatives, hypnotics	Versed® (midazolam), Halcion® (triazolam)

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

.

FORTOVASE causes increased blood levels of these compounds. This can lead to serious or life-threatening reactions such as irregular heartbeat or prolonged sedation.
Your doctor may want to change your medicine if you are taking rifampin (known as Rifadin®, Rifamate®, Rifater® or Rimactane®) or Mycobutin® (rifabutin); these drugs substantially reduce the level of FORTOVASE in the blood.

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

Does FORTOVASE cure HIV/AIDS?

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

What else should I discuss with my doctor?

Inform your doctor:

- If you are pregnant or become pregnant while taking FORTOVASE. The effects of FORTOVASE on pregnant women or unborn babies are not yet fully known. In addition, experts advise against breast-feeding if you are HIV positive, to reduce the risk of passing the virus to your baby.

- If you are taking nucleoside analogues. Your doctor may want to change one or more of your anti-HIV drugs in order to achieve the best results when you start treatment with FORTOVASE.

- If you have diabetes or a family history of diabetes, or if you have hemophilia, hepatitis or other liver disease, your doctor should decide if FORTOVASE is right for you.

- If you have ever taken INVIRASE, discuss with your doctor whether FORTOVASE is right for you.

How is FORTOVASE supplied?

FORTOVASE is available as beige-colored soft gel capsules in a 200-mg strength.
FORTOVASE comes in bottles of 180 capsules. For added convenience, FORTOVASE can be prescribed and dispensed three bottles at a time (a 30-day supply).

How should I store FORTOVASE?

Refrigerated 2° to 8°C (36° to 46°F) capsules of FORTOVASE remain stable until the expiration

date on the bottle. Once brought to room temperature (at or below 25°C or 77°F), capsules should be used within 3 months. If you live in a hot climate or your home is hot in the summer, you should keep FORTOVASE refrigerated. Capsules should not be frozen. The bottles should be kept tightly closed.

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

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

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

- In a small number of patients studied, it has been shown that FORTOVASE blood levels may decrease over time; however, it is unknown whether this affects the anti-HIV activity of the drug.

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

‡ Dosages greater than 400 mg twice a day of either ritonavir or saquinavir were associated with an increase in side effects.

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

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

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If you have any questions about FORTOVASE, call toll free at 1-800-463-1875, or visit our Web site at www.FORTOVASE.com.

FORTOVASE® (saquinavir) PPI

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FORTOVASE® (saquinavir) COMMERCIAL CONTAINER (BOTTLE) LABEL

HLR 04/27/01

FORTOVASE® (saquinavir) FREE GOODS CONTAINER (BOTTLE) LABEL

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