



INVIRASE

(saquinavir mesylate)

CAPSULES and TABLETS

R_x only

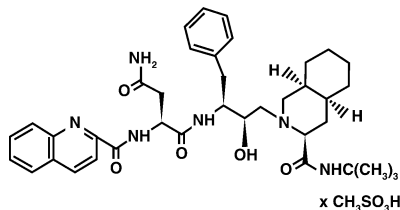
Product identification in this document includes: INVIRASE in reference to saquinavir mesylate; saquinavir soft gel capsules in reference to saquinavir 200 mg soft gel capsule formulation¹, and saquinavir in reference to the active base.

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.

INVIRASE is also available as a light orange to greyish- or brownish-orange, oval cylindrical, biconvex film-coated tablet for oral administration in a 500-mg strength (as saquinavir free base). Each tablet also contains the inactive ingredients lactose, microcrystalline cellulose, povidone K30, croscarmellose sodium, and magnesium stearate. Each film coat contains hypromellose, titanium dioxide, talc, iron oxide yellow, iron oxide red, and triacetin.

The chemical name for saquinavir mesylate is N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide methanesulfonate with a molecular formula C₃₈H₅₀N₆O₅·CH₄O₃S and a molecular weight of 766.96. The molecular weight of the free base is 670.86. Saquinavir mesylate has the following structural formula:



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

¹ The term "saquinavir soft gel capsules" used in this label refers to the drug product formerly marketed as "Fortovase" (saquinavir 200 mg soft gel capsule formulation). This formulation has been withdrawn from the market.

31 **MICROBIOLOGY**

32 **Mechanism of Action**

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

39 **Antiviral Activity**

40 In vitro antiviral activity of saquinavir was assessed in lymphoblastoid and monocytic
41 cell lines and in peripheral blood lymphocytes. Saquinavir inhibited HIV activity in both
42 acutely and chronically infected cells. IC₅₀ and IC₉₀ values (50% and 90% inhibitory
43 concentrations) were in the range of 1 to 30 nM and 5 to 80 nM, respectively. In the
44 presence of 40% human serum, the mean IC₅₀ of saquinavir against laboratory strain HIV-
45 1 RF in MT4 cells was 37.7± 5 nM representing a 4-fold increase in the IC₅₀ value. In cell
46 culture, saquinavir demonstrated additive to synergistic effects against HIV-1 in
47 combination with reverse transcriptase inhibitors (didanosine, lamivudine, nevirapine,
48 stavudine, zalcitabine and zidovudine) without enhanced cytotoxicity. Saquinavir in
49 combination with the protease inhibitors amprenavir, atazanavir, or lopinavir resulted in
50 synergistic antiviral activity. Saquinavir displayed antiviral activity in vitro against HIV-
51 1 clades A-H (IC₅₀ ranged from 0.9 to 2.5 nM). The IC₅₀ and IC₉₀ values of saquinavir
52 against HIV-2 isolates in vitro ranged from 0.25 nM to 14.6 nM and 4.65 nM to 28.6 nM,
53 respectively.

54 **Drug Resistance**

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

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

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

71 currently available to address the development of resistance in patients receiving
72 saquinavir/ritonavir.

73 **Cross-resistance**

74 Among protease inhibitors, variable cross-resistance has been observed. In one clinical
75 study, 22 HIV-1 isolates with reduced susceptibility (>4-fold increase in the IC₅₀ value)
76 to saquinavir following therapy with INVIRASE were evaluated for cross-resistance to
77 amprenavir, indinavir, nelfinavir and ritonavir. Six of the 22 isolates (27%) remained
78 susceptible to all 4 protease inhibitors, 12 of the 22 isolates (55%) retained susceptibility
79 to at least one of the PIs and 4 out of the 22 isolates (18%) displayed broad cross-
80 resistance to all PIs. Sixteen (73%) and 11 (50%) of the 22 isolates remained susceptible
81 (<4-fold) to amprenavir and indinavir, respectively. Four of 16 (25%) and nine of 21
82 (43%) with available data remained susceptible to nelfinavir and ritonavir, respectively.

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

87 **CLINICAL PHARMACOLOGY**

88 **Pharmacokinetics**

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

94 HIV-infected patients administered INVIRASE (600-mg tid) had AUC and maximum
95 plasma concentration (C_{max}) values approximately 2-2.5 times those observed in healthy
96 volunteers receiving the same treatment regimen.

97 Similar bioavailability was demonstrated when INVIRASE 500 mg FCT (2 x 500 mg)
98 and INVIRASE 200 mg capsule (5 x 200 mg) were administered with low-dose ritonavir
99 (100 mg) under fed conditions. The ratio of mean exposures (90% confidence intervals)
100 of tablets vs capsules were 1.10 (1.04-1.16) for AUC_{0-∞} and 1.19 (1.14-1.25) for C_{max}.

101 **Absorption and Bioavailability in Adults**

102 Absolute bioavailability of saquinavir administered as INVIRASE averaged 4% (CV
103 73%, range: 1% to 9%) in 8 healthy volunteers who received a single 600-mg dose (3 x
104 200 mg) of saquinavir mesylate following a high-fat breakfast (48 g protein, 60 g
105 carbohydrate, 57 g fat; 1006 kcal). The low bioavailability is thought to be due to a
106 combination of incomplete absorption and extensive first-pass metabolism.

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

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

Dosing Regimen	N	AUC _τ (ng·h/mL)	AUC _{24h} (ng·h/mL)	C _{min} (ng/mL)
INVIRASE 600 mg tid (arithmetic mean, %CV)	10	866 (62)	2598	79
Saquinavir soft gel capsules 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)
Saquinavir soft gel capsules 1000 mg bid + ritonavir 100 mg bid (geometric mean and 95% CI)	24	19085 (13943-26124)	38170	433 (301-622)

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

114 Food Effect

115 No food effect data are available for INVIRASE in combination with ritonavir.

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

123 Saquinavir exposure was similar when saquinavir soft gel capsules plus ritonavir (1000-
 124 mg/100-mg bid) were administered following a high-fat (45 g fat) or moderate-fat (20 g
 125 fat) breakfast.

126 Distribution in Adults

127 The mean steady-state volume of distribution following intravenous administration of a
 128 12-mg dose of saquinavir (n=8) was 700 L (CV 39%), suggesting saquinavir partitions
 129 into tissues. Saquinavir was approximately 98% bound to plasma proteins over a
 130 concentration range of 15 to 700 ng/mL. In 2 patients receiving saquinavir mesylate 600
 131 mg tid, cerebrospinal fluid concentrations were negligible when compared to
 132 concentrations from matching plasma samples.

133 Metabolism and Elimination in Adults

134 In vitro studies using human liver microsomes have shown that the metabolism of
 135 saquinavir is cytochrome P450 mediated with the specific isoenzyme, CYP3A4,
 136 responsible for more than 90% of the hepatic metabolism. Based on in vitro studies,
 137 saquinavir is rapidly metabolized to a range of mono- and di-hydroxylated inactive
 138 compounds. In a mass balance study using 600 mg ¹⁴C-saquinavir mesylate (n=8), 88%
 139 and 1% of the orally administered radioactivity was recovered in feces and urine,

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

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

150 Special Populations

151 *Hepatic or Renal Impairment*

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

155 *Gender, Race, and Age*

156 A gender difference was observed, with females showing higher saquinavir exposure than
157 males (mean AUC increase of 56%, mean C_{max} increase of 26%), in the relative
158 bioavailability study comparing INVIRASE 500 mg film-coated tablets to the
159 INVIRASE 200 mg capsules in combination with ritonavir. There was no evidence that
160 age and body weight explained the gender difference in this study. A clinically significant
161 difference in safety and efficacy between men and women has not been reported with the
162 approved dosage regimen (saquinavir 1000-mg/ritonavir 100-mg bid).

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

164 *Pediatric Patients*

165 The pharmacokinetics of saquinavir when administered as INVIRASE have not been
166 sufficiently investigated in pediatric patients.

167 *Geriatric Patients*

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

170 Drug Interactions (see **PRECAUTIONS: Drug Interactions**)

171 Several drug interaction studies have been completed with both INVIRASE and the
172 saquinavir soft gel capsule formulation. Because ritonavir is coadministered, prescribers
173 should refer to the prescribing information for ritonavir regarding drug interactions
174 associated with this drug.

175 **Table 2** summarizes the effect of saquinavir soft gel capsules on the geometric mean
176 AUC and C_{max} of coadministered drugs. **Table 3** summarizes the effect of coadministered
177 drugs on the geometric mean AUC and C_{max} of saquinavir.

178
179

Table 2 Effect of saquinavir soft gel capsules on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug	Saquinavir soft gel capsules or saquinavir soft gel capsules/ 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 7 days	12V	↑45% (17-81%) ↓24% (5-40%)	↑39% (10-76%) ↓34% (14-50%)
Midazolam 7.5-mg oral single dose	1000/100 mg bid x 15 days	16V	↑1144% (975-1339%) [^]	↑327% (264-402%) [^]
Ketoconazole 400 mg once daily	1200 mg tid	12V	↔	↔
Enfuvirtide 90 mg SC q12h (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%
Sildenafil 100-mg single dose	1200 mg tid x 8 days	27V	↑210% (150-300%)	↑140% (80-230%)
Efavirenz 600 mg	1200 mg tid	13V	↓12%	↓13%
Digoxin 0.5 mg single dose	1000/100 mg bid x 16 days	16V	↑49% (32-69%) [^]	↑27% (5-54%) [^]
R-Methadone 60-120 mg once daily	1000/100 mg bid x 14 days	12M	↓19% (9-29%) [^]	NA

180 ↑ Denotes an average increase in exposure by the percentage indicated.
 181 ↓ Denotes an average decrease in exposure by the percentage indicated.
 182 ↔ Denotes no statistically significant change in exposure was observed.
 183 [^] 90% Confidence Interval
 184 P Patient
 185 V Healthy Volunteers
 186 M Methadone-dependent, HIV negative patients
 187 NA Not Available

188
189

Table 3 Effect of Coadministered Drugs on saquinavir soft gel capsules or INVIRASE Pharmacokinetics

Coadministered Drug	Saquinavir soft gel capsules Dose	N	% Change for Saquinavir	
			AUC (95% CI)	C _{max} (95% CI)
Clarithromycin 500 mg bid x 7 days	1200 mg tid x 7 days	12V	↑177% (108-269%)	↑187% (105-300%)
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%
Ritonavir 400 mg bid x 14 days	400 mg bid x 14 days†	8V	↑121% (7-359%)	↑64%§
Lopinavir/ritonavir Evidence from several clinical trials indicates that saquinavir concentrations achieved with saquinavir 1000 mg + lopinavir/ritonavir 400/100 mg BID are similar to those achieved following saquinavir/ritonavir 1000/100 mg BID.				

190

Coadministered Drug	INVIRASE or INVIRASE/Ritonavir Dose	N	% Change for Saquinavir	
			AUC (95% CI)	C _{max} (95% CI)
Atazanavir 300 mg once daily	1600 mg qd + 100 mg ritonavir qd	18P	↑60% (16-122%)	↑42% (10-84%)
Fosamprenavir 700 mg bid	1000 mg bid + 100 mg ritonavir bid	18P	↓15% (-33% to 9%)	↔
Rifabutin 150 mg every 3 days or 300 mg every 7 days	400 mg bid + 400 mg ritonavir bid	24P	↑19%	↑39%
Ritonavir 100 mg bid	1000 mg bid †	24P	↑1124%	↑1325%
Tenofovir 300 mg once daily	1000 mg bid + 100 mg ritonavir bid	18P	↔	↔
Tipranavir 500 mg + ritonavir 200 mg bid	600 mg bid + 100 mg ritonavir bid	20P	↓76% (68-81%) [^]	↓70% (60-77%) [^]
Omeprazole 40 mg QD x 5 days	1000 mg/ritonavir 100 mg BID x 15 days	19V	↑82% (37-234%) [^]	↑75% (31-234%) [^]

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

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

193 ↔ Mean change <10%

194 † Compared to standard saquinavir soft gel capsules 1200 mg tid regimen (n=33).

195 ‡ Compared to standard INVIRASE 600 mg tid regimen (n=114).

196 § Did not reach statistical significance.

197 [^] 90% Confidence Interval

198 P Patient

199 V Healthy Volunteers

200

201 For information regarding clinical recommendations, see **PRECAUTIONS: Drug**
202 **Interactions, Table 6.**

203 INDICATIONS AND USAGE

204 INVIRASE in combination with ritonavir and other antiretroviral agents is indicated for
205 the treatment of HIV infection. The twice daily administration of INVIRASE in
206 combination with ritonavir is supported by safety data from the MaxCmin 1 study (see
207 **Table 7**) and pharmacokinetic data (see **Table 1**). The efficacy of INVIRASE with
208 ritonavir has not been compared against the efficacy of antiretroviral regimens currently
209 considered standard of care.

210 Description of Clinical Studies

211 In a randomized, double-blind clinical study (NV14256) in ZDV-experienced, HIV-
212 infected patients, INVIRASE in combination with HIVID was shown to be superior to
213 either INVIRASE or HIVID monotherapy in decreasing the cumulative incidence of
214 clinical disease progression to AIDS-defining events or death. Furthermore, in a
215 randomized study (ACTG229/NV14255), patients with advanced HIV infection with
216 history of prolonged ZDV treatment and who were given INVIRASE 600 mg tid + ZDV

217 + HIVID experienced greater increases in CD₄ cell counts as compared to those who
218 received INVIRASE + ZDV or HIVID + ZDV. It should be noted that HIV treatment
219 regimens that were used in these initial clinical studies of INVIRASE are no longer
220 considered standard of care.

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

227 **CONTRAINDICATIONS**

228 INVIRASE must be used in combination with ritonavir, which significantly inhibits
229 saquinavir's metabolism and provides increased plasma saquinavir levels.

230 INVIRASE is contraindicated in patients with clinically significant hypersensitivity to
231 saquinavir or to any of the components contained in the capsule or tablet.

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

237 INVIRASE/ritonavir should not be given together with rifampin, due to the risk of severe
238 hepatocellular toxicity if the three drugs are given together (see **PRECAUTIONS: Drug**
239 **Interactions**).

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

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

244 **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, methylergonovine
Antimycobacterial Agents	Rifampin

GI Motility Agent	Cisapride
Neuroleptics	Pimozide
Sedative/Hypnotics	Triazolam, midazolam

245 **WARNINGS**

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

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

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

256 **Interaction with Rifampin**

257 Rifampin should not be administered in patients taking ritonavir-boosted INVIRASE as
 258 part of an ART regimen due to the risk of severe hepatocellular toxicity observed in a
 259 drug-drug interaction study in healthy volunteers (see **PRECAUTIONS: Drug**
 260 **Interactions**).

261 **Interaction with St. John’s Wort (hypericum perforatum)**

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

268 **Interaction with Digoxin**

269 Caution should be exercised when INVIRASE and digoxin are coadministered; serum
 270 concentration of digoxin should be monitored and the dose of digoxin may need to be
 271 reduced (see **PRECAUTIONS: Drug Interactions**).

272 **Interaction with Garlic Capsules**

273 No data are available for the coadministration of INVIRASE/ritonavir and garlic capsules
 274 (see **Table 5 Drugs That Should Not Be Coadministered With**
 275 **INVIRASE/Ritonavir**).

276 **Interaction with Fluticasone**

277 A drug interaction study in healthy subjects has shown that ritonavir significantly
278 increases plasma fluticasone propionate exposures, resulting in significantly decreased
279 serum cortisol concentrations. Concomitant use of INVIRASE with ritonavir and
280 fluticasone propionate is expected to produce the same effects. Systemic corticosteroid
281 effects including Cushing's syndrome and adrenal suppression have been reported during
282 postmarketing use in patients receiving ritonavir and inhaled or intranasally administered
283 fluticasone propionate. Therefore, coadministration of fluticasone propionate and
284 INVIRASE/ritonavir is not recommended unless the potential benefit to the patient
285 outweighs the risk of systemic corticosteroid side effects (see **PRECAUTIONS: Drug**
286 **Interactions**).

287 **Diabetes Mellitus and Hyperglycemia**

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

297 **PRECAUTIONS**

298 **General**

299 **INVIRASE must be used in combination with ritonavir.**

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

306 **Hepatic Effects**

307 The use of INVIRASE (in combination with ritonavir) by patients with hepatic
308 impairment has not been studied. In the absence of such studies, caution should be
309 exercised, as increases in saquinavir levels and/or increases in liver enzymes may occur.
310 In patients with underlying hepatitis B or C, cirrhosis, chronic alcoholism and/or other
311 underlying liver abnormalities there have been reports of worsening liver disease.

312 **Renal Effects**

313 Renal clearance is only a minor elimination pathway; the principal route of metabolism
314 and excretion for saquinavir is by the liver. Therefore, no initial dose adjustment is
315 necessary for patients with renal impairment. However, patients with severe renal

316 impairment have not been studied, and caution should be exercised when prescribing
317 saquinavir in this population.

318 Hemophilia

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

324 Hyperlipidemia

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

331 Lactose Intolerance

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

334 Fat Redistribution

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

340 Immune Reconstitution Syndrome

341 Immune reconstitution syndrome has been reported in patients treated with combination
342 antiretroviral therapy, including INVIRASE. During the initial phase of combination
343 antiretroviral treatment, patients whose immune system responds may develop an
344 inflammatory response to indolent or residual opportunistic infections (such as
345 *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia
346 (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

347 **Resistance/Cross-resistance**

348 Varying degrees of cross-resistance among protease inhibitors have been observed.
349 Continued administration of INVIRASE therapy following loss of viral suppression may
350 increase the likelihood of cross-resistance to other protease inhibitors (see
351 **MICROBIOLOGY**).

352 **Information for Patients**

353 A statement to patients and health care providers is included on the product's bottle label:

354 **ALERT: Find out about medicines that should NOT be taken with INVIRASE.**

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

358 Patients should be informed that INVIRASE is not a cure for HIV infection and that they
359 may continue to acquire illnesses associated with advanced HIV infection, including
360 opportunistic infections. Patients should be advised that **INVIRASE must be used in**
361 **combination with ritonavir, which significantly inhibits saquinavir's metabolism to**
362 **provide increased plasma saquinavir levels.**

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

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

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

377 **Laboratory Tests**

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

384 **Drug Interactions**

385 **Several drug interaction studies have been completed with both INVIRASE and**
386 **saquinavir soft gel capsules. Observations from drug interaction studies with**
387 **saquinavir soft gel capsules may not be predictive for INVIRASE.** Because ritonavir
388 is coadministered, prescribers should also refer to the prescribing information for
389 ritonavir regarding drug interactions associated with this agent.

390 The metabolism of saquinavir is mediated by cytochrome P450, with the specific
391 isoenzyme CYP3A4 responsible for 90% of the hepatic metabolism. Additionally,

392 saquinavir is a substrate for P-Glycoprotein (Pgp). Therefore, drugs that affect CYP3A4
393 and/or Pgp, may modify the pharmacokinetics of saquinavir. Similarly, saquinavir might
394 also modify the pharmacokinetics of other drugs that are substrates for CYP3A4 or Pgp.

395 Drugs that are contraindicated specifically due to the expected magnitude of interaction
396 and potential for serious adverse events are listed in **Table 4** under
397 CONTRAINDICATIONS. Additional drugs that are not recommended for
398 coadministration with INVIRASE and ritonavir are included in **Table 5**. These
399 recommendations are based on either drug interaction studies or predicted interactions
400 due to the expected magnitude of interaction and potential for serious events or loss of
401 efficacy.

402 Drug interactions that have been established based on drug interaction studies are listed
403 with the pharmacokinetic results in **Table 2**, which summarizes the effect of saquinavir,
404 administered as saquinavir soft gel capsules or INVIRASE, on the geometric mean AUC
405 and C_{max} of coadministered drugs and **Table 3**, which summarizes the effect of
406 coadministered drugs on the geometric mean AUC and C_{max} of saquinavir. Clinical dose
407 recommendations can be found in **Table 6**. The magnitude of the interactions may be
408 different when INVIRASE is given with ritonavir.

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

413
414

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

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, methylergonovine	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. Rifampin should not be administered in patients taking ritonavir-boosted INVIRASE as part of an ART regimen due to the risk of severe hepatocellular toxicity.
Garlic Capsules	No data are available for the coadministration of INVIRASE/ritonavir and garlic capsules. WARNING coadministration of garlic capsules and saquinavir is not recommended due to the potential for garlic capsules to induce the metabolism of saquinavir which may result in sub-therapeutic saquinavir concentrations.
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.

Drug Class: Drug Name	Clinical Comment
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.

415 * No longer marketed in the US.

416 **Table 6** **Established and Other Potentially Significant Drug**
417 **Interactions: Alteration in Dose or Regimen May Be**
418 **Recommended Based on Drug Interaction Studies or**
419 **Predicted Interaction (Information in the table applies to**
420 **INVIRASE/ritonavir)**

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Delavirdine	↑ Saquinavir Effect on delavirdine is not well established INVIRASE/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: Efavirenz*, nevirapine	↓ Saquinavir ↓ Efavirenz INVIRASE/ritonavir Interaction has not been evaluated	Appropriate doses of the combination of efavirenz or nevirapine and INVIRASE/ritonavir with respect to safety and efficacy have not been established.
HIV protease inhibitor: Atazanavir*	INVIRASE/ritonavir ↑ Saquinavir ↑ Ritonavir ↔ Atazanavir	No data are available on the combination of INVIRASE 1000 mg/ritonavir 100 mg bid with atazanavir 300 mg qd. Appropriate dosing recommendations for this combination, with respect to efficacy and safety, have not been

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
		established.
HIV protease inhibitor: Indinavir*	↑ Saquinavir Effect on indinavir is not well established INVIRASE/ritonavir Interaction has not been evaluated	Appropriate doses of the combination of indinavir and INVIRASE/ritonavir with respect to safety and efficacy have not been established.
HIV protease inhibitor: Nelfinavir*	↑ Saquinavir ↑ Nelfinavir INVIRASE/ritonavir Interaction has not been evaluated	Saquinavir 1200 mg bid with nelfinavir 1250 mg bid results in adequate plasma drug concentrations for both protease inhibitors.
HIV protease inhibitor: Ritonavir*	↑ Saquinavir ↔ Ritonavir	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)*	↔ Saquinavir ↔ Lopinavir ↓ Ritonavir	Evidence from several clinical trials indicates that saquinavir concentrations achieved with the saquinavir and lopinavir/ritonavir combination are similar to those achieved following saquinavir/ritonavir 1000/100 mg. The recommended dose for this combination is saquinavir 1000 mg plus lopinavir/ritonavir 400/100 mg bid.
HIV protease inhibitor: Tipranavir/ritonavir	↓ Saquinavir	Combining saquinavir with tipranavir/ritonavir is not recommended.
HIV fusion inhibitor: Enfuvirtide*	Saquinavir soft gel capsules/ritonavir	No clinically significant interaction was noted from a study in 12 HIV

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
	↔ enfuvirtide	patients who received enfuvirtide concomitantly with saquinavir soft gel capsules/ritonavir 1000/100 mg bid. No dose adjustments are required.
Other Agents		
Antiarrhythmics: Lidocaine (systemic)	↑ Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics given with INVIRASE/ritonavir.
Anticoagulant: Warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin	↓ Saquinavir Effect on carbamazepine, phenobarbital, and phenytoin is not well established INVIRASE/ritonavir 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.
Anti-infective: Clarithromycin*	↑ Saquinavir ↑ Clarithromycin INVIRASE/ritonavir Interaction has not been evaluated	Appropriate doses of the combination of clarithromycin and INVIRASE/ritonavir with respect to safety and efficacy have not been established. Due to the known effect of ritonavir on clarithromycin concentrations, the following dose adjustments are recommended: For patients with renal impairment, the following dosage adjustments should be considered: • For patients with CL _{CR} 30 to

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
		<p>60 mL/min the dose of clarithromycin should be reduced by 50%.</p> <ul style="list-style-type: none"> 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>
Antifungal: Ketoconazole*, itraconazole	INVIRASE/ritonavir Interaction has not been evaluated	<p>Appropriate doses of the combination of ketoconazole or itraconazole and INVIRASE/ritonavir with respect to safety and efficacy have not been established.</p>
Antimycobacterial: Rifabutin*	↓ Saquinavir ↑ Rifabutin	<p>Appropriate doses of the combination of rifabutin and INVIRASE/ritonavir with respect to safety and efficacy have not been established.</p>
Benzodiazepines: Alprazolam, clorazepate, diazepam, flurazepam	↑ Benzodiazepines	<p>Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.</p>
Calcium channel blockers: Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine	↑ Calcium channel blockers	<p>Caution is warranted and clinical monitoring of patients is recommended.</p>
Corticosteroid: Dexamethasone	↓ Saquinavir INVIRASE/ritonavir Interaction has not been evaluated	<p>Use with caution, saquinavir may be less effective due to decreased saquinavir plasma concentrations in patients taking these agents concomitantly.</p>

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
Digitalis Glycosides: Digoxin	↑ Digoxin Increases in serum digoxin concentration were greater in female subjects as compared to male subjects when digoxin was coadministered with INVIRASE/ritonavir.	Concomitant use of INVIRASE/ritonavir with digoxin results in a significant increase in serum concentrations of digoxin. Caution should be exercised when INVIRASE/ritonavir and digoxin are coadministered; serum digoxin concentrations should be monitored and the dose of digoxin may need to be reduced when coadministered with INVIRASE/ritonavir (see WARNINGS).
Inhaled/nasal steroid: Fluticasone	INVIRASE/ritonavir ↑ Fluticasone	Concomitant use of fluticasone propionate and INVIRASE/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Coadministration of fluticasone propionate and INVIRASE/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see WARNINGS).
Histamine H₂-receptor antagonist: Ranitidine	↑ Saquinavir INVIRASE/ritonavir Interaction has not been evaluated	Appropriate doses of the combination of ranitidine and INVIRASE/ritonavir with respect to safety has not been established.
HMG-CoA reductase inhibitors: Atorvastatin, rosuvastatin	↑ Atorvastatin ↑ Rosuvastatin	Use lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as fluvastatin in combination with Invirase/ritonavir.
Immunosuppressants: Cyclosporine,	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
tacrolimus, rapamycin		immunosuppressant agents when coadministered with INVIRASE/ritonavir.
Narcotic analgesic: Methadone	↓ Methadone	Dosage of methadone may need to be increased when coadministered with INVIRASE/ritonavir.
Oral contraceptives: Ethinyl estradiol	↓ Ethinyl estradiol	Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and INVIRASE/ritonavir are coadministered.
PDE5 inhibitors (phosphodiesterase type 5 inhibitors): 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.
Antidepressant: Trazodone	↑ Trazodone	Concomitant use of trazodone and INVIRASE/ritonavir may increase plasma concentration of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
		a CYP3A4 inhibitor such as INVIRASE/ritonavir, the combination should be used with caution and lower dose of trazodone should be considered.
Tricyclic antidepressants: Amitriptyline, imipramine	↑ Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with INVIRASE/ritonavir.
Proton pump inhibitors: Omeprazole	↑ Saquinavir	When INVIRASE/ritonavir is coadministered with omeprazole, saquinavir concentrations are increased significantly. If omeprazole or another proton pump inhibitor is taken concomitantly with INVIRASE/ritonavir, caution is advised and monitoring for potential saquinavir toxicities is recommended, particularly gastrointestinal symptoms, increased triglycerides, and deep vein thrombosis.

421 *See **CLINICAL PHARMACOLOGY: Pharmacokinetics, Table 2** and **Table 3** for
422 magnitude of interactions.

423 **Drugs That Are Mainly Metabolized by CYP3A4**

424 Although specific studies have not been performed, coadministration with drugs that are
425 mainly metabolized by CYP3A4 (eg, calcium channel blockers, dapsone, disopyramide,
426 quinine, amiodarone, quinidine, warfarin, tacrolimus, cyclosporine, ergot derivatives,
427 pimozone, carbamazepine, fentanyl, alfentanyl, alprazolam, and triazolam) may have
428 elevated plasma concentrations when coadministered with saquinavir; therefore, these
429 combinations should be used with caution. Since INVIRASE is coadministered with
430 ritonavir, the ritonavir label should be reviewed for additional drugs that should not be
431 coadministered.

432 **Inducers of CYP3A4**

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

436 Rifampin

437 In a Phase I, randomized, open-label, multiple-dose study involving 28 healthy
438 volunteers, 11 of 17 (65%) healthy volunteers exposed concomitantly to rifampin 600 mg
439 once daily and INVIRASE 1000 mg/ritonavir 100 mg given twice daily (ritonavir-
440 boosted INVIRASE) developed severe hepatocellular toxicity during the 28-day study
441 period. Therefore, rifampin should not be administered concomitantly in patients taking
442 ritonavir-boosted INVIRASE as part of an ART regimen (see
443 **CONTRAINDICATIONS**).

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

445 Carcinogenesis

446 Carcinogenicity studies found no indication of carcinogenic activity in rats and mice
447 administered saquinavir for approximately 2 years. Because of limited bioavailability of
448 saquinavir in animals, the plasma exposures (AUC values) in the respective species were
449 approximately 29% (using rat) and 65% (using mouse) of those obtained in humans at the
450 recommended clinical dose boosted with ritonavir.

451 Mutagenesis

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

458 Impairment of Fertility

459 No adverse effects were reported in fertility and reproductive performance study
460 conducted in rats. Because of limited bioavailability of saquinavir in animals, the
461 maximal plasma exposures achieved in rats were approximately 26% of those obtained in
462 humans at the recommended clinical dose boosted with ritonavir.

463 **Pregnancy**

464 Teratogenic Effects: Category B

465 Reproduction studies conducted with saquinavir have shown no embryotoxicity or
466 teratogenicity in both rats and rabbits. Because of limited bioavailability of saquinavir in
467 animals and/or dosing limitations, the plasma exposures (AUC values) in the respective
468 species were approximately 29% (using rat) and 21% (using rabbit) of those obtained in
469 humans at the recommended clinical dose boosted with ritonavir. Clinical experience in
470 pregnant women is limited. Saquinavir should be used during pregnancy only if the
471 potential benefit justifies the potential risk to the fetus.

472 **Antiretroviral Pregnancy Registry**

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

476 **Nursing Mothers**

477 **The Centers for Disease Control and Prevention recommend that HIV-infected**
478 **mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.**

479 It is not known whether saquinavir is excreted in human milk. Because of both the
480 potential for HIV transmission and the potential for serious adverse reactions in nursing
481 infants, **mothers should be instructed not to breast-feed if they are receiving**
482 **antiretroviral medications, including INVIRASE.**

483 **Pediatric Use**

484 Safety and effectiveness of INVIRASE in HIV-infected pediatric patients younger than
485 16 years of age have not been established.

486 **Geriatric Use**

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

492 **ADVERSE REACTIONS (see PRECAUTIONS)**

493 INVIRASE must be used in combination with ritonavir, which significantly inhibits
494 saquinavir's metabolism to provide increased plasma saquinavir levels.

495 **Concomitant Therapy with Ritonavir Adverse Reactions**

496 In combination with ritonavir the recommended dose of INVIRASE is 1000 mg two
497 times daily with ritonavir 100 mg two times daily in combination with other antiretroviral
498 agents. **Table 7** lists grade 2, 3 and 4 related adverse events that occurred in $\geq 2\%$ of
499 patients receiving saquinavir soft gel capsules with ritonavir (1000/100 mg bid).

500 **Table 7** **Grade 2, 3 and 4 Related Adverse Events (All Causality)**
 501 **Reported in $\geq 2\%$ of Adult Patients in the MaxCmin 1 Study of**
 502 **saquinavir soft gel capsules in Combination with Ritonavir**
 503 **1000/100 mg bid**

	Saquinavir soft gel capsules 1000 mg plus Ritonavir 100 mg bid (48 weeks) N=148 n (%=n/N)
Endocrine Disorders	
Diabetes mellitus/hyperglycemia	4 (2.7)
Lipodystrophy	8 (5.4)
Gastrointestinal Disorders	
Nausea	16 (10.8)
Vomiting	11 (7.4)
Diarrhea	12 (8.1)
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)
Pruritus	5 (3.4)
Dry lips/skin	3 (2.0)
Eczema	3 (2.0)

504 Includes events with unknown relationship to study drug

505 Limited experience is available from three studies investigating the pharmacokinetics of
 506 the INVIRASE 500 mg film-coated tablet compared to the INVIRASE 200 mg capsule in
 507 healthy volunteers (n=140). In two of these studies saquinavir was boosted with ritonavir;
 508 in the other study, saquinavir was administered as single drug. The INVIRASE tablet and
 509 the capsule formulations were similarly tolerated. The most common adverse events were
 510 gastrointestinal disorders (such as diarrhea). Similar bioavailability was demonstrated and
 511 no clinically significant differences in saquinavir exposures were seen. Thus, similar
 512 safety profiles are expected between the two INVIRASE formulations.

513 In a study investigating the drug-drug interaction of rifampin 600 mg/day daily and
514 INVIRASE 1000 mg/ritonavir 100 mg twice daily (ritonavir-boosted INVIRASE)
515 involving 28 healthy volunteers, 11 of 17 healthy volunteers (65%) exposed
516 concomitantly to rifampin and ritonavir-boosted INVIRASE developed severe
517 hepatocellular toxicity presented as increased hepatic transaminases. In some subjects,
518 transaminases increased up to >20-fold the upper limit of normal and were associated
519 with gastrointestinal symptoms, including abdominal pain, gastritis, nausea, and
520 vomiting. Following discontinuation of all three drugs, clinical symptoms abated and the
521 increased hepatic transaminases normalized (see **CONTRAINDICATIONS**).

522 **Additional Adverse Reactions Reported with Saquinavir**

523 Additionally, adverse experiences of any intensity, at least remotely related to saquinavir,
524 that were reported from clinical trials using INVIRASE or saquinavir soft gel capsules
525 with or without ritonavir, are listed below by body system:

526 **Body as a Whole:** allergic reaction, anorexia, asthenia, chest pain, drug fever, edema,
527 fatigue, fever, intoxication, mucosa damage, parasites external, retrosternal pain,
528 shivering, wasting syndrome, weakness generalized, weight decrease,
529 redistribution/accumulation of body fat (see **PRECAUTIONS: Fat Redistribution**)

530 **Cardiovascular:** cyanosis, heart murmur, heart valve disorder, hypertension,
531 hypotension, peripheral vasoconstriction, syncope, thrombophlebitis, vein distended

532 **Endocrine/Metabolic:** appetite decrease, appetite disturbance, dehydration, diabetes
533 mellitus, dry eye syndrome, hypercalcemia, hyperglycemia, hyperkalemia,
534 hypernatremia, hyperphosphatemia, hypertriglyceridemia, hypocalcemia, hypokalemia,
535 hyponatremia, hypophosphatemia, weight increase, xerophthalmia

536 **Gastrointestinal:** ascites, abdominal discomfort, buccal mucosa ulceration, cheilitis,
537 colic abdominal, constipation, dyspepsia, dysphagia, esophagitis, eructation, exacerbation
538 of chronic liver disease with grade 4 LFT, feces bloodstained, feces discolored,
539 flatulence, gastralgia, gastritis, gastrointestinal inflammation, intestinal obstruction,
540 gingivitis, glossitis, hemorrhage rectum, hemorrhoids, hepatitis, hepatomegaly,
541 hepatosplenomegaly, hyperbilirubinemia, infectious diarrhea, jaundice, liver enzyme
542 disorder, melena, pain pelvic, painful defecation, pancreatitis, parotid disorder, portal
543 hypertension, right and left upper quadrant abdominal pain, salivary glands disorder,
544 stomach upset, stomatitis, toothache, tooth disorder, vomiting

545 **Hematologic:** anemia, bleeding dermal, hemolytic anemia, leucopenia,
546 microhemorrhages, neutropenia, pancytopenia, splenomegaly, thrombocytopenia,
547 thrombocytopenia leading to death

548 **Investigations:** ALT increase, AST increase, GGT increase, increased alkaline
549 phosphatase, increased creatine phosphokinase, increased gamma GT, isolated increase in
550 transaminase, raised amylase, raised LDH, TSH increase

551 **Musculoskeletal:** arthralgia, arthritis, back pain, cramps leg, cramps muscle, creatine
552 phosphokinase increased, musculoskeletal disorders, musculoskeletal pain, myalgia,
553 stiffness, tissue changes, trauma

554 **Neoplasms benign, malignant and unspecified: acute myeloblastic leukemia**

555 **Neurological:** ataxia, bowel movements frequent, confusion, convulsions, dizziness,
556 dysarthria, dysesthesia, extremity numbness, headache, heart rate disorder, hyperesthesia,
557 hyperreflexia, hyporeflexia, light-headed feeling, mouth dry, myelopolyradiculoneuritis,
558 numbness face, pain facial, paresis, paresthesia, peripheral neuropathy, poliomyelitis,
559 prickly sensation, progressive multifocal leukoencephalopathy, seizures, spasms, tremor,
560 unconsciousness

561 **Psychological:** agitation, amnesia, anxiety, anxiety attack, depression, dreaming
562 excessive, euphoria, hallucination, insomnia, intellectual ability reduced, irritability,
563 lethargy, libido disorder, overdose effect, psychic disorder, psychosis, somnolence,
564 speech disorder, suicide attempt

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

566 **Resistance Mechanism:** abscess, angina tonsillaris, candidiasis, cellulitis, herpes
567 simplex, herpes zoster, infection bacterial, infection mycotic, infection staphylococcal,
568 influenza, lymphadenopathy, moniliasis, tumor

569 **Respiratory:** bronchitis, cough, dyspnea, epistaxis, hemoptysis, laryngitis, pharyngitis,
570 pneumonia, pulmonary disease, respiratory disorder, rhinitis, sinusitis, upper respiratory
571 tract infection

572 **Skin and Appendages:** acne, alopecia, bullous skin eruption and polyarthritis,
573 chalazion, dermatitis, dermatitis seborrheic, eczema, erythema, folliculitis, furunculosis,
574 hair changes, hot flushes, nail disorder, night sweats, papillomatosis, photosensitivity
575 reaction, pigment changes skin, rash maculopapular, severe cutaneous reaction associated
576 with increased liver function tests, skin disorder, skin nodule, skin ulceration, Stevens-
577 Johnson syndrome, sweating increased, urticaria, verruca, xeroderma

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

580 **Urinary System:** micturition disorder, nephrolithiasis, renal calculus, urinary tract
581 bleeding, urinary tract infection

582 **Postmarketing Experience with INVIRASE**

583 Additional adverse events that have been observed during the postmarketing period are
584 similar to those seen in clinical trials with INVIRASE and saquinavir soft gel capsules
585 alone or in combination with zidovudine.

586 **OVERDOSAGE**

587 No acute toxicities or sequelae were noted in 1 patient who ingested 8 grams of
588 INVIRASE as a single dose. The patient was treated with induction of emesis within 2 to
589 4 hours after ingestion. A second patient ingested 2.4 grams of INVIRASE in
590 combination with 600 mg of zidovudine and experienced pain in the throat that lasted for 6
591 hours and then resolved. In an exploratory Phase II study of oral dosing with INVIRASE

592 at 7200 mg/day (1200 mg q4h), there were no serious toxicities reported through the first
593 25 weeks of treatment.

594 **DOSAGE AND ADMINISTRATION**

595 **INVIRASE must be used in combination with ritonavir, because it significantly**
596 **inhibits saquinavir's metabolism to provide increased plasma saquinavir levels.**

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

- 598 • INVIRASE 1000-mg bid (5 x 200-mg capsules or 2 x 500-mg tablets) in combination
599 with ritonavir 100-mg bid.
- 600 • Ritonavir should be taken at the same time as INVIRASE.
- 601 • INVIRASE and ritonavir should be taken within 2 hours after a meal.

602 **Concomitant Therapy: INVIRASE with Lopinavir/Ritonavir**

603 When administered with lopinavir/ritonavir 400/100 mg bid, the appropriate dose of
604 INVIRASE is 1000 mg bid (with no additional ritonavir).

605 **Monitoring of Patients**

606 Clinical chemistry tests, viral load, and CD₄ count should be performed prior to initiating
607 INVIRASE therapy and at appropriate intervals thereafter. For comprehensive patient
608 monitoring recommendations for other nucleoside analogues, physicians should refer to
609 the complete product information for these drugs.

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

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

620 **HOW SUPPLIED**

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

623 INVIRASE 500-mg film-coated tablets are light orange to greyish- or brownish-orange,
624 oval cylindrical, biconvex tablets with ROCHE and SQV 500 imprinted on the tablet
625 face—bottles of 120 (NDC 0004-0244-51).

626 The capsules and tablets should be stored at 25°C (77°F); excursions permitted to 15° to
627 30°C (59° to 86°F) [see USP Controlled Room Temperature] in tightly closed bottles.

628 HIVID and VERSED are registered trademarks of Hoffmann-La Roche Inc.

629 KALETRA is a registered trademark of Abbott Laboratories.

630 Capsules Manufactured by:

631 F. Hoffmann-La Roche Ltd., Basel, Switzerland

632 Tablets Manufactured by:

633 Roche Farma, S.A., Leganes, Spain

634 Distributed by:



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