



**INVIRASE®**  
**(saquinavir mesylate)**  
**CAPSULES**

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**R<sub>x</sub> only**

**WARNING:**

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

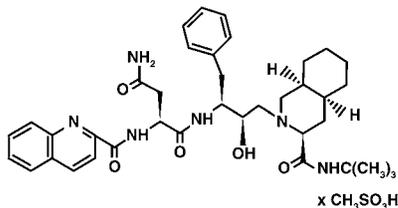
**Product identification in this document includes: INVIRASE in reference to saquinavir mesylate; FORTOVASE in reference to saquinavir soft gel formulation, and saquinavir in reference to the active base.**

**DESCRIPTION**

INVIRASE brand of saquinavir mesylate is an inhibitor of the human immunodeficiency virus (HIV) protease. INVIRASE is available as light brown and green, opaque hard gelatin capsules for oral administration in a 200-mg strength (as saquinavir free base). Each capsule also contains the inactive ingredients lactose, microcrystalline cellulose, povidone K30, sodium starch glycolate, talc, and magnesium stearate. Each capsule shell contains gelatin and water with the following dye systems: red iron oxide, yellow iron oxide, black iron oxide, FD&C Blue #2, and titanium dioxide. The chemical name for saquinavir mesylate is N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginy]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide methanesulfonate with a molecular formula  $C_{38}H_{50}N_6O_5 \cdot CH_4O_3S$  and a molecular weight

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28 of 766.96. The molecular weight of the free base is 670.86. Saquinavir mesylate has the  
29 following structural formula:



31 Saquinavir mesylate is a white to off-white, very fine powder with an aqueous solubility  
32 of 2.22 mg/mL at 25°C.

33 **MICROBIOLOGY**

34 **Mechanism of Action**

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

41 **Antiviral Activity**

42 In vitro antiviral activity of saquinavir was assessed in lymphoblastoid and monocytic  
43 cell lines and in peripheral blood lymphocytes. Saquinavir inhibited HIV activity in both  
44 acutely and chronically infected cells. IC<sub>50</sub> and IC<sub>90</sub> values (50% and 90% inhibitory  
45 concentrations) were in the range of 1 to 30 nM and 5 to 80 nM, respectively. In the  
46 presence of 40% human serum, the mean IC<sub>50</sub> of saquinavir against laboratory strain  
47 HIV-1 RF in MT4 cells was 37.7 ± 5nM representing a 4-fold increase in the IC<sub>50</sub> value.  
48 In cell culture, saquinavir demonstrated additive to synergistic effects against HIV-1 in  
49 combination with reverse transcriptase inhibitors (didanosine, lamivudine, nevirapine,  
50 stavudine, zalcitabine and zidovudine) without enhanced cytotoxicity. Saquinavir in  
51 combination with the protease inhibitors amprenavir, atazanavir, or lopinavir resulted in  
52 synergistic antiviral activity.

53 **Drug Resistance**

54 HIV-1 mutants with reduced susceptibility to saquinavir have been selected during in  
55 vitro passage. Genotypic analyses of these isolates showed several substitutions in the  
56 HIV protease gene. Only the G48V and L90M substitutions were associated with reduced  
57 susceptibility to saquinavir, and conferred an increase in the IC<sub>50</sub> value of 8- and 3-fold,  
58 respectively.

59 HIV-1 isolates with reduced susceptibility (≥4-fold increase in the IC<sub>50</sub> value) to  
60 saquinavir emerged in some patients treated with INVIRASE. Genotypic analysis of  
61 these isolates identified resistance conferring primary mutations in the protease gene

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62 G48V and L90M, and secondary mutations L10I/R/V, I54V/L, A71V/T, G73S, V77I,  
63 V82A and I84V that contributed additional resistance to saquinavir. Forty-one isolates  
64 from 37 patients failing therapy with INVIRASE had a median decrease in susceptibility  
65 to saquinavir of 4.3 fold.

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

72 **Cross-resistance**

73 Among protease inhibitors, variable cross resistance has been observed. In one clinical  
74 study, 22 HIV-1 isolates with reduced susceptibility (>4-fold increase in the IC<sub>50</sub> value)  
75 to saquinavir following therapy with INVIRASE were evaluated for cross-resistance to  
76 amprenavir, indinavir, nelfinavir and ritonavir. Six of the 22 isolates (27%) remained  
77 susceptible to all 4 protease inhibitors, 12 of the 22 isolates (55%) retained susceptibility  
78 to at least one of the PIs and 4 out of the 22 isolates (18%) displayed broad cross-  
79 resistance to all PIs. Sixteen (73%) and 11 (50%) of the 22 isolates remained susceptible  
80 (<4-fold) to amprenavir and indinavir, respectively. Four of 16 (25%) and nine of 21  
81 (43%) with available data remained susceptible to nelfinavir and ritonavir, respectively.

82 After treatment failure with amprenavir, cross-resistance to saquinavir was evaluated.  
83 HIV-1 isolates from 22/22 patients failing treatment with amprenavir and containing one  
84 or more mutations M46L/I, I50V, I54L, V32I, I47V, and I84V were susceptible to  
85 saquinavir.

86 **CLINICAL PHARMACOLOGY**

87 **Pharmacokinetics**

88 The pharmacokinetic properties of INVIRASE have been evaluated in healthy volunteers  
89 (n=351) and HIV-infected patients (n=270) after single- and multiple-oral doses of 25,  
90 75, 200, and 600 mg tid and in healthy volunteers after intravenous doses of 6, 12, 36 or  
91 72 mg (n=21). The pharmacokinetics of INVIRASE/ritonavir 400/400 mg bid and  
92 INVIRASE/ritonavir 1000/100 mg bid have also been evaluated in HIV-infected patients.

93 HIV-infected patients administered INVIRASE (600-mg TID) had AUC and maximum  
94 plasma concentration (C<sub>max</sub>) values approximately 2-2.5 times those observed in healthy  
95 volunteers receiving the same treatment regimen.

96 **Absorption and Bioavailability in Adults**

97 Absolute bioavailability of saquinavir administered as INVIRASE averaged 4% (CV  
98 73%, range: 1% to 9%) in 8 healthy volunteers who received a single 600-mg dose (3 x  
99 200 mg) of saquinavir mesylate following a high-fat breakfast (48 g protein, 60 g  
100 carbohydrate, 57 g fat; 1006 kcal). The low bioavailability is thought to be due to a

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101 combination of incomplete absorption and extensive first-pass metabolism. Following  
 102 single 600-mg doses, the relative bioavailability of saquinavir as FORTOVASE  
 103 compared to saquinavir administered as INVIRASE was estimated at 331% (95% CI  
 104 207% to 530%).

105 When administered as the sole protease inhibitor, it has been shown that FORTOVASE  
 106 1200 mg tid provides an 8-fold increase in AUC compared with INVIRASE 600 mg tid  
 107 (see Table 1).

108 INVIRASE in combination with ritonavir at doses of 1000/100 mg bid or 400/400 mg bid  
 109 provides saquinavir systemic exposures over a 24-hour period similar to or greater than  
 110 those achieved with FORTOVASE 1200 mg tid (see Table 1).

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 <sub>τ</sub> (ng·h/mL)	AUC <sub>24h</sub> (ng·h/mL)	C <sub>min</sub> (ng/mL)
INVIRASE 600 mg tid (arithmetic mean, %CV)	10	866 (62)	2598	79
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 No food effect data are available for INVIRASE in combination with ritonavir.

117 The mean 24-hour AUC after a single 600-mg oral dose (6 x 100 mg) in healthy  
 118 volunteers (n=6) was increased from 24 ng·h/mL (CV 33%), under fasting conditions, to  
 119 161 ng·h/mL (CV 35%) when INVIRASE was given following a high-fat breakfast (48 g  
 120 protein, 60 g carbohydrate, 57 g fat; 1006 kcal). Saquinavir 24-hour AUC and C<sub>max</sub> (n=6)  
 121 following the administration of a higher calorie meal (943 kcal, 54 g fat) were on average  
 122 2 times higher than after a lower calorie, lower fat meal (355 kcal, 8 g fat). The effect of  
 123 food has been shown to persist for up to 2 hours.

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

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130 into tissues. Saquinavir was approximately 98% bound to plasma proteins over a  
131 concentration range of 15 to 700 ng/mL. In 2 patients receiving saquinavir mesylate 600  
132 mg tid, cerebrospinal fluid concentrations were negligible when compared to  
133 concentrations from matching plasma samples.

134 **Metabolism and Elimination in Adults**

135 In vitro studies using human liver microsomes have shown that the metabolism of  
136 saquinavir is cytochrome P450 mediated with the specific isoenzyme, CYP3A4,  
137 responsible for more than 90% of the hepatic metabolism. Based on in vitro studies,  
138 saquinavir is rapidly metabolized to a range of mono- and di-hydroxylated inactive  
139 compounds. In a mass balance study using 600 mg <sup>14</sup>C-saquinavir mesylate (n=8), 88%  
140 and 1% of the orally administered radioactivity was recovered in feces and urine,  
141 respectively, within 5 days of dosing. In an additional 4 subjects administered 10.5 mg  
142 <sup>14</sup>C-saquinavir intravenously, 81% and 3% of the intravenously administered  
143 radioactivity was recovered in feces and urine, respectively, within 5 days of dosing. In  
144 mass balance studies, 13% of circulating radioactivity in plasma was attributed to  
145 unchanged drug after oral administration and the remainder attributed to saquinavir  
146 metabolites. Following intravenous administration, 66% of circulating radioactivity was  
147 attributed to unchanged drug and the remainder attributed to saquinavir metabolites,  
148 suggesting that saquinavir undergoes extensive first-pass metabolism.

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

151 **Special Populations**

152 *Hepatic or Renal Impairment*

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

156 *Gender, Race, and Age*

157 Pharmacokinetic data were available for 17 women in the Phase I/II studies. Pooled data  
158 did not reveal an apparent effect of gender on the pharmacokinetics of saquinavir

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

160 *Pediatric Patients*

161 The pharmacokinetics of saquinavir when administered as INVIRASE has not been  
162 sufficiently investigated in pediatric patients.

163 *Geriatric Patients*

164 The pharmacokinetics of saquinavir when administered as INVIRASE have not been  
165 sufficiently investigated in patients >65 years of age.

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166 Drug Interactions (see PRECAUTIONS: Drug Interactions)  
 167 Several drug interaction studies have been completed with both INVIRASE and  
 168 FORTOVASE. It is important to be aware that, when INVIRASE is coadministered with  
 169 ritonavir, the occurrence and magnitude of drug interactions may differ from those seen  
 170 with FORTOVASE when administered as the sole protease inhibitor. Because ritonavir is  
 171 coadministered, prescribers should refer to the prescribing information for ritonavir  
 172 regarding drug interactions associated with this drug.

173 Table 2 summarizes the effect of FORTOVASE on the geometric mean AUC and C<sub>max</sub> of  
 174 coadministered drugs. Table 3 summarizes the effect of coadministered drugs on the  
 175 geometric mean AUC and C<sub>max</sub> of saquinavir.

176 **Table 2 Effect of FORTOVASE or INVIRASE on the Pharmacokinetics of**  
 177 **Coadministered Drugs**

Coadministered Drug	FORTOVASE or FORTOVASE/ ritonavir Dose	N	% Change for Coadministered Drug	
			AUC (95%CI)	C <sub>max</sub> (95%CI)
Clarithromycin 500 mg bid x 7 days Clarithromycin 14-OH clarithromycin metabolite	1200 mg tid x 7 days	12V	↑45% (17-81%) ↓24% (5-40%)	↑39% (10-76%) ↓34% (14-50%)
Midazolam 7.5-mg oral single dose	1200 mg tid x 5 days	6V	↑514%	↑235%
Ketoconazole 400mg once daily	1200 mg tid	12V	↔	↔
Enfuvirtide 90mg SCq 12h (bid) for 7 days	1000/100 mg bid	12P	↔	↔
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 $\phi$ 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%

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

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

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

181 \* FORTOVASE or INVIRASE/ritonavir should not be coadministered with terfenadine (see  
 182 PRECAUTIONS: Drug Interactions).

183 P Patient

184 V Healthy Volunteers

185  $\phi$  No longer marketed in the US.

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**Table 3 Effect of Coadministered Drugs on FORTOVASE or INVIRASE Pharmacokinetics**

Coadministered Drug	FORTOVASE Dose	N	% Change for Saquinavir	
			AUC (95%CI)	C <sub>max</sub> (95%CI)
Clarithromycin 500 mg bid x 7 days	1200 mg tid x 7 days	12V	↑177% (108-269%)	↑187% (105-300%)
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%	↓39%
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 day combo vs. 1200 tid, 5 days alone	14V	↑9.62-fold (8.05, 11.49)^	↑6.34-fold (5.32, 7.55)^
400/100 bid, 20 days	1200 bid, 10 day combo vs. 1200 tid, 5 days alone	10V	↑9.91-fold (8.28, 11.86)^	↑6.44 -fold (5.59, 7.41)^

188

Coadministered Drug	INVIRASE Dose	N	% Change for Saquinavir	
			AUC (95%CI)	C <sub>max</sub> (95%CI)
Rifabutin 150 mg every 3 days or 300 mg every 7 days	400 mg bid + 400 mg ritonavir bid	24P	↑19%	↑39%
Ritonavir 400 mg bid steady state*	400 mg bid steady state‡	7P	↑1587% (808-3034%)	↑1277% (577-2702%)
Ritonavir 100 mg bid	1000 mg bid‡	24P	↑1124%	↑1325%

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↑ Denotes an average increase in exposure by the percentage indicated.  
↓ Denotes an average decrease in exposure by the percentage indicated.  
↔ Denotes no statistically significant change in exposure was observed.  
\* When ritonavir was combined with the same dose of either INVIRASE or FORTOVASE, actual mean plasma exposures (AUC<sub>12</sub>, 18200 ng·h/mL, 20000 ng·h/mL, respectively) were not significantly different.

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- 195 ^ 90% CI reported  
196 † Compared to standard FORTOVASE 1200 mg tid regimen (n=33).  
197 ‡ Compared to standard INVIRASE 600 mg tid regimen (n=114).  
198 § Did not reach statistical significance.  
199 P Patient  
200 V Healthy Volunteers  
201

202 For information regarding clinical recommendations, see PRECAUTIONS: Drug  
203 Interactions, Table 7.

204 **INDICATIONS AND USAGE**

205 INVIRASE in combination with ritonavir and other antiretroviral agents is indicated for  
206 the treatment of HIV infection. The twice daily administration of INVIRASE in  
207 combination with ritonavir is supported by safety data from the MaxCmin 1 study (see  
208 Table 7) and pharmacokinetic data (see Table 1). The efficacy of INVIRASE with  
209 ritonavir or FORTOVASE (with or without ritonavir coadministration) has not been  
210 compared against the efficacy of antiretroviral regimens currently considered standard of  
211 care.

212 **Description of Clinical Studies**

213 In a randomized, double-blind clinical study (NV14256) in ZDV-experienced, HIV-  
214 infected patients, INVIRASE in combination with HIVID was shown to be superior to  
215 either INVIRASE or HIVID monotherapy in decreasing the cumulative incidence of  
216 clinical disease progression to AIDS-defining events or death. Furthermore, in a  
217 randomized study (ACTG229/NV14255), patients with advanced HIV infection with  
218 history of prolonged ZDV treatment and who were given INVIRASE 600 mg tid + ZDV  
219 + HIVID experienced greater increases in CD4 cell counts as compared to those who  
220 received INVIRASE + ZDV or HIVID + ZDV. It should be noted that HIV treatment  
221 regimens that were used in these initial clinical studies of INVIRASE are no longer  
222 considered standard of care.

223 FORTOVASE 1000 mg bid co-administered with ritonavir 100 mg bid was studied in a  
224 heterogeneous population of 148 HIV-infected patients (MaxCmin 1 study). At baseline  
225 42 were treatment naïve and 106 were treatment experienced (of which 52 had an HIV  
226 RNA level <400 copies/mL at baseline). Results showed that 91/148 (61%) subjects  
227 achieved and/or sustained an HIV RNA level <400 copies/mL at the completion of 48  
228 weeks.

229

230 **CONTRAINDICATIONS**

231 INVIRASE may be used only if it is combined with ritonavir, which significantly inhibits  
232 saquinavir's metabolism and provides plasma saquinavir levels at least equal to those  
233 achieved with FORTOVASE.

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234 INVIRASE is contraindicated in patients with clinically significant hypersensitivity to  
235 saquinavir or to any of the components contained in the capsule.

236 INVIRASE/ritonavir should not be administered concurrently with terfenadine, cisapride,  
237 astemizole, pimozone, triazolam, midazolam or ergot derivatives. Inhibition of CYP3A4  
238 by saquinavir could result in elevated plasma concentrations of these drugs, potentially  
239 causing serious or life-threatening reactions, such as cardiac arrhythmias or prolonged  
240 sedation (see PRECAUTIONS: Drug Interactions).

241 INVIRASE when administered with ritonavir is contraindicated in patients with severe  
242 hepatic impairment.

243 INVIRASE should not be administered concurrently with drugs listed in Table 4 (also see  
244 PRECAUTIONS: Drug Interactions, Table 5).

245 **Table 4                    Drugs That Are Contraindicated With INVIRASE/Ritonavir**

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

246 \*INVIRASE used as a sole protease inhibitor

247 **WARNINGS**

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

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

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

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

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

265 **Interaction with Garlic Capsules**

266 Garlic capsules should not be used while taking saquinavir as the sole protease inhibitor  
267 due to the risk of decreased saquinavir plasma concentrations. No data are available for  
268 the coadministration of INVIRASE/ritonavir or FORTOVASE/ritonavir and garlic  
269 capsules.

270 **Diabetes Mellitus and Hyperglycemia**

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

280 **PRECAUTIONS**

281 **General**

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

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

294 **Hepatic Effects**

295 The use of INVIRASE (in combination with ritonavir) by patients with hepatic  
296 impairment has not been studied. In the absence of such studies, caution should be

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297 exercised, as increases in saquinavir levels and/or increases in liver enzymes may occur.  
298 In patients with underlying hepatitis B or C, cirrhosis, chronic alcoholism and/or other  
299 underlying liver abnormalities there have been reports of worsening liver disease.

300 **Renal Effects**

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

306 **Hemophilia**

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

312 **Hyperlipidemia**

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

319 **Lactose Intolerance**

320 Each capsule contains lactose (anhydrous) 63.3 mg. This quantity should not induce  
321 specific symptoms of intolerance.

322 **Fat Redistribution**

323 Redistribution/accumulation of body fat including central obesity, dorsocervical fat  
324 enlargement (buffalo hump), facial wasting, peripheral wasting, breast enlargement, and  
325 “cushingoid appearance” have been observed in patients receiving antiretroviral therapy.  
326 A causal relationship between protease-inhibitor therapy and these events has not been  
327 established and the long-term consequences are currently unknown.

328 **Resistance/Cross-resistance**

329 Varying degrees of cross-resistance among protease inhibitors have been observed.  
330 Continued administration of INVIRASE therapy following loss of viral suppression may  
331 increase the likelihood of cross-resistance to other protease inhibitors (see  
332 **Microbiology**).

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333 **Information for Patients**

334 A statement to patients and health care providers is included on the product's bottle label:  
335 **ALERT: Find out about medicines that should NOT be taken with INVIRASE.**

336 Patients should be informed that any change from INVIRASE to FORTOVASE or  
337 FORTOVASE to INVIRASE coadministered with a drug which inhibits its metabolism,  
338 such as ritonavir, should be made only under the supervision of a physician.

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

342 Patients should be informed that INVIRASE is not a cure for HIV infection and that they  
343 may continue to acquire illnesses associated with advanced HIV infection, including  
344 opportunistic infections. Patients should be advised that **INVIRASE may be used only if**  
345 **it is combined with, ritonavir, which significantly inhibits saquinavir's metabolism**  
346 **to provide plasma saquinavir levels at least equal to those achieved with**  
347 **FORTOVASE.**

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

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

354 Patients should be advised that INVIRASE administered with ritonavir should be taken  
355 within 2 hours after a full meal (see CLINICAL PHARMACOLOGY:  
356 Pharmacokinetics). When INVIRASE is taken without food, concentrations of saquinavir  
357 in the blood are substantially reduced and may result in no antiviral activity. Patients  
358 should be advised of the importance of taking their medication every day, as prescribed,  
359 to achieve maximum benefit. Patients should not alter the dose or discontinue therapy  
360 without consulting their physician. If a dose is missed, patients should take the next dose  
361 as soon as possible. However, the patient should not double the next dose.

362 **Laboratory Tests**

363 Clinical chemistry tests, viral load, and CD<sub>4</sub> count should be performed prior to initiating  
364 INVIRASE therapy and at appropriate intervals thereafter. Elevated nonfasting  
365 triglyceride levels have been observed in patients in saquinavir trials. Triglyceride levels  
366 should be periodically monitored during therapy. For comprehensive information  
367 concerning laboratory test alterations associated with use of other antiretroviral therapies,  
368 physicians should refer to the complete product information for these drugs.

369 **Drug Interactions**

370 **Several drug interaction studies have been completed with both INVIRASE and**  
371 **FORTOVASE. Observations from drug interaction studies with FORTOVASE may**

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372 **not be predictive for INVIRASE.** Because ritonavir is coadministered, prescribers  
373 should also refer to the prescribing information for ritonavir regarding drug interactions  
374 associated with this agent.

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

380 Drugs that are contraindicated specifically due to the expected magnitude of interaction  
381 and potential for serious adverse events are listed in Table 4 under  
382 CONTRAINDICATIONS. Additional drugs that are not recommended for  
383 coadministration with INVIRASE and ritonavir are included in Table 5. These  
384 recommendations are based on either drug interaction studies or predicted interactions  
385 due to the expected magnitude of interaction and potential for serious events or loss of  
386 efficacy.

387 Drug interactions that have been established based on drug interaction studies are listed  
388 with the pharmacokinetic results in Table 2, which summarizes the effect of saquinavir,  
389 administered as FORTOVASE or INVIRASE, on the geometric mean AUC and  $C_{max}$  of  
390 coadministered drugs and Table 3, which summarizes the effect of coadministered drugs  
391 on the geometric mean AUC and  $C_{max}$  of saquinavir. Clinical dose recommendations can  
392 be found in Table 6. The magnitude of the interactions may be different when  
393 INVIRASE or FORTOVASE are given with ritonavir

394 When coadministering INVIRASE/ritonavir with any agent having a narrow therapeutic  
395 margin, such as anticoagulants, anticonvulsants, and antiarrhythmics, special attention is  
396 warranted. With some agents, the metabolism may be induced, resulting in decreased  
397 concentrations. Examples and clinical dose recommendations can be found in Table 6.

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**Table 5      Drugs That Should Not Be Coadministered With  
 INVIRASE/Ritonavir**

<b>Drug Class: Drug Name</b>	<b>Clinical Comment</b>
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	CONTRAINDICATED since the coadministration of this product with saquinavir in an antiretroviral regimen reduces the plasma concentrations of saquinavir.
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.
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 INVIRASE 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.

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<b>Drug Class: Drug Name</b>	<b>Clinical Comment</b>
Sedatives/Hypnotics: triazolam, midazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

400 \* No longer marketed in the US.

401 **Table 6**      **Established and Other Potentially Significant Drug**  
402 **Interactions: Alteration in Dose or Regimen May Be**  
403 **Recommended Based on Drug Interaction Studies or**  
404 **Predicted Interaction (Information in the table applies to**  
405 **INVIRASE/ritonavir)**

<b>Concomitant Drug Class:</b>  <b>Drug Name</b>	<b>Effect on Concentration of Saquinavir or Concomitant Drug</b>	<b>Clinical Comment</b>
<b>HIV-Antiviral Agents</b>		
<b>Non-nucleoside reverse transcriptase inhibitor:</b> Delavirdine	↑ Saquinavir  Effect on delavirdine is not well established  <b>INVIRASE/ritonavir</b> Interaction has not been evaluated	Appropriate doses of the combination with respect to safety and efficacy have not been established.
<b>Non-nucleoside reverse transcriptase inhibitor:</b> Efavirenz*, nevirapine	↓ Saquinavir ↓ Efavirenz  <b>INVIRASE/ritonavir</b> Interaction has not been evaluated	INVIRASE should not be given as the sole protease inhibitor to patients.  Appropriate doses of the combination of efavirenz or nevirapine and INVIRASE/ritonavir with respect to safety and efficacy have not been established.
<b>HIV protease inhibitor:</b> Indinavir*	↑ Saquinavir  Effect on indinavir is not well established	Appropriate doses of the combination of indinavir and INVIRASE/ritonavir with respect to safety and

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<b>Concomitant Drug Class: Drug Name</b>	<b>Effect on Concentration of Saquinavir or Concomitant Drug</b>	<b>Clinical Comment</b>
	<b>INVIRASE/ritonavir</b> Interaction has not been evaluated	efficacy have not been established.
<b>HIV protease inhibitor: Nelfinavir*</b>	↑ Saquinavir ↑ Nelfinavir  <b>INVIRASE/ritonavir</b> Interaction has not been evaluated	Saquinavir 1200 mg bid with nelfinavir 1250 mg bid results in adequate plasma drug concentrations for both protease inhibitors.
<b>HIV protease inhibitor: Ritonavir*</b>	↑ Saquinavir ↔ Ritonavir	The recommended dose regimen when ritonavir is given to increase saquinavir concentrations is 1000 mg saquinavir plus ritonavir 100 mg twice daily.
<b>HIV protease inhibitor: Lopinavir/ritonavir (coformulated capsule)*</b>	↑ Saquinavir  Effect on lopinavir is not well established	FORTOVASE (SQV) 800 mg bid + KALETRA produces ↑ AUC, ↑ C <sub>max</sub> , and ↑ C <sub>min</sub> relative to FORTOVASE 1200 mg tid (see CLINICAL PHARMACOLOGY: Table 3)
<b>HIV fusion inhibitor: Enfuvirtide*</b>	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.
<b>Other Agents</b>		
<b>Antiarrhythmics: Lidocaine (systemic)</b>	↑ Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics given with

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<b>Concomitant Drug Class:</b>  <b>Drug Name</b>	<b>Effect on Concentration of Saquinavir or Concomitant Drug</b>	<b>Clinical Comment</b>
<b>Anticoagulant:</b> Warfarin		INVIRASE/ritonavir Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
<b>Anticonvulsants:</b> Carbamazepine, phenobarbital, phenytoin	↓ Saquinavir Effect on carbamazepine, phenobarbital, and phenytoin is not well established  <b>INVIRASE/ritonavir</b> Interaction has not been evaluated	Use with caution, saquinavir may be less effective due to decreased saquinavir plasma concentrations in patients taking these agents concomitantly.
<b>Anti-infective:</b> Clarithromycin*	↑ Saquinavir ↑ Clarithromycin  <b>INVIRASE/ritonavir</b> Interaction has not been evaluated	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). For patients with renal impairment, the following dosage adjustments should be considered: <ul style="list-style-type: none"> <li>• For patients with CL<sub>CR</sub> 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%.</li> <li>• For patients with CL<sub>CR</sub> &lt;30 mL/min the dose of clarithromycin should be decreased by 75%.</li> </ul> No dose adjustment for

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<b>Concomitant Drug Class:</b>  <b>Drug Name</b>	<b>Effect on Concentration of Saquinavir or Concomitant Drug</b>	<b>Clinical Comment</b>
		patients with normal renal function is necessary.
<b>Antifungal:</b> Ketoconazole*, itraconazole	↑ Saquinavir ↔ Ketoconazole  <b>INVIRASE/ritonavir</b> Interaction has not been evaluated	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.
<b>Antimycobacterial</b> Rifabutin*	↓ Saquinavir ↑ Rifabutin  <b>INVIRASE/ritonavir</b> Interaction has not been evaluated	INVIRASE should not be given as the sole protease inhibitor to patients.  Appropriate doses of the combination of rifabutin and INVIRASE/ritonavir with respect to safety and efficacy have not been established.
<b>Antimycobacterial</b> Rifampin*	↓ Saquinavir  <b>INVIRASE/ritonavir</b> Interaction has not been evaluated	INVIRASE should not be given as the sole protease inhibitor to patients.  Appropriate doses of the combination of rifampin and INVIRASE/ritonavir with respect to safety and efficacy have not been established.
<b>Benzodiazepines:</b> Alprazolam, clorazepate, diazepam, flurazepam	↑ Benzodiazepines	Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.
<b>Calcium channel blockers:</b> Diltiazem, felodipine,	↑ Calcium channel blockers	Caution is warranted and clinical monitoring of

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<b>Concomitant Drug Class:</b>  <b>Drug Name</b>	<b>Effect on Concentration of Saquinavir or Concomitant Drug</b>	<b>Clinical Comment</b>
nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine		patients is recommended.
<b>Corticosteroid:</b> Dexamethasone	↓ Saquinavir  <b>INVIRASE/ritonavir</b> Interaction has not been evaluated	Use with caution, saquinavir may be less effective due to decreased saquinavir plasma concentrations in patients taking these agents concomitantly.
<b>Histamine H<sub>2</sub>-receptor antagonist:</b> Ranitidine	↑ Saquinavir  <b>INVIRASE/ritonavir</b> 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 INVIRASE/ritonavir with respect to safety and efficacy have not been established.
<b>HMG-CoA reductase inhibitors:</b> Simvastatin, lovastatin, atorvastatin	↑ HMG-CoA reductase inhibitors	The combination of INVIRASE/ritonavir 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.
<b>Immunosuppressants:</b> Cyclosporine, tacrolimus, rapamycin	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with INVIRASE/ritonavir.

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<b>Concomitant Drug Class: Drug Name</b>	<b>Effect on Concentration of Saquinavir or Concomitant Drug</b>	<b>Clinical Comment</b>
<b>Narcotic analgesic:</b> Methadone	↓ Methadone	Dosage of methadone may need to be increased when coadministered with INVIRASE/ritonavir
<b>Oral contraceptives:</b> Ethinyl estradiol	↓ Ethinyl estradiol	Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and INVIRASE/ritonavir are coadministered.
<b>PDE5 inhibitors (phosphodiesterase type 5 inhibitors):</b> Sildenafil*, vardenafil, tadalafil	↑ Sildenafil ↔ Saquinavir  ↑ Vardenafil  ↑ Tadalafil	Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring of adverse events when administered concomitantly with INVIRASE/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 INVIRASE/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 INVIRASE/ritonavir.
<b>Tricyclic antidepressants:</b> Amitriptyline, imipramine	↑ Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with INVIRASE/ritonavir.

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

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407 *Drugs That Are Mainly Metabolized by CYP3A4:*

408 Although specific studies have not been performed, coadministration with drugs that are  
409 mainly metabolized by CYP3A4 (eg, calcium channel blockers, dapsone, disopyramide,  
410 quinine, amiodarone, quinidine, warfarin, tacrolimus, cyclosporine, ergot derivatives,  
411 pimozide, carbamazepine, fentanyl, alfentanyl, alprazolam, and triazolam) may have  
412 elevated plasma concentrations when coadministered with saquinavir; therefore, these  
413 combinations should be used with caution. Since INVIRASE is coadministered with  
414 ritonavir, the ritonavir label should be reviewed for additional drugs that should not be  
415 coadministered.

416 *Inducers of CYP3A4:*

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

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

421 **Carcinogenesis:**

422 Carcinogenicity studies found no indication of carcinogenic activity in rats and mice  
423 administered saquinavir for approximately 2 years. The plasma exposures (AUC values)  
424 in the respective species were up to 6-fold (using rat) and 12-fold (using mouse) higher  
425 than those obtained in humans at the recommended clinical dose.

426 **Mutagenesis:**

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

433 **Impairment of Fertility:**

434 Fertility and reproductive performance were not affected in rats at plasma exposures  
435 (AUC values) up to 5 times those achieved in humans at the recommended dose.

436 **Pregnancy**

437 **Teratogenic Effects: Category B.**

438 Reproduction studies conducted with saquinavir in rats have shown no embryotoxicity or  
439 teratogenicity at plasma exposures (AUC values) up to 5 times those achieved in humans  
440 at the recommended dose or in rabbits at plasma exposures 4 times those achieved at the  
441 recommended clinical dose. Studies in rats indicated that exposure to saquinavir from late  
442 pregnancy through lactation at plasma concentrations (AUC values) up to 5 times those  
443 achieved in humans at the recommended dose had no effect on the survival, growth, and  
444 development of offspring to weaning. Clinical experience in pregnant women is limited.

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445 Saquinavir should be used during pregnancy only if the potential benefit justifies the  
446 potential risk to the fetus.

447 **Antiretroviral Pregnancy Registry**

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

451 **Nursing Mothers**

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

458 **Pediatric Use**

459 Safety and effectiveness of INVIRASE in HIV-infected pediatric patients younger than  
460 16 years of age have not been established.

461 **Geriatric Use**

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

467 **ADVERSE REACTIONS (see PRECAUTIONS)**

468 INVIRASE may be used only if it is combined with ritonavir, which significantly inhibits  
469 saquinavir's metabolism to provide plasma saquinavir levels at least equal to those  
470 achieved with FORTOVASE. See the Concomitant Therapy with Ritonavir Adverse  
471 Reactions' section for safety information with the recommended dosage regimen.

472 The safety of INVIRASE was studied in patients who received the drug either alone or in  
473 combination with zidovudine and/or HIVID (zalcitabine, ddC). The majority of adverse  
474 events were of mild intensity. The most frequently reported adverse events among  
475 patients receiving INVIRASE in clinical trials (excluding those toxicities known to be  
476 associated with zidovudine and HIVID when used in combinations) were diarrhea,  
477 abdominal discomfort, and nausea.

478 The following grade 2 to grade 4 adverse events, (considered at least possibly related to  
479 study drug or of unknown relationship) occurred in  $\geq 2\%$  of patients receiving  
480 INVIRASE 600 mg tid alone or in combination with zidovudine and/or HIVID:  
481 abdominal discomfort, abdominal pain, appetite disturbances, asthenia, buccal mucosa  
482 ulceration, diarrhea, dizziness, dyspepsia, extremity numbness, headache, mucosa

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483 damage, musculoskeletal pain, myalgia, nausea, paresthesia, peripheral neuropathy,  
 484 pruritus, and rash.

485 Rare occurrences of the following serious adverse experiences have been reported during  
 486 clinical trials of INVIRASE and were considered at least possibly related to use of study  
 487 drugs: confusion, ataxia, and weakness; acute myeloblastic leukemia; hemolytic anemia;  
 488 attempted suicide; Stevens-Johnson syndrome; seizures; severe cutaneous reaction  
 489 associated with increased liver function tests; isolated elevation of transaminases;  
 490 thrombophlebitis; headache; thrombocytopenia; exacerbation of chronic liver disease  
 491 with Grade 4 elevated liver function tests, jaundice, ascites, and right and left upper  
 492 quadrant abdominal pain; drug fever; bullous skin eruption and polyarthrits; pancreatitis  
 493 leading to death; nephrolithiasis; thrombocytopenia and intracranial hemorrhage leading  
 494 to death; peripheral vasoconstriction; portal hypertension; intestinal obstruction. These  
 495 events were reported from a database of >6000 patients. Over 100 patients on INVIRASE  
 496 therapy have been followed for >2 years.

497 **Concomitant Therapy with Ritonavir Adverse Reactions**

498 In combination with ritonavir the recommended dose of INVIRASE is 1000 mg two  
 499 times daily with ritonavir 100 mg two times daily in combination with other antiretroviral  
 500 agents. Table 7 lists grades 2, 3 and 4 related adverse events that occurred in ≥2% of  
 501 patients receiving FORTOVASE with ritonavir (1000/100 mg bid).

502 **Table 7**                    **Grade 2, 3 and 4 Related Adverse Events (All Causality)**  
 503                                    **Reported in ≥2% of Adult Patients in the MaxCmin 1 Study of**  
 504                                    **FORTOVASE in Combination with Ritonavir 1000/100 mg bid**

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

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Pneumonia	8 (5.4)
Bronchitis	4 (2.7)
Influenza	4 (2.7)
Sinusitis	4 (2.7)
<b>Dermatological Disorders</b>	
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 Additionally, adverse events that occurred in clinical trials with FORTOVASE, which are  
507 not listed above, are listed for completeness. However, due to the higher bioavailability  
508 of FORTOVASE, these adverse events might not be predictive of the safety profile of  
509 INVIRASE.

510 **Experience from Clinical Trials with FORTOVASE**

511 The safety of FORTOVASE was studied in more than 500 patients who received the drug  
512 either alone or in combination with other antiretroviral agents. The most frequently  
513 reported adverse events among patients receiving FORTOVASE in combination with  
514 other antiretroviral agents were diarrhea, nausea, abdominal discomfort, and dyspepsia.  
515 Clinical adverse events of at least moderate intensity, which occurred in  $\geq 2\%$  of patients  
516 in 2 studies with FORTOVASE, which are not listed above, are listed below by body  
517 system.

518 Gastrointestinal Disorders: constipation, flatulence, vomiting

519 Body as a Whole: appetite decreased, chest pain, fatigue

520 Psychological: depression, insomnia, anxiety, libido disorder

521 Special Senses: taste alteration

522 Skin and Appendages: verruca, eczema

523 **Laboratory Abnormalities with INVIRASE**

524 Grade 3 and 4 lab abnormalities have been observed with FORTOVASE in combination  
525 with ritonavir. At 48 weeks, lab abnormalities included increased ALT, anemia,  
526 increased AST, increased GGT, hyperglycemia, hypertriglyceridemia, increased TSH,  
527 neutropenia, raised amylase, raised LDH, and thrombocytopenia.

528 **INVIRASE may be used only if it is combined with ritonavir, which significantly**  
529 **inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal**  
530 **to those achieved with FORTOVASE.**

531 In studies NV14255/ACTG 229 and NV14256, the following grade 3 or grade 4  
532 abnormalities in laboratory tests were reported among patients receiving INVIRASE 600  
533 mg tid alone or in combination with ZDV and/or HIVID:

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534 **Biochemistry**

- 535 • Incidence between <1% and 4%-hypoglycemia, hyper- or hypocalcemia,  
536 hypophosphatemia, hyper- or hypokalemia, hyper- or hyponatremia, raised serum  
537 amylase grade 3 or 4 elevations in transaminases (SGOT [AST] SGPT [ALT]),  
538 hyperbilirubinemia
- 539 • Incidence of ≤5%: hyperglycemia. Incidence of between 7% and 12%: elevated  
540 creatine phosphokinase.

541 **Hematology**

- 542 • Incidence of ≤2%: thrombocytopenia and anemia: incidence between 1% and 8% -  
543 leucopenia.

544 Additional marked lab abnormalities have been observed with FORTOVASE. These  
545 include: alkaline phosphatase (high), gamma GT (high), and triglycerides (high).

546 **Monotherapy and Combination Studies**

547 Other clinical adverse experiences of any intensity, at least remotely related to  
548 INVIRASE, including those in <2% of patients on arms containing INVIRASE in studies  
549 NV14255/ACTG229 and NV14256, and those in smaller clinical trials, are listed below  
550 by body system.

551 **Body as a Whole:** allergic reaction, anorexia, chest pain, edema, fatigue, fever,  
552 intoxication, parasites external, retrosternal pain, shivering, wasting syndrome, weakness  
553 generalized, weight decrease, redistribution/accumulation of body fat (see  
554 PRECAUTIONS: Fat Redistribution)

555 **Cardiovascular:** cyanosis, heart murmur, heart valve disorder, hypertension,  
556 hypotension, syncope, vein distended

557 **Endocrine/Metabolic:** dehydration, diabetes mellitus, dry eye syndrome, hyperglycemia,  
558 weight increase, xerophthalmia

559 **Gastrointestinal:** cheilitis, colic abdominal, constipation, dyspepsia, dysphagia,  
560 esophagitis, eructation, feces bloodstained, feces discolored, flatulence, gastralgia,  
561 gastritis, gastrointestinal inflammation, gingivitis, glossitis, hemorrhage rectum,  
562 hemorrhoids, hepatitis, hepatomegaly, hepatosplenomegaly, infectious diarrhea, jaundice,  
563 liver enzyme disorder, melena, pain pelvic, painful defecation, pancreatitis, parotid  
564 disorder, salivary glands disorder, stomach upset, stomatitis, toothache, tooth disorder,  
565 vomiting

566 **Hematologic:** anemia, bleeding dermal, microhemorrhages, neutropenia, pancytopenia,  
567 splenomegaly, thrombocytopenia

568 **Musculoskeletal:** arthralgia, arthritis, back pain, cramps leg, cramps muscle, creatine  
569 phosphokinase increased, musculoskeletal disorders, stiffness, tissue changes, trauma

570 **Neurological:** ataxia, bowel movements frequent, confusion, convulsions, dysarthria,  
571 dysesthesia, heart rate disorder, hyperesthesia, hyperreflexia, hyporeflexia, light-headed  
572 feeling, mouth dry, myelopolyradiculoneuritis, numbness face, pain facial, paresis,

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573 poliomyelitis, prickly sensation, progressive multifocal leukoencephalopathy, spasms,  
574 tremor, unconsciousness

575 **Psychological:** agitation, amnesia, anxiety, anxiety attack, depression, dreaming  
576 excessive, euphoria, hallucination, insomnia, intellectual ability reduced, irritability,  
577 lethargy, libido disorder, overdose effect, psychic disorder, psychosis, somnolence,  
578 speech disorder, suicide attempt

579 **Reproductive System:** impotence, prostate enlarged, vaginal discharge

580 **Resistance Mechanism:** abscess, angina tonsillaris, candidiasis, cellulitis, herpes  
581 simplex, herpes zoster, infection bacterial, infection mycotic, infection staphylococcal,  
582 influenza, lymphadenopathy, moniliasis, tumor

583 **Respiratory:** bronchitis, cough, dyspnea, epistaxis, hemoptysis, laryngitis, pharyngitis,  
584 pneumonia, pulmonary disease, respiratory disorder, rhinitis, sinusitis, upper respiratory  
585 tract infection

586 **Skin and Appendages:** acne, alopecia, chalazion, dermatitis, dermatitis seborrheic,  
587 eczema, erythema, folliculitis, furunculosis, hair changes, hot flushes, nail disorder, night  
588 sweats, papillomatosis, photosensitivity reaction, pigment changes skin, rash  
589 maculopapular, skin disorder, skin nodule, skin ulceration, sweating increased, urticaria,  
590 verruca, xeroderma

591 **Special Senses:** blepharitis, earache, ear pressure, eye irritation, hearing decreased,  
592 otitis, taste alteration, tinnitus, visual disturbance

593 **Urinary System:** micturition disorder, renal calculus, urinary tract bleeding, urinary tract  
594 infection

595 **Postmarketing Experience with INVIRASE and FORTOVASE**

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

599 **OVERDOSAGE**

600 No acute toxicities or sequelae were noted in 1 patient who ingested 8 grams of  
601 INVIRASE as a single dose. The patient was treated with induction of emesis within 2 to  
602 4 hours after ingestion. A second patient ingested 2.4 grams of INVIRASE in  
603 combination with 600 mg of ritonavir and experienced pain in the throat that lasted for 6  
604 hours and then resolved. In an exploratory Phase II study of oral dosing with INVIRASE  
605 at 7200 mg/day (1200 mg q4h), there were no serious toxicities reported through the first  
606 25 weeks of treatment.

607 **DOSAGE AND ADMINISTRATION**

608 **INVIRASE (saquinavir mesylate) capsules and FORTOVASE (saquinavir) soft**  
609 **gelatin capsules are not bioequivalent and cannot be used interchangeably.**  
610 **INVIRASE may be used only if it is combined with ritonavir, because it significantly**

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611 **inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal**  
612 **to those achieved with FORTOVASE at the recommended dose of 1200 mg tid.**  
613 **When using saquinavir as the sole protease inhibitor in an antiretroviral regimen,**  
614 **FORTOVASE is the recommended formulation (see CLINICAL**  
615 **PHARMACOLOGY: Drug Interactions).**

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

- 617 • INVIRASE 1000-mg bid (5 x 200-mg capsules) in combination with ritonavir 100-  
618 mg bid.
- 619 • Ritonavir should be taken at the same time as INVIRASE.
- 620 • INVIRASE and ritonavir should be taken within 2 hours after a meal

621 **Monitoring of Patients**

622 Clinical chemistry tests, viral load, and CD<sub>4</sub> count should be performed prior to initiating  
623 INVIRASE therapy and at appropriate intervals thereafter. For comprehensive patient  
624 monitoring recommendations for other nucleoside analogues, physicians should refer to  
625 the complete product information for these drugs.

626 **Dose Adjustment for Combination Therapy with INVIRASE**

627 For serious toxicities that may be associated with INVIRASE, the drug should be  
628 interrupted. INVIRASE at doses less than 1000 mg with 100 mg ritonavir bid are not  
629 recommended since lower doses have not shown antiviral activity. For recipients of  
630 combination therapy with INVIRASE and ritonavir, dose adjustments may be necessary.  
631 These adjustments should be based on the known toxicity profile of the individual agent  
632 and the pharmacokinetic interaction between saquinavir and the coadministered drug (see  
633 PRECAUTIONS: Drug Interactions). Physicians should refer to the complete product  
634 information for these drugs for comprehensive dose adjustment recommendations and  
635 drug-associated adverse reactions of nucleoside analogues.

636 **HOW SUPPLIED**

637 INVIRASE 200-mg capsules are light brown and green opaque capsules with ROCHE  
638 and 0245 imprinted on the capsule shell — bottles of 270 (NDC 0004-0245-15).

639 The capsules should be stored at 59° to 86°F (15° to 30°C) in tightly closed bottles.

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641 Inc.

642 KALETRA is a registered trademark of Abbott Laboratories.

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