



# **FORTOVASE®**

## **(saquinavir)**

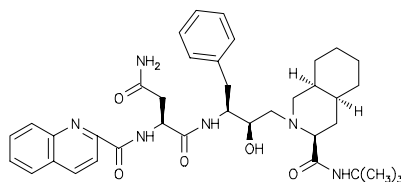
### **SOFT GELATIN CAPSULES**

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Before prescribing, please refer to printed complete product information.

## **Complete Product Information**

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**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-quinolylylcarbonyl)-L-asparaginy]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<sup>®</sup> (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<sub>8</sub> in Patients Treated With FORTOVASE and INVIRASE (Week 3)**

<b>Treatment</b>	<b>n</b>	<b>AUC<sub>8</sub> ng·h/mL</b>	<b>± SD</b>
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 <sup>14</sup>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 <sup>14</sup>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<sub>max</sub> of coadministered drugs. Table 3 summarizes the effect of coadministered drugs on the geometric mean AUC and C<sub>max</sub> of saquinavir.

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

Coadministered Drug	FORTOVASE Dose	N	% Change for Coadministered Drug	
			AUC (95%CI)	C <sub>max</sub> (95%CI)
Clarithromycin 500 mg bid x 7 days Clarithromycin 14-OH clarithromycin metabolite	1200 mg tid x 7 days	12V	↑45% (17-81%) ↓24% (5-40%)	↑39% (10-76%) ↓34% (14-50%)
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 Drug	FORTOVASE Dose	N	% Change for Saquinavir	
			AUC (95%CI)	C <sub>max</sub> (95%CI)
Clarithromycin 500 mg bid x 7 days	1200 mg tid x 7 days	12V	↑177% (108-269%)	↑187% (105-300%)
Indinavir 800 mg q8h x 2 days	800-mg single dose	6V	↑620% (273-1288%)	↑551% (320-908%)
	1200-mg single dose	6V	↑364% (190-644%)	↑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 <sup>†</sup>	8V	↑121% (7-359%)	↑64% <sup>§</sup>

Coadministered Drug	INVIRASE Dose	N	% Change for Saquinavir	
			AUC (95%CI)	C <sub>max</sub> (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% <sup>§</sup>	↑74% (16-161%)
Rifabutin 300 mg qd x 14 days	600 mg tid x 14 days	12P	↓43% (29-53%)	↓30% <sup>§</sup>
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 <sup>‡</sup>	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  $\mu\text{g}\cdot\text{h}/\text{mL}$ , 20.0  $\mu\text{g}\cdot\text{h}/\text{mL}$ , 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<sup>®</sup> (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.

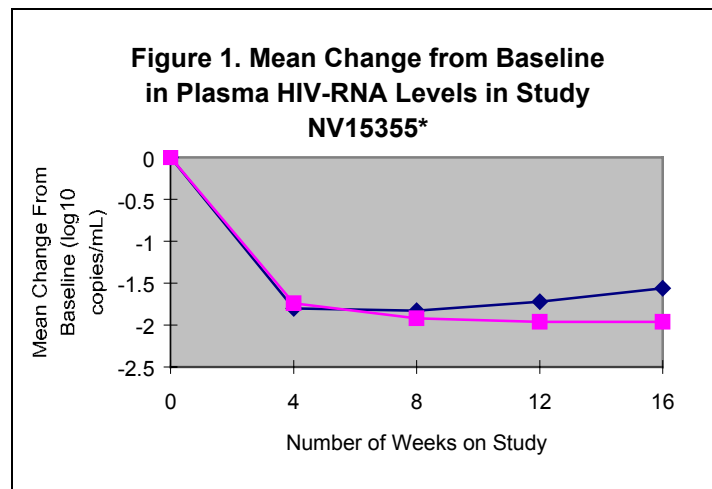
***Description of Clinical Studies: STUDIES WITH FORTOVASE (saquinavir):***

*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-naïve patients. The median age was 35 (range: 18 to 63), 92% of patients were male, and 68% were Caucasian. Mean baseline CD<sub>4</sub> cell count was 429 cells/mm<sup>3</sup>, and mean baseline plasma HIV-RNA was 4.8 log<sub>10</sub> 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<sup>™</sup> Test).

At week 16, mean changes from baseline in CD<sub>4</sub> cell counts and plasma HIV-RNA levels between the two treatment arms were statistically indistinguishable. The mean change in CD<sub>4</sub> cell count was 97 cells/mm<sup>3</sup> for the FORTOVASE arm and 115 cells/mm<sup>3</sup> 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 <sup>†</sup>
FORTOVASE	90	83	79	78	75 <sup>†</sup>

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

<sup>†</sup> 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<sub>4</sub> cell count was 227 cells/mm<sup>3</sup> and mean baseline HIV-RNA was 4.14 log<sub>10</sub> copies/mL. The safety results from this study are displayed in the ADVERSE REACTIONS section.

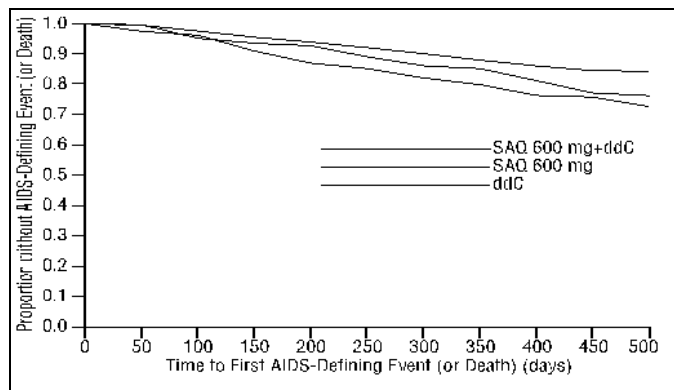
#### *STUDIES WITH INVIRASE (saquinavir mesylate):*

##### *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<sub>4</sub> cell count at study entry of 170 cells/mm<sup>3</sup>. 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.

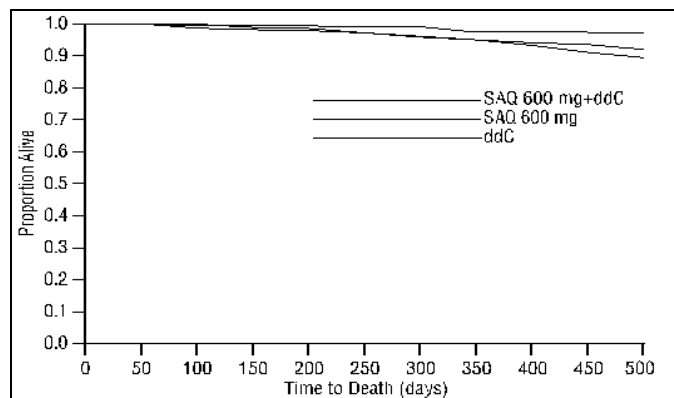
The analysis of clinical endpoints from this study showed that the 18-month cumulative incidence of clinical disease progression to AIDS-defining event or death was 17.7% for patients randomized to INVIRASE + HIVID compared to 30.7% for patients randomized to HIVID monotherapy and 28.3% for patients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

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

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

\* Studied with INVIRASE.

<sup>†</sup> Studied with FORTOVASE.

<sup>‡</sup> 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.

#### *ANTI-HISTAMINES:*

*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<sub>2</sub> 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  $\geq 2\%$  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 myeloblastic leukemia; hemolytic anemia; thrombocytopenia; thrombocytopenia and intracranial hemorrhage leading to death; attempted suicide; Stevens-Johnson syndrome; bullous skin eruption and polyarthritits; 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.

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

ADVERSE EVENT	NV15182 (48 weeks)	NV15355 (16 weeks) Naive Patients	
	FORTOVASE + TOC <sup>†</sup> N=442	INVIRASE + 2 RTIs <sup>‡</sup> N=81	FORTOVASE + 2 RTIs <sup>‡</sup> N=90
<b>GASTROINTESTINAL</b>			
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
<b>BODY AS A WHOLE</b>			
Fatigue	4.8	6.2	6.7
<b>CENTRAL AND PERIPHERAL NERVOUS SYSTEM</b>			
Headaches	5.0	4.9	8.9
<b>PSYCHIATRIC DISORDERS</b>			
Depression	2.7	–	–
Insomnia	–	1.2	5.6
Anxiety	–	2.5	2.2
Libido Disorder	–	–	2.2
<b>SPECIAL SENSES DISORDERS</b>			
Taste Alteration	–	1.2	4.4
<b>MUSCULOSKELETAL DISORDERS</b>			
Pain	–	3.7	3.3
<b>DERMATOLOGICAL DISORDERS</b>			
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).

<sup>†</sup> Antiretroviral Treatment of Choice.

<sup>‡</sup> Reverse Transcriptase Inhibitor.

**Table 5. Percentage of Patients With Marked Laboratory Abnormalities\***

		<b>NV15182 (48 weeks)</b>	<b>NV15355 (16 weeks) Naive Patients</b>	
		<b>FORTOVASE + TOC† N=442</b>	<b>INVIRASE + 2 RTIs‡ N=81</b>	<b>FORTOVASE + 2 RTIs‡ N=90</b>
<b>BIOCHEMISTRY</b>	<b>Limit</b>			
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
<b>HEMATOLOGY</b>				
Hemoglobin	<7.0 gm/dL	0.7	0.0	1.2
Absolute Neutrophil Count	<750 mm <sup>3</sup>	2.9	2.9	1.2
Platelets	<50,000 mm <sup>3</sup>	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, paresthesia, 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

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