



FORTOVASE®

(saquinavir)

SOFT GELATIN CAPSULES

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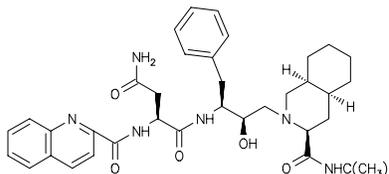
5 **Rx only**

6 **Product identification in this document includes: INVIRASE® in reference to**
7 **saquinavir mesylate; FORTOVASE in reference to saquinavir, and saquinavir in**
8 **reference to the active base.**

9 **DESCRIPTION**

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

19 Saquinavir has the following structural formula:



20

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

22 **MICROBIOLOGY**

23 **Mechanism of Action**

24 Saquinavir is an inhibitor of HIV protease. HIV protease is an enzyme required for the
25 proteolytic cleavage of viral polyprotein precursors into individual functional proteins
26 found in infectious HIV. Saquinavir is a peptide-like substrate analogue that binds to the

27 protease active site and inhibits the activity of the enzyme. Saquinavir inhibition prevents
28 cleavage of the viral polyproteins resulting in the formation of immature noninfectious
29 virus particles.

30 **Antiviral Activity**

31 In vitro antiviral activity of saquinavir was assessed in lymphoblastoid and monocytic
32 cell lines and in peripheral blood lymphocytes. Saquinavir inhibited HIV activity in both
33 acutely and chronically infected cells. IC₅₀ and IC₉₀ values (50% and 90% inhibitory
34 concentrations) were in the range of 1 to 30 nM and 5 to 80 nM, respectively. In the
35 presence of 40% human serum, the mean IC₅₀ of saquinavir against laboratory strain
36 HIV-1 RF in MT4 cells was 37.7 ± 5nM, representing a 4-fold increase in IC₅₀ value. In
37 cell culture, saquinavir demonstrated additive to synergistic effects against HIV-1 in
38 combination with reverse transcriptase inhibitors (didanosine, lamivudine, nevirapine,
39 stavudine, zalcitabine and zidovudine) without enhanced cytotoxicity. Saquinavir in
40 combination with the protease inhibitors amprenavir, atazanavir, or lopinavir resulted in
41 synergistic antiviral activity.

42 **Drug Resistance**

43 HIV-1 mutants with reduced susceptibility to saquinavir have been selected during in
44 vitro passage. Genotypic analyses of these isolates showed several substitutions in the
45 HIV protease gene. Only the G48V and L90M substitutions were associated with reduced
46 susceptibility to saquinavir, and conferred an increase in the IC₅₀ value of 8- and 3-fold,
47 respectively.

48 HIV-1 isolates with reduced susceptibility (≥ 4-fold increase in the IC₅₀ value) to
49 saquinavir emerged in some patients treated with INVIRASE. Genotypic analysis of
50 these isolates identified resistance conferring primary mutations in the protease gene
51 G48V and L90M, and secondary mutations L10I/R/V, I54V/L, A71V/T, G73S, V77I,
52 V82A and I84V that contributed additional resistance to saquinavir. Forty-one isolates
53 from 37 patients failing therapy with INVIRASE had a median decrease in susceptibility
54 to saquinavir of 4.3 fold.

55 The degree of reduction in in vitro susceptibility to saquinavir of clinical isolates bearing
56 substitutions G48V and L90M depends on the number of secondary mutations present. In
57 general, higher levels of resistance are associated with greater number of mutations only
58 in association with either or both of the primary mutations G48V and L90M. No data are
59 currently available to address the development of resistance in patients receiving
60 saquinavir/ritonavir.

61 **.Cross-resistance**

62 Among protease inhibitors, variable cross resistance has been observed. In one clinical
63 study, 22 HIV-1 isolates with reduced susceptibility (>4-fold increase in the IC₅₀ value)
64 to saquinavir following therapy with INVIRASE were evaluated for cross-resistance to
65 amprenavir, indinavir, nelfinavir and ritonavir. Six of the 22 isolates (27%) remained
66 susceptible to all 4 protease inhibitors, 12 of the 22 isolates (55%) retained susceptibility
67 to at least one of the PIs and 4 out of the 22 isolates (18%) displayed broad cross-

68 resistance to all PIs. Sixteen (73%) and 11 (50%) of the 22 isolates remained susceptible
69 (<4-fold) to amprenavir and indinavir, respectively. Four of 16 (25%) and 9 of 21 (43%)
70 with available data remained susceptible to nelfinavir and ritonavir, respectively. After
71 treatment failure with amprenavir, cross-resistance to saquinavir was evaluated. HIV-1
72 isolates from 22/22 patients failing treatment with amprenavir and containing one or
73 more mutations M46L/I, I50V, I54L, V32I, I47V, and I84V were susceptible to
74 saquinavir.

75 **CLINICAL PHARMACOLOGY**

76 **Pharmacokinetics**

77 The pharmacokinetic properties of saquinavir when administered as FORTOVASE have
78 been evaluated in healthy volunteers (n=207) and HIV-infected patients (n=91) after
79 single-oral doses (range: 300 mg to 1200 mg) and multiple-oral doses (range: 400 mg to
80 1200 mg tid). The disposition properties of saquinavir have been studied in healthy
81 volunteers after intravenous doses of 6, 12, 36 or 72 mg (n=21).

82 HIV-infected patients administered FORTOVASE (1200 mg tid) had AUC and
83 maximum plasma concentration (C_{max}) values approximately twice those observed in
84 healthy volunteers receiving the same treatment regimen. The mean AUC values at week
85 1 were 4159 (CV 88%) and 8839 (CV 82%) ng·h/mL, and C_{max} values were 1420 (CV
86 81%) and 2477 (CV 76%) ng/mL for healthy volunteers and HIV-infected patients,
87 respectively.

88 **Absorption and Bioavailability in Adults**

89 The absolute bioavailability of saquinavir administered as FORTOVASE has not been
90 assessed. However, following single 600-mg doses, the relative bioavailability of
91 saquinavir as FORTOVASE compared to saquinavir administered as INVIRASE was
92 estimated as 331% (95% CI: 207% to 530%). The absolute bioavailability of saquinavir
93 administered as INVIRASE averaged 4% (CV 73%, range: 1% to 9%) in 8 healthy
94 volunteers who received a single 600-mg dose (3 x 200 mg) of INVIRASE following a
95 high-fat breakfast (48 g protein, 60 g carbohydrate, 57 g fat; 1006 kcal). In healthy
96 volunteers receiving single doses of FORTOVASE (300 mg to 1200 mg) and in HIV-
97 infected patients receiving multiple doses of FORTOVASE (400 mg to 1200 mg tid), a
98 greater than dose-proportional increase in saquinavir plasma concentrations has been
99 observed.

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

104 Saquinavir plasma concentrations remained stable over a 60-week period of continued
105 treatment in patients in a phase III substudy.

106 When administered as the sole protease inhibitor, it has been shown that FORTOVASE
107 1200 mg tid provides an 8-fold increase in AUC compared with INVIRASE 600 mg tid.

108 FORTOVASE in combination with ritonavir at doses of 400/400 mg bid, or 1000/100 mg
109 bid provide saquinavir systemic exposures over a 24-hour period similar to or greater
110 than those achieved with FORTOVASE 1200 mg tid.

111 **Table 1 Pharmacokinetic Parameters of Saquinavir at Steady-State**
112 **After Administration of Different Regimens in HIV-Infected**
113 **Patients**

Dosing Regimen	n	AUC _{0-τ} (ng·h/mL)	AUC _{0-24h} (ng·h/mL)	C _{min} (ng/mL)
FORTOVASE 1200 mg tid (arithmetic mean)	31	7249	21747	216
INVIRASE 400 mg bid + ritonavir 400 mg bid (arithmetic mean ±SD)	7	16000±8000	32000	480±360
INVIRASE 1000 mg bid + ritonavir 100 mg bid (geometric mean and 95% CI)	24	14607 (10218-20882)	29214	371 (245-561)
FORTOVASE 1000 mg bid + ritonavir 100 mg bid (geometric mean and 95% CI)	24	19085 (13943-26124)	38170	433 (301-622)

114 τ is the dosing interval (ie, 8h if tid and 12h if bid).

115 Food Effect

116 The mean 12-hour AUC after a single 800-mg oral dose of saquinavir in healthy
117 volunteers (n=12) was increased from 167 ng·h/mL (CV 45%), under fasting conditions,
118 to 1120 ng·h/mL (CV 54%) when FORTOVASE was given following a high-fat
119 breakfast (45 g protein, 76 g carbohydrate, 55 g fat; 961 kcal). The effect of food with
120 INVIRASE has been shown to persist for up to 2 hours. The mean 12-hour AUC after a
121 single 1200-mg oral dose of FORTOVASE in healthy volunteers (n=12) was increased
122 from 952 ng·h/mL, following a light meal (21 g protein, 50 g carbohydrate, 28 g fat; 524
123 kcal) to 1388 ng·h/mL when FORTOVASE was given following a high-fat breakfast
124 (45 g protein, 76 g carbohydrate, 55 g fat; 961 kcal).

125 Saquinavir exposure was similar when FORTOVASE plus ritonavir (1000-mg/100-mg
126 BID) was administered following a high fat (45 g fat) or moderate fat (20 g fat) breakfast.

127 Distribution in Adults

128 The mean steady-state volume of distribution following intravenous administration of a
129 12-mg dose of saquinavir (n=8) was 700 L (CV 39%), suggesting saquinavir partitions
130 into tissues. It has been shown that saquinavir, up to 30 µg/mL, is approximately 97%
131 bound to plasma proteins.

132 Metabolism and Elimination in Adults

133 In vitro studies using human liver microsomes have shown that the metabolism of
134 saquinavir is cytochrome P450 mediated with the specific isoenzyme, CYP3A4,
135 responsible for more than 90% of the hepatic metabolism. Based on in vitro studies,
136 saquinavir is rapidly metabolized to a range of mono- and di-hydroxylated inactive
137 compounds. In a mass balance study using 600 mg ¹⁴C-saquinavir mesylate (n=8), 88%

138 and 1% of the orally administered radioactivity was recovered in feces and urine,
139 respectively, within 5 days of dosing. In an additional 4 subjects administered 10.5 mg
140 ¹⁴C-saquinavir intravenously, 81% and 3% of the intravenously administered
141 radioactivity was recovered in feces and urine, respectively, within 5 days of dosing. In
142 mass balance studies, 13% of circulating radioactivity in plasma was attributed to
143 unchanged drug after oral administration and the remainder attributed to saquinavir
144 metabolites. Following intravenous administration, 66% of circulating radioactivity was
145 attributed to unchanged drug and the remainder attributed to saquinavir metabolites,
146 suggesting that saquinavir undergoes extensive first-pass metabolism.

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

149 Special Populations

150 *Hepatic or Renal Impairment*

151 Saquinavir pharmacokinetics in patients with hepatic or renal impairment has not been
152 investigated (see PRECAUTIONS). Only 1% of saquinavir is excreted in the urine, so
153 the impact of renal impairment on saquinavir elimination should be minimal.

154 *Gender, Race and Age*

155 The effect of gender was investigated in healthy volunteers receiving single 1200-mg
156 doses of FORTOVASE (n=12 females, 18 males). No effect of gender was apparent on
157 the pharmacokinetics of saquinavir in this study.

158 The effect of race on the pharmacokinetics of saquinavir has not been investigated.

159 Pediatric Patients

160 The pharmacokinetics of saquinavir in pediatric patients differs significantly from that in
161 adults. Children have a markedly higher apparent clearance than adults and
162 administration of saquinavir alone will not give consistently therapeutic plasma levels.
163 The pharmacokinetics of saquinavir when coadministered with ritonavir to pediatric
164 patients is under investigation.

165 Geriatric Patients

166 The pharmacokinetics of saquinavir when administered as FORTOVASE have not been
167 sufficiently investigated in patients >65 years of age.

168 Drug Interactions (see PRECAUTIONS: Drug Interactions)

169 It is important to be aware that, when coadministered with ritonavir, the occurrence and
170 magnitude of drug interactions may differ from those seen with FORTOVASE when
171 administered as the sole protease inhibitor. When ritonavir is coadministered, prescribers
172 should refer to the prescribing information for ritonavir regarding drug interactions
173 associated with this drug.

174 Table 2 summarizes the effect of FORTOVASE on the geometric mean AUC and C_{max} of
175 coadministered drugs. Table 3 summarizes the effect of coadministered drugs on the
176 geometric mean AUC and C_{max} of saquinavir.

177 **Table 2 Effect of FORTOVASE on the Pharmacokinetics of**
178 **Coadministered Drugs**

Coadministered Drug	FORTOVASE or FORTOVASE/ ritonavir Dose	N	% Change for Coadministered Drug	
			AUC (95%CI)	C _{max} (95%CI)
Clarithromycin 500 mg bid x 7 days Clarithromycin 14-OH clarithromycin metabolite	1200 mg tid x 7days	12V	↑45% (17-81%) ↓24% (5-40%)	↑39% (10-76%) ↓34% (14-50%)
Midazolam 7.5-mg oral single dose	1200 mg tid x 5 days	6V	↑514%	↑235%
Nelfinavir 750-mg single dose	1200 mg tid x 4 days	14P	↑18% (5-33%)	↔
Rifabutin 300 mg once daily	1200 mg tid	14P	↑44%	↑45%
Ritonavir 400 mg bid x 14 days	400 mg bid x 14 days	8V	↔	↔
Sildenafil 100-mg single dose	1200 mg tid x 8 days	27V	↑210% (150-300%)	↑140% (80-230%)
Terfenadine ϕ 60 mg bid x 11 days* Terfenadine Terfenadine acid metabolite	1200 mg tid x 4 days	12V	↑368% (257-514%) ↑120% (89-156%)	↑253% (164-373%) ↑93% (59-133%)
Efavirenz 600 mg	1200 mg tid	13V	↓12%	↓13%
Ketoconazole 400mg once daily	1200 mg tid	12 V	↔	↔
Enfuvirtide 90mg SC q12h (bid) for 7 days	1000/100 mg bid	12 P	↔	↔

179 ↑ Denotes an average increase in exposure by the percentage indicated.

180 ↓ Denotes an average decrease in exposure by the percentage indicated.

181 ↔ Denotes no statistically significant change in exposure was observed.

182 * FORTOVASE should not be coadministered with terfenadine (see PRECAUTIONS: Drug
183 Interactions).

184 P Patient

185 V Healthy Volunteers

186 ϕ No longer marketed in the US.

187 **Table 3 Effect of Coadministered Drugs on FORTOVASE**
188 **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 7days	12V	↑177% (108-269%)	↑187% (105-300%)
Efavirenz 600 mg	1200 mg tid	13V	↓62%	↓50%
Indinavir 800 mg q8h x 2 days	1200-mg single dose	6V	↑364% (190-644%)	↑299% (138-568%)
Ketoconazole 400 mg once daily	1200 mg tid	12V	↑190%	↑171%
Nelfinavir 750 mg x 4 days	1200-mg single dose	14P	↑392% (271-553%)	↑179% (105-280%)
Rifabutin 300 mg once daily	1200 mg tid	14P	↓47%	↓31%
Rifampin 600 mg once daily	1200 mg tid x 14 days	14V	↓70%	↓65%
Ritonavir 100 mg bid	1000 mg bid†	24P	↑176%	↑153%
Ritonavir 400 mg bid x 14 days*	400 mg bid x 14 days†	8V	↑121% (7-359%)	↑64%§
Lopinavir/ritonavir 400/100 mg bid, 15 days	800 bid, 10 days combo vs. 1200 tid, 5 days alone	14V	↑9.62-fold (8.05, 11.49)^	↑6.34-fold (5.32, 7.55)^
		10V	↑9.91-fold (8.28, 11.86)^	↑6.44 –fold (5.59, 7.41)^

189 ↑ Denotes an average increase in exposure by the percentage indicated.

190 ↓ Denotes an average decrease in exposure by the percentage indicated.

191 * When ritonavir was combined with the same dose of either INVIRASE or FORTOVASE, actual mean
192 plasma exposures (AUC₀₋₁₂, 18200 ng·h/mL, 20000 ng·h/mL, respectively) were not significantly
193 different.

194 ^ 90% CI reported

195 † Compared to standard FORTOVASE 1200 mg tid regimen (n=33).

196 P Patient

197 V Healthy Volunteers

198

199 For information regarding clinical recommendations, see PRECAUTIONS: Drug
200 Interactions, Table 6.

201 INDICATIONS AND USAGE

202 FORTOVASE is indicated for use in combination with other antiretroviral agents for the
203 treatment of HIV infection. This indication is based on studies that showed increased
204 saquinavir concentrations and improved antiviral activity for FORTOVASE 1200 mg tid
205 compared to INVIRASE 600 mg tid.

206 In treatment-naïve and treatment experienced patients, the efficacy of FORTOVASE
207 (with or without ritonavir coadministration) has not been compared against the efficacy
208 of antiretroviral regimens currently considered standard of care.

209 **Description of Clinical Studies**

210 When used in combination with other antiretroviral agents, FORTOVASE and
211 INVIRASE have been shown to decrease plasma HIV RNA levels and increase CD₄ cell
212 counts in an open-label randomized study (NV15355) in treatment-naïve, HIV-infected
213 patients. In addition, in a randomized, double-blind study (NV14256) in ZDV-
214 experienced, HIV-infected patients, a combination regimen of FORTOVASE and HIVID
215 was shown to be superior to either INVIRASE or HIVID monotherapy in decreasing the
216 cumulative incidence of clinical disease progression to AIDS-defining events or death. It
217 should be noted that HIV treatment regimens that were used in the initial clinical studies
218 of INVIRASE are no longer considered standard of care.

219 FORTOVASE 100 mg bid co-administered with ritonavir 100 mg bid was studied in a
220 heterogeneous population of 148 HIV infected patients (MaxCmin 1 study). At baseline
221 42 were treatment naive and 106 were treatment experienced (of which 52 had an HIV
222 RNA level < 400 copies/mL at baseline). Results showed that 91/148 (61%) subjects
223 achieved and/or sustained and HIV RNA level < 400 copies/mL at the completion of 48
224 weeks. Study NV15182 was an open-label safety study of FORTOVASE in combination
225 with other antiretroviral agents in HIV-infected patients. The 48-week safety results from
226 this study are displayed in the ADVERSE REACTIONS section.

227 **CONTRAINDICATIONS**

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

230 FORTOVASE should not be administered concurrently with terfenadine, cisapride,
231 astemizole, pimozone, triazolam, midazolam, or ergot derivatives, because competition
232 for CYP3A4 by saquinavir could result in inhibition of the metabolism of these drugs and
233 create the potential for serious and/or life-threatening reactions, such as cardiac
234 arrhythmias or prolonged sedation (see PRECAUTIONS: Drug Interactions).

235 FORTOVASE is contraindicated in patients with severe hepatic impairment (see
236 PRECAUTIONS: Hepatic Effects).

237 FORTOVASE should not be administered concurrently with drugs listed in Table 4 (also
238 see PRECAUTIONS: Drug Interactions, Table 5).

239 Table 4 Drugs That Are Contraindicated with FORTOVASE

Drug Class	Drugs Within Class That Are Contraindicated with FORTOVASE
Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine
Antihistamines	Astemizole*, Terfenadine*
<u>Ergot Derivatives</u>	<u>Dihydroergotamine, ergonovine, ergotamine, methylgonovine</u>
Antimycobacterial agents	Rifampin
GI Motility Agent	Cisapride*
Neuroleptics	Pimozide
Sedative/Hypnotics	Triazolam, Midazolam

240 * No longer marketed in the US.

241 If FORTOVASE is coadministered with ritonavir, the ritonavir label should be reviewed
242 for additional contraindicated drugs.

243 **WARNINGS**

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

246 **Interaction with HMG-CoA Reductase Inhibitors**

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

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

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

261 **Interaction with Garlic Capsules**

262 Garlic capsules should not be used while taking saquinavir as the sole protease inhibitor
263 due to the risk of decreased saquinavir plasma concentrations. No data are available for

264 the coadministration of FORTOVASE/ritonavir or INVIRASE/ritonavir and garlic
265 capsules.

266 **Diabetes Mellitus and Hyperglycemia**

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

276 **PRECAUTIONS**

277 **General**

278 FORTOVASE (saquinavir) soft gelatin capsules and INVIRASE (saquinavir mesylate)
279 capsules are not bioequivalent and cannot be used interchangeably when used as the sole
280 protease inhibitor. Only FORTOVASE should be used for the initiation of therapy that
281 includes saquinavir as a sole protease inhibitor (see DOSAGE AND
282 ADMINISTRATION) since FORTOVASE soft gelatin capsules provide greater
283 bioavailability and efficacy than INVIRASE capsules.

284 If a serious or severe toxicity occurs during treatment with FORTOVASE, FORTOVASE
285 should be interrupted until the etiology of the event is identified or the toxicity resolves.
286 At that time, resumption of treatment with full-dose FORTOVASE may be considered.
287 For antiretroviral agents used in combination with FORTOVASE, physicians should refer
288 to the complete product information for these drugs for dose adjustment
289 recommendations and for information regarding drug-associated adverse reactions.

290 **Hepatic Effects**

291 The use of FORTOVASE by patients with hepatic impairment has not been studied. In
292 the absence of such studies, caution should be exercised, as increases in saquinavir levels
293 and/or increases in liver enzymes may occur. In patients with underlying hepatitis B or C,
294 cirrhosis, chronic alcoholism and/or other underlying liver abnormalities there have been
295 reports of worsening liver disease

296 **Renal Effects**

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

302 Hemophilia

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

308 Hyperlipidemia

309 Elevated cholesterol and/or triglyceride levels have been observed in some patients
310 taking saquinavir in combination with ritonavir. Marked elevation in triglyceride levels is
311 a risk factor for development of pancreatitis. Cholesterol and triglyceride levels should be
312 monitored prior to initiating combination dosing regimen of FORTOVASE or
313 INVIRASE with ritonavir, and at periodic intervals while on such therapy. In these
314 patients, lipid disorders should be managed as clinically appropriate.

315 Fat Redistribution

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

321 **Resistance/Cross-resistance**

322 Varying degrees of cross-resistance among protease inhibitors have been observed.
323 Continued administration of FORTOVASE therapy following loss of viral suppression
324 may increase the likelihood of cross-resistance to other protease inhibitors (see
325 MICROBIOLOGY).

326 **Information for Patients**

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

330 Patients should be informed that any change from INVIRASE to FORTOVASE or
331 FORTOVASE to INVIRASE coadministered with ritonavir should be made only under
332 the supervision of a physician.

333 FORTOVASE may interact with some drugs; therefore, patients should be advised to
334 report to their doctor the use of any other prescription, nonprescription medication, or
335 herbal products, particularly St. John's wort.

336 Patients should be informed that FORTOVASE is not a cure for HIV infection and that
337 they may continue to acquire illnesses associated with advanced HIV infection, including
338 opportunistic infections. Patients should be advised that FORTOVASE should be used
339 only in combination with other active antiretroviral medications.

340 Patients should be informed that redistribution or accumulation of body fat may occur in
341 patients receiving protease inhibitors and that the cause and long-term health effects of
342 these conditions are not known at this time.

343 Patients should be told that the long-term effects of FORTOVASE are unknown at this
344 time. They should be informed that FORTOVASE therapy has not been shown to reduce
345 the risk of transmitting HIV to others through sexual contact or blood contamination.

346 Patients should be advised that FORTOVASE should be taken within 2 hours after a full
347 meal. When FORTOVASE is coadministered with ritonavir a light meal is sufficient (see
348 CLINICAL PHARMACOLOGY: Pharmacokinetics). Patients should be advised of the
349 importance of taking their medication every day, as prescribed, to achieve maximum
350 benefit. Patients should not alter the dose or discontinue therapy without consulting their
351 physician. If a dose is missed, patients should take the next dose as soon as possible.
352 However, the patient should not double the next dose.

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

356 **Laboratory Tests**

357 Clinical chemistry tests, viral load, and CD₄ count should be performed prior to initiating
358 FORTOVASE therapy and at appropriate intervals thereafter. Elevated nonfasting
359 triglyceride levels have been observed in patients in saquinavir trials. Triglyceride levels
360 should be periodically monitored during therapy. For comprehensive information
361 concerning laboratory test alterations associated with use of other antiretroviral therapies,
362 physicians should refer to the complete product information for these drugs.

363 **Drug Interactions**

364 **Several drug interaction studies have been completed with both INVIRASE and**
365 **FORTOVASE. Observations from drug interaction studies with FORTOVASE may**
366 **not be predictive for INVIRASE.** If ritonavir is coadministered, prescribers should also
367 refer to the prescribing information for ritonavir regarding drug interactions associated
368 with this agent.

369 The metabolism of saquinavir is mediated by cytochrome P450, with the specific
370 isoenzyme CYP3A4 responsible for 90% of the hepatic metabolism. Additionally,
371 saquinavir is a substrate for P-Glycoprotein (Pgp). Therefore, drugs that affect CYP3A4
372 and/or Pgp, may modify the pharmacokinetics of saquinavir. Similarly, saquinavir might
373 also modify the pharmacokinetics of other drugs that are substrates for CYP3A4 or Pgp.

374 Drugs that are contraindicated specifically due to the expected magnitude of interaction
375 and potential for serious adverse events are listed in Table 4 under
376 CONTRAINDICATIONS. Additional drugs that are not recommended for
377 coadministration with FORTOVASE are included in Table 5. These recommendations
378 are based on either drug interaction studies or predicted interactions due to the expected
379 magnitude of interaction and potential for serious events or loss of efficacy.

380 Drug interactions that have been established based on drug interaction studies are listed
381 with the pharmacokinetic results in Table 2, which summarizes the effect of saquinavir,
382 administered as FORTOVASE, on the geometric mean AUC and C_{max} of coadministered
383 drugs and Table 3, which summarizes the effect of coadministered drugs on the
384 geometric mean AUC and C_{max} of saquinavir. Clinical dose recommendations can be
385 found in Table 6. The magnitude of interactions may be different when FORTOVASE is
386 given with ritonavir.

387 **Table 5 Drugs That Should Not Be Coadministered with**
388 **FORTOVASE**

Drug Class: Drug Name	Clinical Comment
Antiarrhythmics: Amiodarone, bepridil, flecainide, propafenone, quinidine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions.
Antihistamines: astemizole*, terfenadine*	CONTRAINDICATED due to potential for serious and/or life-threatening cardiac arrhythmias.
Ergot Derivatives: Dihydroergotamine, ergonovine, ergotamine, methylegonovine	CONTRAINDICATED due to potential for serious and life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Antimycobacterial Agents: rifampin	WARNING coadministration with rifampin is not recommended because rifampin markedly decreases the concentration of saquinavir. The safety and efficacy of this combinations has not been established.
Garlic capsules	Garlic capsules should not be used while taking saquinavir (FORTOVASE) as the sole protease inhibitor due to the risk of decreased saquinavir plasma concentrations No data are available for the coadministration of INVIRASE/ritonavir or FORTOVASE/ritonavir and garlic capsules.

Drug Class: Drug Name	Clinical Comment
GI Motility Agent: cisapride*	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	WARNING coadministration may lead to loss of virologic response and possible resistance to FORTOVASE or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	WARNING potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Sedatives/Hypnotics: triazolam, midazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

389 * No longer marketed in the US.

390 If FORTOVASE is coadministered with ritonavir, the ritonavir label should be reviewed
391 for additional drugs that should not be coadministered.

392 **Table 6 Established and Other Potentially Significant Drug Interactions:**
393 **Alteration in Dose or Regimen May Be Recommended Based on**
394 **Drug Interaction Studies or Predicted Interaction (Information in**
395 **the table applies to FORTOVASE with or without ritonavir,**
396 **unless otherwise indicated)**

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Delavirdine	FORTOVASE ↑ Saquinavir Effect on delavirdine is not well established FORTOVASE/ritonavir Interaction has not been evaluated.	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Non-nucleoside reverse transcriptase inhibitor:	FORTOVASE ↓ Saquinavir	FORTOVASE should not be given as the sole

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
Efavirenz*, nevirapine	<p>↓ Efavirenz</p> <p>FORTOVASE/ritonavir Interaction has not been evaluated</p>	<p>protease inhibitor to patients taking efavirenz or nevirapine.</p> <p>Appropriate doses of the combination of efavirenz or nevirapine and FORTOVASE/ritonavir with respect to safety and efficacy have not been established.</p>
HIV protease inhibitor: Indinavir*	<p>FORTOVASE ↑ Saquinavir</p> <p>Effect on indinavir is not well established</p> <p>FORTOVASE/ritonavir Interaction has not been evaluated</p>	Appropriate doses of the combination with respect to safety and efficacy have not been established.
HIV protease inhibitor: Nelfinavir*	<p>FORTOVASE ↑ Saquinavir ↑ Nelfinavir</p> <p>FORTOVASE/ritonavir Interaction has not been evaluated</p>	Saquinavir 1200 mg bid with nelfinavir 1250 mg bid results in adequate plasma drug concentrations for both protease inhibitors.
HIV protease inhibitor: Ritonavir*	<p>FORTOVASE ↑ Saquinavir ↔ Ritonavir</p>	The recommended dose regimen when ritonavir is given to increase saquinavir concentrations is 1000 mg saquinavir plus ritonavir 100 mg twice daily.
HIV protease inhibitor: Lopinavir/ritonavir (coformulated capsule)*	<p>FORTOVASE ↑ Saquinavir</p> <p>Effect on lopinavir is not</p>	FORTOVASE (SQV) 800 mg bid + KALETRA produces ↑ AUC, ↑ C _{max} , and ↑ C _{min} relative to

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
	well established	FORTOVASE 1200 mg tid (see CLINICAL PHARMACOLOGY: Table 3)
HIV fusion inhibitor: Enfuvirtide*	FORTOVASE Interaction has not been evaluated FORTOVASE/ritonavir ↔Enfuvirtide	No clinically significant interaction was noted from a study in 12 HIV patients who received enfuvirtide concomitantly with FORTOVASE/ritonavir 1000/100 mg bid. No dose adjustments are required.
Other Agents		
<u>Antiarrhythmics:</u> lidocaine (systemic)	↑- <u>Antiarrhythmics</u>	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics given with FORTOVASE or FORTOVASE/ritonavir
Anticoagulant: Warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin	FORTOVASE ↓ Saquinavir Effect on carbamazepine, phenobarbital, and phenytoin is not well established	Use with caution, FORTOVASE may be less effective due to decreased saquinavir plasma concentrations in patients taking these agents concomitantly.

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
	<p>FORTOVASE/ritonavir Interaction has not been evaluated</p>	
<p>Anti-infective: Clarithromycin*</p>	<p>FORTOVASE ↑ Saquinavir ↑ Clarithromycin</p> <p>FORTOVASE/ritonavir Interaction has not been evaluated</p>	<p>No dose adjustment is required when the two drugs are coadministered for a limited time at the doses studied (clarithromycin 500 mg bid and FORTOVASE 1200 mg tid for 7 days).</p> <p>For patients with renal impairment, the following dosage adjustments should be considered:</p> <ul style="list-style-type: none"> • For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} <30 mL/min the dose of clarithromycin should be decreased by 75%. <p>No dose adjustment for patients with normal renal function is necessary.</p>
<p>Antifungal: Ketoconazole*, itraconazole</p>	<p>FORTOVASE ↑ Saquinavir ↔ Ketoconazole</p> <p>FORTOVASE/ritonavir Interaction has not been</p>	<p>No dose adjustment is required when the two drugs are coadministered for a limited time at the doses studied (ketoconazole 400 mg qd and FORTOVASE 1200 mg tid). A similar increase in plasma concentrations of saquinavir could occur with itraconazole.</p>

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
	evaluated	
Antimycobacterial Rifabutin*	↓ Saquinavir ↑ Rifabutin	FORTOVASE should not be given as the sole protease inhibitor to patients taking rifabutin. Appropriate doses of the combination of rifabutin and FORTOVASE/ritonavir with respect to safety and efficacy have not been established.
Antimycobacterial Rifampin*	FORTOVASE ↓ Saquinavir FORTOVASE/ritonavir Interaction has not been evaluated	FORTOVASE should not be given as the sole protease inhibitor to patients taking rifampin. Appropriate doses of the combination of rifampin and FORTOVASE/ritonavir with respect to safety and efficacy have not been established.
Benzodiazepines: Alprazolam, clorazepate, diazepam, flurazepam	↑ Benzodiazepines	Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.
Calcium channel blockers: Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine	↑ Calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	FORTOVASE ↓ Saquinavir FORTOVASE/ritonavir Interaction has not been	Use with caution, FORTOVASE may be less effective due to decreased saquinavir plasma concentrations in patients taking these agents concomitantly.

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
	evaluated	
Histamine H₂-receptor antagonist: Ranitidine	FORTOVASE ↑ Saquinavir FORTOVASE/ritonavir Interaction has not been evaluated	The increase is not thought to be clinically relevant and no dose adjustment of FORTOVASE is recommended. Appropriate doses of the combination of ranitidine and FORTOVASE/ritonavir with respect to safety and efficacy have not been established.
HMG-CoA reductase inhibitors: Simvastatin, lovastatin, atorvastatin	↑ HMG-CoA reductase inhibitors	The combination of FORTOVASE with simvastatin and lovastatin should be avoided. Use lowest possible dose of atorvastatin and with careful monitoring or consider other HMG-CoA reductase inhibitors such as pravastatin, fluvastatin and rosuvastatin.
Immunosuppressants: Cyclosporine, tacrolimus, rapamycin	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with FORTOVASE or FORTOVASE/ritonavir.
Narcotic analgesic: Methadone	FORTOVASE/ritonavir ↓ Methadone	Dosage of methadone may need to be increased when coadministered with FORTOVASE/ritonavir
Oral contraceptives: Ethinyl estradiol	FORTOVASE/ritonavir ↓ Ethinyl estradiol	Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and FORTOVASE/ritonavir are

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
PDE5 inhibitor (phosphodiesterase type 5 inhibitors): Sildenafil*, vardenafil, tadalafil	↑ Sildenafil ↔ Saquinavir ↑ Vardenafil ↑ Tadalafil FORTOVASE/ritonavir Interaction has not been evaluated, but expect increased concentrations of PDE5 inhibitors.	coadministered. Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring of adverse events when administered concomitantly with FORTOVASE or FORTOVASE/ritonavir. Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring of adverse events when administered concomitantly with FORTOVASE or FORTOVASE/ritonavir. Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring of adverse events when administered concomitantly with FORTOVASE or FORTOVASE/ritonavir.
Tricyclic antidepressants: Amitriptyline, imipramine	↑ Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with FORTOVASE/ritonavir.

397 *See CLINICAL PHARMACOKINETICS, Tables 2 and 3 for magnitude of interactions

398

399 *Drugs That Are Mainly Metabolized by CYP3A4:*

400 Although specific studies have not been performed, coadministration with drugs that are
 401 mainly metabolized by CYP3A4 (eg, calcium channel blockers, dapsone, disopyramide,
 402 quinine, amiodarone, quinidine, warfarin, tacrolimus, cyclosporine, ergot derivatives,
 403 pimozide, carbamazepine, fentanyl, alfentanil, alprazolam, nefazodone and triazolam)
 404 may have elevated plasma concentrations when coadministered with saquinavir;
 405 therefore, these combinations should be used with caution. If FORTOVASE is

406 coadministered with ritonavir, the ritonavir label should be reviewed for additional drugs
407 that should not be coadministered.

408 *Inducers of CYP3A4:*

409 Coadministration with compounds that are potent inducers of CYP3A4 (eg,
410 phenobarbital, phenytoin, dexamethasone, carbamazepine) may result in decreased
411 plasma levels of saquinavir.

412 **Carcinogenesis, Mutagenesis and Impairment of Fertility**

413 **Carcinogenesis**

414 Carcinogenicity studies found no indication of carcinogenic activity in rats and mice
415 administered saquinavir for approximately 2 years. The plasma exposures (AUC values)
416 in the respective species were up to approximately 60% of (using rat) and equivalent to
417 (using mouse) those obtained in humans at the recommended clinical dose
418 (FORTOVASE 1200 mg TID).

419 **Mutagenesis**

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

426 **Impairment of Fertility**

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

430 **Pregnancy**

431 **Teratogenic Effects**

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

438 Studies in rats indicated that exposure to saquinavir from late pregnancy through
439 lactation at plasma concentrations (AUC values) approximately 50% of those achieved in
440 humans at the recommended dose of FORTOVASE had no effect on the survival, growth
441 and development of offspring to weaning. Clinical experience in pregnant women is
442 limited. Saquinavir should be used during pregnancy only if the potential benefit justifies
443 the potential risk to the fetus.

444 **Antiretroviral Pregnancy Registry**

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

448 **Nursing Mothers**

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

455 **Pediatric Use**

456 FORTOVASE should not be administered as a sole protease inhibitor to pediatric
457 patients ≤ 16 years of age due to the risk of reduced saquinavir plasma concentrations
458 compared to adults.

459 Safety and effectiveness of saquinavir when coadministered with ritonavir to pediatric
460 patients is under investigation.

461 **Geriatric Use**

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

467 **ADVERSE REACTIONS (see PRECAUTIONS)**

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

473 Clinical adverse events of at least moderate intensity, which occurred in $\geq 2\%$ of patients
474 in studies NV15182 (an open-label, single-arm safety study) and NV15355 (an open-
475 label randomized study comparing FORTOVASE and INVIRASE) are summarized in
476 Table 7. The median duration of treatment in studies NV15182 and NV15355 were 52
477 and 18 weeks, respectively. In NV15182, more than 300 patients were on treatment for
478 approximately 1 year.

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

483 Rare occurrences of the following serious adverse experiences have been reported during
484 clinical trials of FORTOVASE and/or INVIRASE and were considered at least possibly
485 related to use of study drugs: confusion, ataxia and weakness; seizures; headache; acute
486 myeloblastic leukemia; hemolytic anemia; thrombocytopenia; thrombocytopenia and
487 intracranial hemorrhage leading to death; attempted suicide; Stevens-Johnson syndrome;
488 bullous skin eruption and polyarthritis; severe cutaneous reaction associated with
489 increased liver function tests; isolated elevation of transaminases; exacerbation of chronic
490 liver disease with Grade 4 elevated liver function tests, jaundice, ascites, and right and
491 left upper quadrant abdominal pain; pancreatitis leading to death; intestinal obstruction;
492 portal hypertension; thrombophlebitis; peripheral vasoconstriction; drug fever;
493 nephrolithiasis; and acute renal insufficiency.

494 **Table 7** **Percentage of Patients With Treatment-Emergent Adverse**
 495 **Events* of at Least Moderate Intensity, Occurring in ≥2% of**
 496 **Patients**

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

497 * Includes adverse events at least possibly related to study drug or of unknown intensity and/or
 498 relationship to treatment (corresponding to ACTG Grade 2, 3 and 4).

499 † Antiretroviral Treatment of Choice.

500 ‡ Reverse Transcriptase Inhibitor.

501 **Concomitant Therapy with Ritonavir**

502 **Table 8 Grade 2, 3 and 4 Adverse Events (All Causality) Reported in $\geq 2\%$**
503 **of Adult Patients in the MaxCmin 1 Study of FORTOVASE in**
504 **Combination with Ritonavir 1000/100 mg bid**

	<u>FORTOVASE 1000 mg plus Ritonavir 100 mg bid (48 weeks)</u> <u>N=148</u> <u>n(>=n/N)</u>
Endocrine Disorders	
Diabetes mellitus/hyperglycemia	4 (2.7)
Lipodystrophy	8 (5.4)
Gastrointestinal Disorders	
Nausea	16 (10.8)
Vomiting	11 (7.4)
Diarrhea	12 (6.8)
Abdominal Pain	9 (6.1)
Constipation	3 (2.0)
General Disorders and Administration Site Conditions	
Fatigue	9 (6.1)
Fever	5 (3.4)
Musculoskeletal Disorders	
Back Pain	3 (2.0)
Respiratory Disorders	
Pneumonia	8 (5.4)
Bronchitis	4 (2.7)
Influenza	4 (2.7)
Sinusitis	4 (2.7)
Dermatological Disorders	
Rash	5 (3.4)
Pruritis	5 (3.4)
Dry lips/skin	3 (2.0)
Eczema	3 (2.0)

505 Includes events with unknown relationship to study drug.

506 **Laboratory Abnormalities**

507 In the MaxCmin 1 study, Grade 3 and 4 thrombocytopenia (2.0% of patients) and anemia
508 (2.0%) were observed with FORTOVASE in combination with ritonavir. At 48 weeks,
509 other lab abnormalities included increased ALT, increased AST, increased GGT,
510 hyperglycemia, hypertriglyceridemia, increased TSH, neutropenia, raised amylase, and
511 increased LDH.

512 Table 9 summarizes the percentage of patients with marked laboratory abnormalities in
513 study NV15182 and NV15355 (median duration of treatment was 52 and 18 weeks,

514 respectively). In study NV15182, by 48 weeks <1% of patients discontinued treatment
515 due to laboratory abnormalities.

516 In the safety study (NV15182), 27% to 33% of subjects experienced ≥1 grade shifts
517 in ALT and AST during the 48-week study period. In 46% of such events, there was a
518 single abnormal transaminase level with no evidence of persistently elevated enzyme
519 values during the course of study. Only 3% to 4% of patients had ≥3 grade shifts in
520 transaminase levels and less than 0.5% of patients had to discontinue the study for
521 increased liver function test values.

522 **Table 9 Percentage of Patients with Marked Laboratory Abnormalities***

		NV15182 (48 weeks)	NV15355 (48 weeks) Naive Patients
		FORTOVASE + TOC [†] N=442	FORTOVASE + 2 RTIs [‡] N=90
BIOCHEMISTRY	Limit		
Alkaline Phosphatase (high)	>5 x ULN [§]	0.5	0.0
Calcium (high)	>12.5 mg/dL	0.2	0.0
Creatine Kinase (high)	>4 x ULN [§]	7.8	6.0
Gamma GT (high)	>5 x ULN [§]	5.7	5.0
Glucose (low)	>5 x ULN [§]	6.4	3.5
Glucose (high)	<40 mg/dL	1.4	0.0
Phosphate (low)	>250 mg/dL	0.5	1.0
Potassium (high)	<1.5 mg/dL	2.7	3.5
Serum Amylase (high)	>6.5 mEq/L	1.9	ND
SGOT (AST) (high)	>2 x ULN [§]	4.1	0.0
SGPT (ALT) (high)	>5 x ULN [§]	5.7	1.0
Sodium (high)	>5 x ULN [§]	0.7	0.0
Sodium (low)	>5 x ULN [§]	0.0	1.0
Total Bilirubin (high)	>157 mEq/L	1.6	0.0
Triglycerides (high)	>2.5 x ULN [§]	0.0	2.0
HEMATOLOGY			
Hemoglobin (low)	<7.0 gm/dL	0.7	1.0
Absolute Neutrophil Count (low)	<750 mm ³	2.9	1.0
Platelets (low)	<50,000 mm ³	0.9	0.0

523 * ACTG Grade 3 or above.

524 [†] Antiretroviral Treatment of Choice.

525 [‡] Reverse Transcriptase Inhibitor.

526 [§] ULN = Upper limit of normal range.

527 ND Not done.

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

530 **Monotherapy and Combination Studies**

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

534 **Autonomic Nervous System**

535 Mouth dry, night sweats, sweating increased

536 **Body as a Whole**

537 Allergic reaction, anorexia, appetite decreased, appetite disturbances, asthenia, chest
538 pain, edema, fever, intoxication, malaise, olfactory disorder, pain body, pain pelvic,
539 retrosternal pain, shivering, trauma, wasting syndrome, weakness generalized, weight
540 decrease, redistribution/accumulation of body fat (see PRECAUTIONS: Fat
541 Redistribution)

542 **Cardiovascular/Cerebrovascular**

543 Cyanosis, heart murmur, heart rate disorder, heart valve disorder, hypertension,
544 hypotension, stroke, syncope, vein distended

545 **Central and Peripheral Nervous System**

546 Ataxia, cerebral hemorrhage, confusion, convulsions, dizziness, dysarthria, dysesthesia,
547 hyperesthesia, hyperreflexia, hyporeflexia, light-headed feeling,
548 myelopolyradiculoneuritis, neuropathy, numbness extremities, numbness face, paresis,
549 paresthesia, peripheral neuropathy, poliomyelitis, prickly sensation, progressive
550 multifocal leukoencephalopathy, spasms, tremor, unconsciousness

551 **Dermatological**

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

557 **Endocrine/Metabolic**

558 Dehydration, diabetes mellitus, hyperglycemia, hypoglycemia, hypothyroidism, thirst,
559 triglyceride increase, weight increase

560 **Gastrointestinal**

561 Abdominal distention, bowel movements frequent, buccal mucosa ulceration, canker
562 sores oral, cheilitis, colic abdominal, dysphagia, esophageal ulceration, esophagitis,
563 eructation, fecal incontinence, feces bloodstained, feces discolored, gastralgia, gastritis,
564 gastroesophageal reflux, gastrointestinal inflammation, gingivitis, glossitis, hemorrhage
565 rectum, hemorrhoids, infectious diarrhea, melena, painful defecation, parotid disorder,

566 pruritus ani, pyrosis, salivary glands disorder, stomach upset, stomatitis, taste unpleasant,
567 toothache, tooth disorder, ulcer gastrointestinal

568 **Hematologic**

569 Anemia, neutropenia, pancytopenia, splenomegaly

570 **Liver and Biliary**

571 Cholangitis sclerosing, cholelithiasis, hepatitis, hepatomegaly, hepatosplenomegaly,
572 jaundice, liver enzyme disorder, pancreatitis

573 **Musculoskeletal**

574 Arthralgia, arthritis, back pain, cramps leg, cramps muscle, lumbago, musculoskeletal
575 disorders, myalgia, myopathy, pain facial, pain jaw, pain leg, pain musculoskeletal,
576 stiffness, tissue changes

577 **Neoplasm**

578 Kaposi's sarcoma, tumor

579 **Platelet, Bleeding, Clotting**

580 Bleeding dermal, hemorrhage, microhemorrhages, thrombocytopenia

581 **Psychiatric**

582 Agitation, amnesia, anxiety attack, behavior disturbances, dreaming excessive, euphoria,
583 hallucination, intellectual ability reduced, irritability, lethargy, overdose effect, psychic
584 disorder, psychosis, somnolence, speech disorder

585 **Reproductive System**

586 Epididymitis, erectile impotence, impotence, menstrual disorder, menstrual irregularity,
587 penis disorder, prostate enlarged, vaginal discharge

588 **Resistance Mechanism**

589 Abscess, angina tonsillaris, candidiasis, cellulitis, herpes simplex, herpes zoster, infection
590 bacterial, infection mycotic, infection staphylococcal, infestation parasitic, influenza,
591 lymphadenopathy, molluscum contagiosum, moniliasis

592 **Respiratory**

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

596 **Special Senses**

597 Blepharitis, conjunctivitis, cytomegalovirus retinitis, dry eye syndrome, earache, ear
598 pressure, eye irritation, hearing decreased, otitis, taste unpleasant, tinnitus, visual
599 disturbance, xerophthalmia

600 **Urinary System**

601 Micturition disorder, nocturia, renal calculus, renal colic, urinary tract bleeding, urinary
602 tract infection

603 **Postmarketing Experience with INVIRASE and FORTOVASE**

604 Additional adverse events that have been observed during the postmarketing period are
605 similar to those seen in clinical trials with INVIRASE and FORTOVASE and
606 administration of INVIRASE and FORTOVASE in combination with ritonavir.

607 **OVERDOSAGE**

608 Two cases of FORTOVASE overdose have been received (one case with unknown
609 amount of FORTOVASE, the second case 3.6 to 4 grams at once). No adverse events
610 have been reported in both cases. There were 2 patients who had overdoses with
611 INVIRASE. No acute toxicities or sequelae were noted in the first patient after ingesting
612 8 grams of INVIRASE as a single dose. The patient was treated with induction of emesis
613 within 2 to 4 hours after ingestion. The second patient ingested 2.4 grams of INVIRASE
614 in combination with 600 mg of ritonavir and experienced pain in the throat that lasted for
615 6 hours and then resolved.

616 **DOSAGE AND ADMINISTRATION**

617 FORTOVASE (saquinavir) soft gelatin capsules and INVIRASE (saquinavir mesylate)
618 capsules are not bioequivalent and cannot be used interchangeably. When using
619 saquinavir as the sole protease inhibitor in an antiviral regimen, FORTOVASE is the
620 recommended formulation. INVIRASE may be considered only if it is combined with
621 ritonavir, which significantly inhibits saquinavir's metabolism to provide plasma
622 saquinavir levels at least equal to those achieved with FORTOVASE at the recommended
623 dose of 1200 mg tid (see CLINICAL PHARMACOLOGY: Drug Interactions).

624 **Adults (Over the Age of 16 Years)**

625 FORTOVASE Administered without Ritonavir:

- 626 • FORTOVASE 1200-mg TID (6 x 200-mg capsules)
- 627 • FORTOVASE should be taken with a meal or up to 2 hours after a meal

628 FORTOVASE Administered with Ritonavir:

- 629 • FORTOVASE 1000-mg BID (5 x 200-mg capsules) in combination with ritonavir
630 100-mg BID
- 631 • Ritonavir should be taken at the same time as FORTOVASE
- 632 • FORTOVASE and ritonavir should be taken within 2 hours after a meal

633 When used in combination with nucleoside analogues, the dosage of FORTOVASE
634 should not be reduced as this will lead to greater than dose proportional decreases in
635 saquinavir plasma levels.

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

642 **Monitoring of Patients**

643 Clinical chemistry tests, viral load, and CD₄ count should be performed prior to initiating
644 FORTOVASE therapy and at appropriate intervals thereafter. For comprehensive patient
645 monitoring recommendations for other antiretroviral therapies, physicians should refer to
646 the complete product information for these drugs.

647 **Dose Adjustment for Combination Therapy with FORTOVASE**

648 For serious toxicities that may be associated with FORTOVASE, the drug should be
649 interrupted. For recipients of combination therapy with FORTOVASE and other
650 antiretroviral agents, dose adjustment of the other antiretroviral agents should be based
651 on the known toxicity profile of the individual drug. FORTOVASE dose adjustments
652 may be required with some other antiretroviral agents (see PRECAUTIONS: Drug
653 Interactions). Physicians should refer to the complete product information for these drugs
654 for comprehensive dose adjustment recommendations and drug-associated adverse
655 reactions.

656 **HOW SUPPLIED**

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

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

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

664 HIVID and INVIRASE are registered trademarks of Hoffmann-La Roche Inc.

665 KALETRA is a registered trademark of Abbott Laboratories.

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