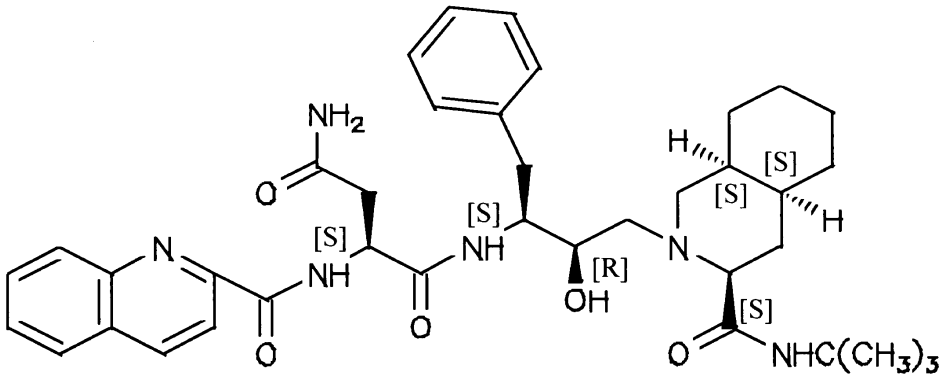
FORTOVASE® soft gelatin capsules

saquinavir (CAS registry number: 127779-20-8)



DESCRIPTION

FORTOVASE (saquinavir), is a highly selective inhibitor of the Human Immunodeficiency Virus enzyme, HIV proteinase (HIV protease).

FORTOVASE is available as beige opaque soft gelatin capsule for oral administration in a 200 mg strength (as saquinavir free base).

The chemical name for saquinavir is N^1-{(1*S*, 2*R*)-1-Benzyl-3-[(3*S*, 4a*S*, 8a*S*)-3-(*tert*-butylcarbamoyl) perhydroisoquinolin-2-yl]-2-hydroxypropyl}-N^2-(2-quinolylcarbonyl)-L-aspartamide. The molecular formula is $C_{38}H_{50}N_6O_5$. Saquinavir has a molecular weight of 670.86.

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

Each capsule also contains the inactive ingredients medium chain mono- and diglycerides, povidone K30 and dl-alpha tocopherol. Each capsule shell contains gelatin and glycerol 85% with the following dye systems: iron oxide red CI77491, iron oxide yellow CI77492 and titanium dioxide CI77891.

PHARMACOLOGY

Pharmacodynamics

Mechanism of action: The HIV proteinase carries out specific cleavages of viral precursor proteins in infected cells, as an essential step in the creation of fully formed, infectious virus particles. These viral precursor proteins contain a type of cleavage site which is recognised only by HIV and closely related viral proteinases. Saquinavir has been designed as a peptide-like structural mimetic of such cleavage sites. As a result, saquinavir fits closely into the HIV-1 and HIV-2 proteinase active sites, acting as an extremely potent and selective inhibitor, with only a weak (at least 50,000-fold lower) affinity for human proteinases.

Pharmacodynamic effect: Unlike nucleoside analogues (zidovudine etc), saquinavir acts directly on its viral target enzyme. It does not require metabolic activation. This extends its potential effectiveness into resting cells. Saquinavir is active at nanomolar concentrations in lymphoblastoid and monocytic lines and in primary cultures of lymphocytes and monocytes infected with laboratory strains or clinical isolates of HIV-1. It displays a high antiviral therapeutic index *in vitro* (> 1000). In cell culture, saquinavir demonstrated additive to synergistic effects against HIV in double- and triple-combination regimens with reverse transcriptase inhibitors zidovudine (ZDV), zalcitabine (ddC), didanosine (ddI), lamivudine (3TC), stavudine (d4T) and nevirapine (NVP) without enhanced cytotoxicity.

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: Cross-resistance between saquinavir and reverse transcriptase inhibitors is unlikely because of their different enzyme targets. HIV isolates resistant to ZDV are sensitive to saquinavir, and conversely, HIV isolates resistant to saquinavir are sensitive to ZDV. Among protease inhibitors variable cross-resistance has been recognised. Analysis of saquinavir-resistant isolates from patients following prolonged (24 to 147 weeks) therapy with INVIRASE showed that a proportion of patients had resistance to at least one of four other protease inhibitors (indinavir, nelfinavir, ritonavir, 141W94). However, twelve of sixteen saquinavir resistant patient isolates examined were sensitive to at least one other protease inhibitor.

Available information from patients who failed or were failing therapy with INVIRASE and were subsequently switched to another protease inhibitor suggests that any loss of sensitivity to the second protease inhibitor may be the result of accessory mutations which arise after the primary codon changes at positions 48 and/or 90. Current guidelines recommend that a change in therapy should include a switch to at least two new antiretroviral agents. If no new agents are available then it is recommended to use those agents which were used in the most distant past.

Further investigations into the clinical significance of cross-resistance are in progress.

Pharmacokinetics

The pharmacokinetic properties of saquinavir have been evaluated in healthy volunteers and HIV-infected patients after single oral doses of 300, 600, 800, 900 and 1200 mg and multiple oral doses of 400, 800 and 1200 mg tid. The disposition properties of saquinavir have been studied in healthy volunteers after intravenous doses of 12 mg administered over 1 hour; and 6, 36 and 72 mg administered over 3 hours.

Absorption and bioavailability: The absolute bioavailability of saquinavir administered as FORTOVASE has not been assessed. However, following single 600 mg doses, the relative bioavailability of saquinavir administered as FORTOVASE compared to saquinavir administered as INVIRASE (hard gelatin capsules) was estimated as 331% (95% CI 207 to 530). In healthy volunteers receiving single doses of FORTOVASE (300 to 1200 mg) and in HIV-infected patients receiving multiple doses of FORTOVASE (400 to 1200 mg tid) a greater than dose-proportional increase in saquinavir plasma concentrations has been observed.

Following multiple dosing of FORTOVASE (1200 mg tid) in HIV-infected patients in study NV15107 (n=31), the steady-state area under the plasma concentration versus time curve (AUC) was 7249 ng·h/mL. This was approximately eightfold higher than following multiple dosing with 600 mg tid of INVIRASE (866 ng·h /mL, n=10) (Figure 1 and Table 1).

Comparison of pharmacokinetic parameters between single- and multiple-dose studies shows that following multiple dosing of FORTOVASE (1200 mg tid) in healthy volunteers, the steady-state area under the plasma concentration versus time curve (AUC) was 1.8 times (95% CI 1.22 to 2.76) higher than that observed after a single 1200 mg dose.

Food Effect: The mean AUC after a single 800 mg oral dose of FORTOVASE in healthy volunteers was increased from 167 ng·h/mL (CV 45%), under fasting conditions, to 1120 ng·h/mL (CV 54%) when FORTOVASE was given following a high fat breakfast (48 g protein, 60 g carbohydrate, 57 g fat; 1006 kcal). The duration for the effect of food with FORTOVASE has not been assessed.

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

Figure 1. Mean AUC_{∞} in Patients Treated with FORTOVASE and INVIRASE (Week 3)

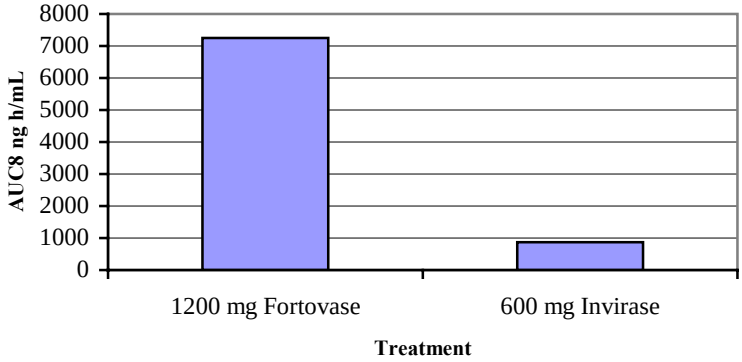


Table 1. Mean AUC_{∞} in Patients Treated With FORTOVASE and INVIRASE (Week 3)

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

Distribution in Adults: The mean steady-state volume of distribution following intravenous administration of a 12 mg dose of saquinavir was 700 L (CV 39%), suggesting saquinavir partitions into tissues. It has been shown that saquinavir is approximately 97% bound to plasma proteins up to a concentration of 30 μg/mL. In 2 patients receiving INVIRASE 600 mg tid, cerebrospinal fluid concentrations were low compared to plasma, as would be expected from saquinavir's high protein binding.

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 metabolised to a range of mono- and di-hydroxylated inactive compounds. In a mass balance study using 600 mg ^{14}C-saquinavir, 88% and 1% of the orally administered radioactivity, was recovered in faeces and urine, respectively, within 5 days of dosing. In additional subjects administered 10.5 mg ^{14}C-saquinavir intravenously, 81% and 3% of the intravenously administered radioactivity was recovered in faeces 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 also **PRECAUTIONS**). Only 1% of

saquinavir is excreted in the urine, so the impact of renal impairment on saquinavir elimination should be minimal.

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

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

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 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	↔	↔
Ritonavir 400 mg bid x 14 days	800 mg bid x 14 days	8V	↔	↔
*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.
If the increase in the stated parameter was 4.6 fold, the % change is [(4.6 - 1)/1] x 100 = 360%

↓ 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**, **Interactions with other drugs** and **CONTRAINDICATIONS**).

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_{max} (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 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%§†
Ritonavir 400 mg bid x 14 days	800 mg bid x 14 days†	8V	↑275% (82-672%)†	↑171% (37-436%)†
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	↑348% (192-587%)	↑317% (165-556%)
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%§
Rifampicin 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 a 400mg dose of INVIRASE or a 400mg dose of FORTOVASE, actual 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**, **Interactions with other drugs.**

CLINICAL TRIALS

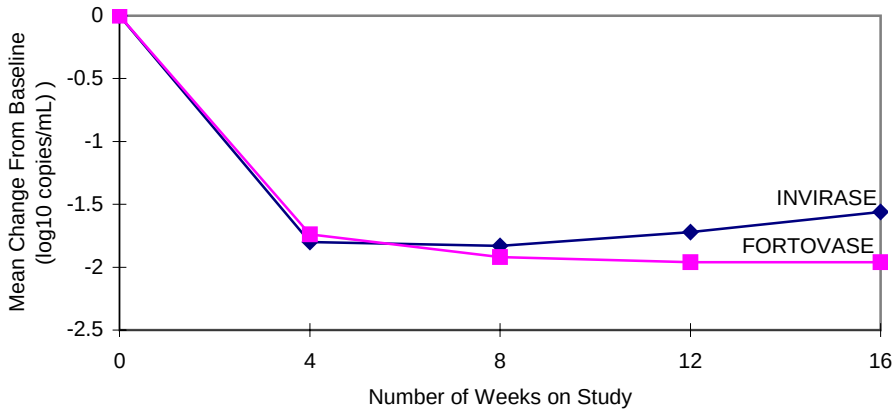
Studies with FORTOVASE (saquinavir free base in soft gelatin capsules):

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 (median age 35 [range: 18 to 63], 92% male, 68% 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.

After 16 weeks, 80% of patients in the FORTOVASE containing arm had viral loads below the limit of quantification (< 400 copies/mL) as compared to 43% of patients in the INVIRASE containing arm (p = 0.001). Mean viral load suppression was -2.0 log_{10} copies/mL and -1.6 log_{10} copies/mL respectively (p = 0.19). The magnitude of the reduction in viral load was limited by the sensitivity of the assay. At 16 weeks, an increase in CD4 cell count of 97 cells/mm^3 was seen for the FORTOVASE arm and 115 cells/mm^3 for the INVIRASE arm.

Figure 2. Mean Change from Baseline in Plasma HIV-RNA Levels in Study NV15355*

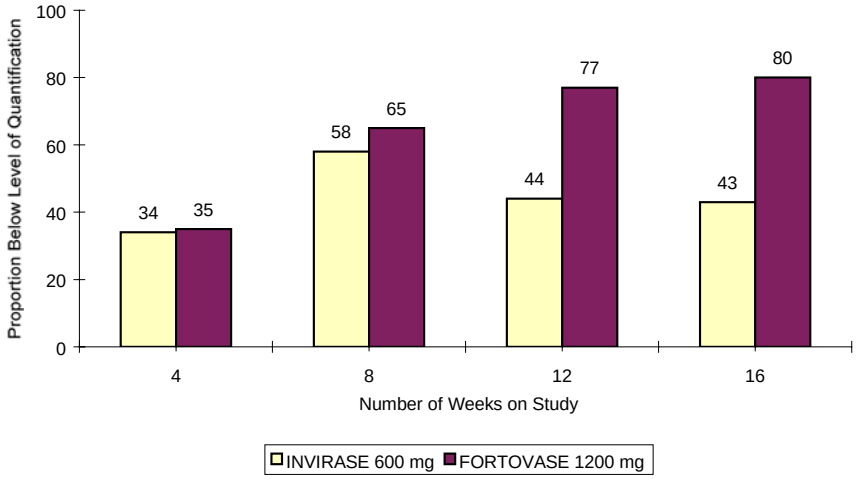


Number of Patients					
Week	0	4	8	12	16
INVIRASE	81	74	71	75	69†
FORTOVASE	90	83	79	78	75†

* 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.

Figure 3. Percent of Patients with HIV-RNA Below Level of Quantification in Study NV15355*



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 in hard gelatin capsules):

Study SV14604: INVIRASE + HIVID + zidovudine (ZDV) versus INVIRASE + zidovudine (ZDV) versus HIVID + zidovudine (ZDV)

SV14604 is a randomised, multi-centre, double blind phase III parallel study of zidovudine + zalcitabine, vs saquinavir + zidovudine, vs saquinavir + zidovudine + zalcitabine, in untreated/minimally treated HIV infected patients. A fourth treatment arm of zidovudine monotherapy was discontinued; patients originally on zidovudine monotherapy were switched to saquinavir + zidovudine + zalcitabine, constituting a "delayed" triple therapy group.

A total of 3485 patients were treated and had follow up data available (the intent to treat population). Median baseline CD_4 across the 3 arms was 199-204 cells/mm^3, and median baseline

HIV RNA was 5.0-5.1 $\log_{10}$ copies/mL. Median duration of study drug treatment was approximately 14 months and the median duration of follow up for AIDS defining events and deaths approximately 17 months.

Progression to first AIDS defining event or death was significantly decreased for patients on saquinavir + zidovudine + zalcitabine with 76 first AIDS defining events/deaths compared to 142 events on zidovudine + zalcitabine (p=0.0001).

INDICATIONS

FORTOVASE soft gelatin capsules are indicated for use in combination with other antiretroviral agents in the treatment of HIV infection. This indication is based on studies of surrogate marker responses in patients who received FORTOVASE in combination with nucleoside analogues.

This indication is also based on two clinical end-point studies in patients who received combination treatments that included INVIRASE (saquinavir mesylate hard gelatin capsules).

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 with amiodarone, terfenadine, cisapride, astemizole, pimozide, triazolam, midazolam or ergot derivatives because competition for CYP3A4 by saquinavir could result in inhibition of the metabolism of these drugs and create the potential for serious and/or life-threatening adverse reactions such as cardiac arrhythmias, prolonged or increased sedation or acute ergot toxicity. In addition to the above combinations, ritonavir boosted FORTOVASE should not be used with flecainide or propafenone, due to the risk of life-threatening cardiac arrhythmias, with rifampicin, due to severe hepatocellular toxicity or with simvastatin or lovastatin, due to the risk of rhabdomyolysis (see also **PRECAUTIONS**, **Interactions with other drugs**).

When used as the sole protease inhibitor, FORTOVASE is contraindicated in patients receiving concomitant administration of drugs which significantly decrease (greater than 50%) plasma concentrations of saquinavir e.g. rifampicin, rifabutin or efavirenz.

FORTOVASE is contraindicated in patients with severe hepatic impairment.

PRECAUTIONS

General

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

Considerations when initiating FORTOVASE therapy

When initiating saquinavir therapy, FORTOVASE is recommended rather than INVIRASE due to the greater bioavailability. For patients taking INVIRASE and who continue to demonstrate an adequate response to INVIRASE therapy, a switch to FORTOVASE may be considered.

Information for Patients

Patients should be informed that any change in saquinavir formulation should be made only under the supervision of a physician as it may result in the need for a change in dosage.

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. Patients should also be advised that they may experience toxicities associated with coadministered medications.

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.

Patients should be advised that FORTOVASE should be taken immediately after a full meal. Patients should be advised of the importance of taking their medication every day, as prescribed, to achieve maximum benefit.

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

Hepatic impairment

Saquinavir is principally metabolised 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 (see **CONTRAINDICATIONS**).

Renal impairment

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

Diabetes and hyperglycaemia (see also **ADVERSE REACTIONS**)

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycaemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycaemic agents for treatment of these events. In some cases diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycaemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, precise estimates of frequency cannot be made.

Body Fat Changes

Redistribution or accumulation of body fat including central obesity, dorsocervical fat enlargement and breast enlargement and loss of body fat from the face, limbs and upper trunk (peripheral lipodystrophy) have been reported in HIV positive patients taking protease inhibitors. Some of these patients had hypertriglyceridaemia and insulin resistance also. The long-term implications of these changes are not known.

Haemophilia (see also **ADVERSE REACTIONS**)

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis, in patients with haemophilia type A and B treated with protease inhibitors. A causal relationship between protease inhibitor therapy and increased bleeding has been invoked, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Patients with diarrhoea or malabsorption

No information on safety and efficacy of saquinavir is available for patients suffering from chronic diarrhoea or malabsorption.

Use in children

The safety and efficacy of FORTOVASE in HIV-infected children (younger than 16 years) have not been established.

Use in elderly patients

The safety and efficacy of FORTOVASE in HIV-infected patients older than 65 years have not been established.

Effects on ability to drive and use machines

It is not known whether saquinavir has an effect on the ability to drive and use machines.

Carcinogenicity, mutagenicity and impairment of fertility

There was no indication of carcinogenic activity in mice or rats administered saquinavir for approximately two years. Plasma exposures (AUC values) in each species, respectively, were approximately equivalent to 60% of those obtained in man at the recommended clinical dose.

Saquinavir, with and without metabolic activation as appropriate, was not mutagenic in the *Salmonella typhimurium* reverse-mutation assay or in the Chinese hamster lung V79/HPRT test, was not clastogenic in the mouse micronucleus assay *in vivo* or in human peripheral blood leucocytes *in vitro*, and did not induce DNA damage in primary rat hepatocytes. Degraded FORTOVASE, with and without metabolic activation, was not mutagenic in *S. typhimurium* (histidine reversion) and *E. coli* (tryptophan reversion) assays, and was not clastogenic in human peripheral blood leucocytes *in vitro*. In addition, the inactive medium-chain mono- and diglycerides in the formulation, with and without metabolic activation, were not mutagenic in *S. typhimurium* and *E. coli* gene mutation assays.

Fertility was not impaired in rats with plasma exposures (based on C_{max}) of about one-quarter of those achieved in patients at the recommended dose.

Use in pregnancy (CATEGORY B1)

Reproduction studies conducted with saquinavir in rats have shown no embryotoxicity or teratogenicity at plasma exposures (based on 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 to 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 and clinical experience in pregnant women is limited, caution should be exercised before saquinavir is prescribed during pregnancy.

Use in lactation

It is not known whether saquinavir is excreted in laboratory animal or human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions to saquinavir in nursing infants, breast feeding should be stopped during treatment with saquinavir.

Interactions with other drugs

(see also ***Pharmacokinetics***, *Drug Interactions* and **CONTRAINDICATIONS**)

Several drug interaction studies have been completed with both INVIRASE and FORTOVASE. Observations from drug interaction studies with INVIRASE may be indicative for FORTOVASE.

Drugs That Should Not Be Coadministered With FORTOVASE (± Ritonavir)	
Drug Class	Drugs Within Class Not to be Coadministered with FORTOVASE (± **Ritonavir)**
Antiarrhythmics	Amiodarone, Flecainide, Propafenone
Antihistamines	Astemizole, Terfenadine
Antimigraine	Ergot derivatives
Antimycobacterial agents	Rifabutin*‡, Rifampicin*‡
GI motility agents	Cisapride
HMG-CoA Reductase Inhibitors	Simvastatin, Lovastatin
Neuroleptics	Pimozide

Sedatives/Hypnotics	Midazolam, Triazolam
Anti-HIV non-nucleoside reverse transcriptase inhibitors	Efavirenz

Clinically Significant Drug Interactions Which Decrease Saquinavir Plasma Concentrations	
Anti-HIV non-nucleoside reverse transcriptase inhibitors	Nevirapine*

Clinically Significant Drug Interactions Which Increase Saquinavir Plasma Concentrations	
Antibiotics	Clarithromycin‡
Anti-HIV Protease Inhibitors	Indinavir‡, Ritonavir*‡, Nelfinavir‡
Anti-HIV non-nucleoside reverse transcriptase inhibitors	Delavirdine*
Antifungal Agents	Ketoconazole*

Other Potential Drug Interactions†	
Anticonvulsants: carbamazepine, phenobarbitone, phenytoin	May decrease saquinavir plasma concentrations
Corticosteroids: Dexamethasone	May decrease saquinavir plasma concentrations

† This table is not all inclusive.

* Studied with INVIRASE.

‡ Studied with FORTOVASE.

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 and Astemizole: 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. 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.

ANTIARRHYTHMICS

Amiodarone, Bepridil, systemic Lidocaine, Quinidine, D*isopyramide, Flecainide, Propafenone:* Concentrations of these products may be increased when co-administered with FORTOVASE. The coadministration of FORTOVASE and amiodarone and of ritonavir boosted FORTOVASE and

flecainide or propafenone are contraindicated (see **CONTRAINDICATIONS**). Caution is warranted and therapeutic monitoring is recommended if the other antiarrhythmics are given with FORTOVASE.

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.

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 1587% greater than historical AUC values from patients who received saquinavir 600 mg tid without ritonavir.

Following approximately 2 weeks of a combination regimen of FORTOVASE (400 mg or 800 mg bid) and ritonavir (400mg bid) in healthy volunteers, saquinavir AUC values were at least 121% and 275% higher respectively than AUC values for patients receiving FORTOVASE 1200 mg tid alone.

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).

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.

In some cases, co-administration of saquinavir and ritonavir has led to severe events, mainly diabetic ketoacidosis and liver disorders, especially with pre-existing liver disease. Therefore prescribers should be alert to the possibility of these events occurring when the combination of saquinavir and ritonavir is used.

Tipranavir: Concomitant use of saquinavir/ritonavir with tipranavir in a dual-boosted regimen results in a significant decrease in plasma concentrations of saquinavir. The clinical relevance of this reduction has not been established. Therefore, the co-administration of saquinavir/ritonavir with tipranavir is not recommended. Currently, there are no safety and efficacy data available from the use of this combination.

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 348% 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.

Efavirenz
FORTOVASE should not be used as the sole protease inhibitor when administered with efavirenz (see **CONTRAINDICATIONS**).

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. Rifabutin and FORTOVASE should not be co-administered (see **CONTRAINDICATIONS**).

Rifampicin: Rifampicin must not be administered to patients taking ritonavir boosted FORTOVASE as part of an ART regimen due to the risk of severe hepatocellular toxicity. Coadministration of rifampicin with INVIRASE resulted in an 84% decrease in saquinavir plasma AUC. Rifampicin and FORTOVASE should not be co-administered (see **CONTRAINDICATIONS**).

BENZODIAZEPINES
Midazolam
Saquinavir without ritonavir (unboosted): Co-administration of a single oral dose of midazolam and FORTOVASE has resulted in increased concentrations of midazolam. The dose of oral midazolam should be greatly reduced when given with unboosted saquinavir and the combination should be used with caution.

Saquinavir with ritonavir (boosted): Co-administration of a single oral dose of midazolam and INVIRASE/ritonavir has resulted in increased concentrations of midazolam. Therefore, the co-administration of FORTOVASE/ritonavir with midazolam is contraindicated.

DIGITALIS GLYCOSIDES
Digoxin: Concomitant use of saquinavir/ritonavir with digoxin results in a significant increase in serum concentrations of digoxin. Caution should be exercised when FORTOVASE/ritonavir and digoxin are co-administered; the dose of digoxin should be reduced and the serum concentration of digoxin monitored.

HMG-CoA REDUCTASE INHIBITORS
Simvastatin, Lovastatin, Atorvastatin, Cerivastatin: Plasma concentrations of HMG-CoA reductase inhibitors mainly metabolised by cytochrome P450 3A4, such as simvastatin and lovastatin, can

increase markedly if co-administered with saquinavir. Since increased concentrations of simvastatin and lovastatin can cause, in rare cases, severe adverse events such as myalgia and rhabdomyolysis, the combination of saquinavir with these drugs should not be used (see **CONTRAINDICATIONS**). The HMG-CoA reductase inhibitors atorvastatin and cerivastatin are also metabolised by CYP3A4 and a clinically relevant interaction of saquinavir with these drugs cannot be excluded; the lowest possible dose should be administered and the patient carefully monitored for signs/symptoms of myopathy (muscle weakness, muscle pain, rising plasma creatinine kinase levels).

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.

METABOLIC ENZYME INHIBITORS
Ketoconazole: See above for the effect of ketoconazole on saquinavir pharmacokinetics. A similar increase in plasma concentration of saquinavir could occur with other compounds in this class, such as fluconazole, itraconazole and miconazole, some macrolide antibiotics such as erythromycin, streptogramin antibiotics such as quinupristin/dalfopristin or with other inhibitors of the CYP3A4 isoenzyme (e.g. nefazodone).

NEUROLEPTICS
Pimozide: Administration of pimozide with FORTOVASE is contraindicated as this may lead to an increase in pimozide exposure (AUC) associated with a prolongation of QTc interval.

ORAL CONTRACEPTIVES
Ethinyloestradiol: The concentration of ethinyloestradiol may be decreased when coadministered with ritonavir boosted FORTOVASE. Alternative or additional contraceptive measures should be used when oestrogen-based oral contraceptives are considered.

PHOSPHODIESTERASE TYPE 5 (PDE5) INHIBITORS
Sildenafil, tadalafil, vardenafil: Particular caution should be used when prescribing PDE5 inhibitors in patients receiving protease inhibitors, including FORTOVASE. Co-administration of a protease inhibitor with a PDE5 inhibitor is expected to substantially increase PDE5 inhibitor concentration and may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension visual changes and priapism.

PROTON PUMP INHIBITORS

If omeprazole or another proton pump inhibitor is taken concomitantly with INVIRASE/ritonavir, monitoring for potential saquinavir toxicities is recommended

OTHER POTENTIAL INTERACTIONS
During the absorption phase of saquinavir, the high presystemic concentrations of saquinavir may decrease the activity of CYP3A4. Certain compounds may compete with saquinavir for their metabolism. These compounds include nifedipine and other dihydropyridine calcium channel

blockers, dapsone, quinine, warfarin, tacrolimus, cyclosporin, nefazodone, carbamazepine, fentanyl, alfentanil and alprazolam. This competition may result in possible increases in the plasma concentrations of such concomitant medications. Patients receiving saquinavir in combination with such drugs should be monitored for any adverse effects associated with these concomitant medications and the combination used with caution.

Additionally, saquinavir is a substrate for p-Glycoprotein (P-gp) as well as CYP3A4. Therefore drugs that either share or modify CYP3A4 or P-gp may modify the pharmacokinetics of saquinavir. Similarly, saquinavir may also modify the pharmacokinetics of other drugs that are substrates for CYP3A4 or P-gp.

Interactions with herbal products: Certain herbal products can contain components that may inhibit or induce CYP3A4 or P-glycoprotein and can therefore lead to a change in saquinavir pharmacokinetics. Concomitant use of protease inhibitors including FORTOVASE with hypericum perforatum (St. John's wort) or garlic capsules may potentially decrease FORTOVASE plasma concentrations. FORTOVASE should not be administered with hypericum perforatum (St John's wort) or garlic capsules because coadministration may be expected to substantially decrease FORTOVASE concentration and may lead to loss of virologic response and possible resistance to FORTOVASE or to the class of protease inhibitors.

Interactions with foods: Constituents of grapefruit juice can suppress the activity of the cytochrome isoenzyme CYP3A4. In a pharmacokinetic study in volunteers, grapefruit juice caused a 50% increase in the bioavailability of FORTOVASE 600 mg when administered as a single dose.

The effects of chronic alcohol ingestion on saquinavir metabolism have not been studied.

ADVERSE REACTIONS (see also **PRECAUTIONS**)

Clinical Trial Data

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

Clinical adverse events of moderate or severe intensity which occurred in ≥ 5% of patients in studies NV15182 and NV15355 are summarised 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.

Table 5 summarises 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.

Marked laboratory abnormalities are defined as a Grade 3 or 4 abnormality in a patient with a normal baseline value or a Grade 4 abnormality in a patient with a Grade 1 abnormality at baseline (ACTG Grading System).

Table 4. Percentage of Patients, by Study Arm, with Clinical Adverse Experiences Considered at Least Possibly Related to Study Drug or of Unknown Relationship and of Moderate, Severe, Life-Threatening or Unknown Intensity, Occurring in ≥ 5% of Patients in NV15182 and NV15355

	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			
Diarrhoea	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
Abdominal Pain	2.3	1.2	7.8
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			
Insomnia	–	1.2	5.6

* Antiretroviral Treatment of Choice.

† Reverse Transcriptase Inhibitor.

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 (raised)	>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 (decreased)	<40 mg/dL	6.4	2.5	3.5
Glucose (raised)	>250 mg/dL	1.4	1.3	1.2
Phosphate	<1.5 mg/dL	0.5	0.0	0.0
Potassium (raised)	>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 (raised)	>157 mEq/L	0.7	0.0	0.0
Total Bilirubin	>2.5 x ULN§	1.6	0.0	0.0
HAEMATOLOGY				
Haemoglobin	<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

† Antiretroviral Treatment of Choice.

‡ Reverse Transcriptase Inhibitor.

§ ULN = Upper limit of normal range.

ND Not done.

Additional marked laboratory abnormalities have been identified using INVIRASE. These include: calcium (decreased), phosphate (decreased), potassium (decreased), sodium (decreased).

Other clinical adverse events of any intensity, recorded in monotherapy and combination studies and at least remotely related to FORTOVASE or INVIRASE, including those in < 5% of patients, are listed below by body system.

Autonomic Nervous System: Dry mouth, night sweats, increased sweating

Body as a Whole: Allergic reaction, anorexia, decreased appetite, appetite disturbances, asthenia, chest pain, oedema, fever, intoxication, malaise, olfactory disorder, body pain, pelvic pain, retrosternal pain, shivering, trauma, wasting syndrome, generalised weakness, weight decrease

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

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

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

Endocrine/Metabolic: Dehydration, diabetes mellitus, hyperglycaemia, hypoglycaemia, hypothyroidism, thirst, triglyceride increase, weight increase

Gastrointestinal: Vomiting, constipation, abdominal distention, frequent bowel movements, buccal mucosa ulceration, oral canker sores, cheilitis, abdominal colic, dysphagia, oesophageal ulceration, esophagitis, eructation, faecal incontinence, bloodstained faeces, discoloured faeces, gastralgia, gastritis, gastroesophageal reflux, gastrointestinal inflammation, gingivitis, glossitis, rectum haemorrhage, haemorrhoids, infectious diarrhoea, melaena, painful defecation, parotid disorder, pruritus ani, pyrosis, salivary glands disorder, upset stomach, stomatitis, unpleasant taste, toothache, tooth disorder, gastrointestinal ulcer

Haematologic: Anaemia, neutropenia, pancytopenia, splenomegaly

Liver and Biliary: Sclerosing cholangitis, cholelithiasis, hepatitis, hepatomegaly, hepatosplenomegaly, jaundice, liver enzyme disorder, pancreatitis

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

Neoplasm: Kaposi’s sarcoma, tumour

Platelet, Bleeding, Clotting: Dermal bleeding, haemorrhage, microhaemorrhages, thrombocytopenia

Psychiatric: Depression, anxiety, libido disorder, agitation, amnesia, anxiety attack, behaviour disturbances, excessive dreaming, euphoria, hallucination, reduced intellectual ability, irritability, lethargy, overdose effect, psychic disorder, psychosis, somnolence, speech disorder

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

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

Respiratory: Bronchial asthma, bronchitis, cough, dyspnoea, epistaxis, haemoptysis, laryngitis, pharyngitis, pneumonia, pulmonary disease, respiratory disorder, rhinitis, allergic atopic rhinitis, sinusitis, upper respiratory tract infection

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

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

Rare occurrences of the following serious adverse events 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 leukaemia; haemolytic anaemia; thrombocytopenia and intracranial haemorrhage 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.

Post Marketing

There have been various reports of the following adverse events in patients taking INVIRASE or FORTOVASE. Experience with FORTOVASE is limited. A direct causal relationship between these adverse events and INVIRASE or FORTOVASE has not been established:

Endocrine/Metabolic

Rare: Diabetes and hyperglycaemia (see also **PRECAUTIONS**).

Haematologic

Rare: Increased bleeding in patients with haemophilia (see also **PRECAUTIONS**).

Dermatologic

Rare: Stevens-Johnson syndrome. (Patient had previously been treated with sulfamethoxizole/trimethoprim and dapsone).

DOSAGE AND ADMINISTRATION

The recommended dose of FORTOVASE is six 200 mg capsules three times daily (1200 mg tid) taken immediately after a meal. Note that food increases the bioavailability of FORTOVASE (see ***Pharmacokinetics***).

Patients should be advised that the optimal use of FORTOVASE, like other protease inhibitors, is in combination with an active antiretroviral therapy. For combination treatment involving other antiretrovirals (eg nelfinavir, ritonavir) dose reduction of FORTOVASE may be required (see ***Pharmacokinetics,*** *Drug Interactions* and **PRECAUTIONS**, **Interactions with other drugs**) Optimal benefit has been observed when new antiretroviral therapies are begun at the same time as FORTOVASE (see **CLINICAL TRIALS)**. 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 those 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 those drugs for comprehensive dose adjustment recommendations and drug-associated adverse reactions.

OVERDOSAGE

There is limited experience of overdose with saquinavir.

Whereas acute or chronic overdose of saquinavir alone did not result in major complications, in combination with other protease inhibitors, overdose symptoms and signs such as general weakness, fatigue, diarrhoea, nausea, vomiting, hair loss, dry mouth, hyponatraemia, weight loss and orthostatic hypotension have been observed.

There is no specific antidote for overdose with saquinavir. Treatment of overdose with saquinavir should consist of general supportive measures, including monitoring of vital signs and ECG, and observations of the patient's clinical status. If indicated, prevention of further absorption can be considered. Since saquinavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

Contact the Poisons Information Centre for advice on management of overdosage.

STORAGE AND STABILITY

The capsules should be refrigerated at 2°C to 8°C in tightly closed bottles.

For patient use, the capsules may be stored at room temperature at or below 25°C for a maximum of 3 months and should not be used after the expiry date printed on the bottle.

PRESENTATION

200 mg soft gelatin capsules – beige opaque capsules with “ROCHE” and “0246” imprinted on the capsule shell — bottles of 180

DISTRIBUTOR

Roche Products Pty Limited
ACN 000 132 865
4-10 Inman Road
Dee Why NSW 2099

TGA Approval Date: **14 August 1998**

Date of most recent amendment: **4 January 2007**