



INVIRASE®

(saquinavir mesylate)

CAPSULES and TABLETS

R_x only

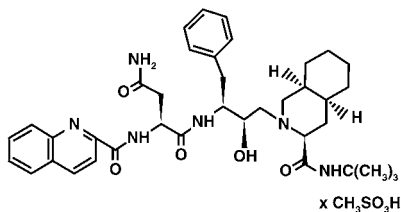
Product identification in this document includes: INVIRASE in reference to saquinavir mesylate; saquinavir soft gel capsules in reference to saquinavir 200 mg soft gel capsule formulation¹, and saquinavir in reference to the active base.

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-quinolylylcarbonyl)-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:



28

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

30

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 This formulation has been withdrawn from the market.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
45 HIV-1 RF in MT4 cells was 37.7± 5 nM representing a 4-fold increase in the IC₅₀ value.
46 In cell culture, saquinavir demonstrated additive to synergistic effects against HIV-1 in
47 combination with reverse transcriptase inhibitors (didanosine, lamivudine, nevirapine,
48 stavudine and zidovudine) without enhanced cytotoxicity. Saquinavir in combination
49 with the protease inhibitors amprenavir, atazanavir, or lopinavir resulted in synergistic
50 antiviral activity. Saquinavir displayed antiviral activity in vitro against HIV-1 clades A-
51 H (IC₅₀ ranged from 0.9 to 2.5 nM). The IC₅₀ and IC₉₀ values of saquinavir against HIV-
52 2 isolates in vitro ranged from 0.25 nM to 14.6 nM and 4.65 nM to 28.6 nM, respectively.

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 IC₅₀ value of 8- and 3-fold,
58 respectively.

59 HIV-1 isolates with reduced susceptibility (≥4-fold increase in the IC₅₀ 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
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 IC₅₀ 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 three times daily and in healthy volunteers after intravenous doses
91 of 6, 12, 36 or 72 mg (n=21). The pharmacokinetics of INVIRASE/ritonavir 1000/100
92 mg twice daily have also been evaluated in HIV-infected patients.

93 Similar bioavailability was demonstrated when INVIRASE 500 mg film-coated tablet
94 (2 x 500 mg) and INVIRASE 200 mg capsule (5 x 200 mg) were administered with low-
95 dose ritonavir (100 mg) under fed conditions. The ratio of mean exposures (90%
96 confidence intervals) of tablets vs capsules were 1.10 (1.04-1.16) for AUC_{0-∞} and 1.19
97 (1.14-1.25) for C_{max}.

98 **Absorption and Bioavailability in Adults**

99 Absolute bioavailability of saquinavir administered as INVIRASE averaged 4% (CV
100 73%, range: 1% to 9%) in 8 healthy volunteers who received a single 600-mg dose (3 x
101 200 mg) of saquinavir mesylate following a high-fat breakfast (48 g protein, 60 g
102 carbohydrate, 57 g fat; 1006 kcal). The low bioavailability is thought to be due to a
103 combination of incomplete absorption and extensive first-pass metabolism.

104 INVIRASE in combination with ritonavir at a dose of 1000/100 mg twice daily provides
105 saquinavir systemic exposures over a 24-hour period that are similar to those achieved
106 with saquinavir soft gel capsules (FORTOVASE) with ritonavir 1000/100 mg twice daily
107 and greater than that achieved with saquinavir soft gel capsules 1200 mg three times daily
108 (see **Table 1**). The 1200 mg three times daily regimen for FORTOVASE was an
109 approved regimen for which efficacy of saquinavir was demonstrated. Thus, the exposure
110 resulting from this FORTOVASE regimen forms the lower bound for efficacy for all
111 subsequent saquinavir dosing regimens.¹

112 **Table 1** **Pharmacokinetic Parameters of Saquinavir at Steady-State**
 113 **After Administration of Different Regimens in HIV-Infected**
 114 **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 (FORTOVASE) 1200 mg tid (arithmetic mean)	31	7249	21747	216
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)

115 τ is the dosing interval (ie, 8h if three times daily and 12h if twice daily)

116 **Food Effect**

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

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

125 Saquinavir exposure was similar when saquinavir soft gel capsules plus ritonavir (1000-
 126 mg/100-mg twice daily) were administered following a high-fat (45 g fat) or moderate-fat
 127 (20 g fat) breakfast.

128 **Distribution in Adults**

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

135 **Metabolism and Elimination in Adults**

136 In vitro studies using human liver microsomes have shown that the metabolism of
 137 saquinavir is cytochrome P450 mediated with the specific isoenzyme, CYP3A4,
 138 responsible for more than 90% of the hepatic metabolism. Based on in vitro studies,
 139 saquinavir is rapidly metabolized to a range of mono- and di-hydroxylated inactive
 140 compounds. In a mass balance study using 600 mg ¹⁴C-saquinavir mesylate (n=8), 88%
 141 and 1% of the orally administered radioactivity was recovered in feces and urine,
 142 respectively, within 5 days of dosing. In an additional 4 subjects administered 10.5 mg
 143 ¹⁴C-saquinavir intravenously, 81% and 3% of the intravenously administered

144 radioactivity was recovered in feces and urine, respectively, within 5 days of dosing. In
145 mass balance studies, 13% of circulating radioactivity in plasma was attributed to
146 unchanged drug after oral administration and the remainder attributed to saquinavir
147 metabolites. Following intravenous administration, 66% of circulating radioactivity was
148 attributed to unchanged drug and the remainder attributed to saquinavir metabolites,
149 suggesting that saquinavir undergoes extensive first-pass metabolism.

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

152 Special Populations

153 *Hepatic or Renal Impairment*

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

157 *Gender, Race, and Age*

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

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

166 *Pediatric Patients*

167 The pharmacokinetics of saquinavir have not been sufficiently investigated in pediatric
168 patients.

169 *Geriatric Patients*

170 The pharmacokinetics of saquinavir have not been sufficiently investigated in patients
171 >65 years of age.

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

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

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

180 **Table 2** **Effect of Saquinavir on the Pharmacokinetics of**
181 **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%)
Rifabutin 300 mg qd	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 qd	1200 mg tid	13V	↓12%	↓13%
	Invirase or Invirase/ritonavir Dose			
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 qd	1000/100 mg bid x 14 days	12M	↓19% (9-29%) [^]	NA
Ketoconazole 200 mg/day	1000/100 mg bid	12V	↑168% (146-193%) [^]	↑45% (32-59%) [^]
Midazolam 7.5 mg oral single dose	1000/100 mg bid	16V	↑1144% (975-1339%) [^]	↑327% (264 - 402%) [^]

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

190
 191

Table 3 Effect of Coadministered Drugs on Saquinavir 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 qd	1200 mg tid	13V	↓62%	↓50%
Indinavir 800 mg q8h x 2 days	1200 mg single dose	6V	↑364% (190-644%)	↑299% (138-568%)
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.				

192

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

- 193 ↑ Denotes an average increase in exposure by the percentage indicated.
194 ↓ Denotes an average decrease in exposure by the percentage indicated.
195 ↔ Mean change <10%
196 [†] Compared to standard saquinavir soft gel capsules 1200 mg tid regimen (n=33).
197 [‡] Compared to standard INVIRASE 600 mg tid regimen (n=114).
198 [§] Did not reach statistical significance.
199 [^] 90% Confidence Interval
200 P Patient
201 V Healthy Volunteers

202

203 For information regarding clinical recommendations, see **PRECAUTIONS: Drug**
204 **Interactions, Table 5.**

205 INDICATIONS AND USAGE

206 INVIRASE in combination with ritonavir and other antiretroviral agents is indicated for
207 the treatment of HIV infection. The twice daily administration of INVIRASE in
208 combination with ritonavir is supported by safety data from the MaxCmin 1 study (see
209 **Table 6**) and pharmacokinetic data (see **Table 1**). The efficacy of INVIRASE with
210 ritonavir has not been compared against the efficacy of antiretroviral regimens currently
211 considered standard of care.

212 Description of Clinical Studies

213 In a randomized, double-blind clinical study (NV14256) in zidovudine-experienced,
214 HIV-infected patients, INVIRASE in combination with zalcitabine was shown to be
215 superior to either INVIRASE or zalcitabine monotherapy in decreasing the cumulative
216 incidence of clinical disease progression to AIDS-defining events or death. Furthermore,
217 in a randomized study (ACTG229/NV14255), patients with advanced HIV infection with
218 history of prolonged zidovudine treatment and who were given INVIRASE 600 mg (three
219 times daily) + zidovudine + zalcitabine experienced greater increases in CD4 cell counts
220 as compared to those who received INVIRASE + zidovudine or zalcitabine + zidovudine.

221 It should be noted that HIV treatment regimens that were used in these initial clinical
222 studies of INVIRASE are no longer considered standard of care.

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

229 **CONTRAINDICATIONS**

230 INVIRASE is contraindicated in patients with clinically significant hypersensitivity (e.g.
231 anaphylactic reaction, Stevens-Johnson syndrome) to saquinavir, saquinavir mesylate, or
232 any of its ingredients including ritonavir.

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

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

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

243 INVIRASE/ritonavir should not be administered concurrently with drugs listed in
244 **Table 4**.

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

Drug Class	Drugs Within Class That Are Contraindicated With INVIRASE	Clinical Comment
Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine	Potential for serious and/or threatening reactions.
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for serious and life threatening reactions such as ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Antimycobacterial Agents	Rifampin	Rifampin should not be administered in patients

		taking ritonavir-boosted INVIRASE part of an ART regimen due to the risk of severe hepatocellular toxicity.
GI Motility Agent	Cisapride	Potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Neuroleptics	Pimozide	Potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics	Triazolam, orally administered midazolam	Potential for serious and/or life threatening reactions such as prolonged or increased sedation or respiratory depression. Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam and orally administered midazolam with INVIRASE/ritonavir may cause large increases in the concentration of these benzodiazepines.
HMG-CoA Reductase Inhibitors	Lovastatin, Simvastatin	Potential for myopathy including rhabdomyolysis.

246 **WARNINGS**

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

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

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

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

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

264 **Interaction with Digoxin**

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

268 **Interaction with Fluticasone**

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

279 **Diabetes Mellitus and Hyperglycemia**

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

289 **PRECAUTIONS**

290 **General**

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

297 **Hepatic Effects**

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

303 **Renal Effects**

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

309 **Hemophilia**

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

315 **Hyperlipidemia**

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

322 **Lactose Intolerance**

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

325 **Fat Redistribution**

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

331 **Immune Reconstitution Syndrome**

332 Immune reconstitution syndrome has been reported in patients treated with combination
333 antiretroviral therapy, including INVIRASE. During the initial phase of combination
334 antiretroviral treatment, patients whose immune system responds may develop an
335 inflammatory response to indolent or residual opportunistic infections (such as
336 *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia
337 [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

338 **Resistance/Cross-resistance**

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

343 **Information for Patients**

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

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

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

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

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

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

368 **Laboratory Tests**

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

375 **Drug Interactions**

376 **Drug interaction studies have been completed with INVIRASE and saquinavir soft**
377 **gel capsules. Observations from drug interaction studies with saquinavir soft gel**

378 **capsules may not be predictive for INVIRASE/ritonavir.** Because ritonavir is
379 coadministered, prescribers should also refer to the prescribing information for ritonavir
380 regarding drug interactions associated with this agent.

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

386 Drugs that are contraindicated specifically due to the expected magnitude of interaction
387 and potential for serious adverse events are listed in **Table 4** under
388 **CONTRAINDICATIONS**. These recommendations are based on either drug interaction
389 studies or predicted interactions due to the expected magnitude of interaction and
390 potential for serious events or loss of efficacy.

391 Drug interactions that have been established based on drug interaction studies are listed
392 with the pharmacokinetic results in **Table 2**, which summarizes the effect of saquinavir,
393 administered as saquinavir soft gel capsules or INVIRASE, on the geometric mean AUC
394 and C_{max} of coadministered drugs and **Table 3**, which summarizes the effect of
395 coadministered drugs on the geometric mean AUC and C_{max} of saquinavir. Clinical dose
396 recommendations can be found in **Table 5**. The magnitude of the interactions may be
397 different when INVIRASE is given with ritonavir (see **CLINICAL**
398 **PHARMACOLOGY**).

399 When coadministering INVIRASE/ritonavir with any agent having a narrow therapeutic
400 margin, such as anticoagulants, anticonvulsants, and antiarrhythmics, special attention is
401 warranted. With some agents, the metabolism may be induced, resulting in decreased
402 concentrations. Examples and clinical dose recommendations can be found in **Table 5**.

403 **Table 5** **Established and Other Potentially Significant Drug**
404 **Interactions: Alteration in Dose or Regimen May Be**
405 **Recommended Based on Drug Interaction Studies or on**
406 **Predicted Interaction with 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^b	↑ Saquinavir Effect on delavirdine is not well established	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Non-nucleoside reverse	↓ Saquinavir	Appropriate doses of the

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
transcriptase inhibitor: Efavirenz ^a , nevirapine ^b	↔ Efavirenz	combination of efavirenz or nevirapine and INVIRASE/ritonavir (1000/100 mg bid) with respect to safety and efficacy have not been established.
HIV protease inhibitor: Atazanavir ^a	INVIRASE/ritonavir ↑ Saquinavir ↑ Ritonavir ↔ Atazanavir	Appropriate dosing recommendations for this combination, with respect to efficacy and safety, have not been established. When 1600 mg INVIRASE/100 mg ritonavir and 300 mg atazanavir were coadministered, plasma concentrations of saquinavir and ritonavir were increased.
HIV protease inhibitor: Indinavir ^b	↑ Saquinavir Effect on indinavir is not well established	Appropriate doses of the combination of indinavir and INVIRASE/ritonavir with respect to safety and efficacy have not been established.
HIV protease inhibitor: Lopinavir/ritonavir ^a (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 ^a	↓ Saquinavir	Combining saquinavir with tipranavir/ritonavir is not recommended.
HIV fusion inhibitor: Enfuvirtide ^a	Saquinavir soft gel capsules/ritonavir ↔ enfuvirtide	No clinically significant interaction was noted from a study in 12 HIV patients who received

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
		enfuvirtide concomitantly with saquinavir soft gel capsules/ritonavir 1000/100 mg bid. No dose adjustments are required.
Other Agents		
Antiarrhythmics: Lidocaine (systemic) ^b	↑ Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics given with INVIRASE/ritonavir.
Anticoagulant: Warfarin ^b	↑ Warfarin	Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: Carbamazepine ^b , phenobarbital ^b , phenytoin ^b	↓ Saquinavir Effect on carbamazepine, phenobarbital, and phenytoin is not well established	Use with caution, saquinavir may be less effective due to decreased saquinavir plasma concentrations in patients taking these agents concomitantly.
Anti-infective: Clarithromycin ^a	↑ Saquinavir ↑ Clarithromycin	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: <ul style="list-style-type: none"> • For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%.

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
		<ul style="list-style-type: none"> For patients with $CL_{CR} < 30$ mL/min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antifungal: Ketoconazole ^a , itraconazole ^b	↔ Saquinavir ↔ Ritonavir ↑ Ketoconazole	Appropriate doses of the combination of ketoconazole or itraconazole and INVIRASE/ritonavir with respect to safety and efficacy have not been established. When INVIRASE/ritonavir and ketoconazole are coadministered, plasma concentration of ketoconazole was increased (see Table 2). Hence, doses of ketoconazole > 200 mg/day are not recommended.
Antimycobacterial: Rifabutin ^a	↓ Saquinavir ↑ Rifabutin	Appropriate doses of the combination of rifabutin and INVIRASE/ritonavir with respect to safety and efficacy have not been established.
Benzodiazepines^b: Alprazolam, clorazepate, diazepam, flurazepam	↑ Benzodiazepines	Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.
Benzodiazepine^b: Intravenously administered Midazolam	↑ Midazolam	Midazolam is extensively metabolized by CYP3A4. Increases in the concentration of midazolam are expected to be significantly higher with oral than parenteral administration. Therefore, INVIRASE should not be given with orally administered midazolam [see Contraindications (4)]. If INVIRASE is coadministered with parenteral midazolam, close clinical monitoring for respiratory

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
		depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.
Calcium channel blockers^b: Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine	↑ Calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone ^b	↓ Saquinavir	Use with caution, saquinavir may be less effective due to decreased saquinavir plasma concentrations in patients taking these agents concomitantly.
Digitalis Glycosides: Digoxin ^a	↑ 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 ^b	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

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
		benefit to the patient outweighs the risk of systemic corticosteroid side effects (see WARNINGS).
HMG-CoA reductase inhibitors^b: 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 (see WARNINGS).
Immunosuppressants^b: Cyclosporine, tacrolimus, rapamycin	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with INVIRASE/ritonavir.
Narcotic analgesic: Methadone ^a	↓ Methadone	Dosage of methadone may need to be increased when coadministered with INVIRASE/ritonavir.
Oral contraceptives: Ethinyl estradiol ^b	↓ 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 ^a , vardenafil ^b , tadalafil ^b	↑ 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

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
		10 mg every 72 hours with increased monitoring of adverse events when administered concomitantly with INVIRASE/ritonavir.
Antidepressant: Trazodone ^b	↑ 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 a CYP3A4 inhibitor such as INVIRASE/ritonavir, the combination should be used with caution and lower dose of trazodone should be considered.
Tricyclic antidepressants^b: Amitriptyline, imipramine	↑ Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with INVIRASE/ritonavir.
Proton pump inhibitors: Omeprazole ^a	↑ 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.
Herbal Products: St. John's wort ^b (hypericum perforatum)	↓ Saquinavir	Coadministration may lead to loss of virologic response and possible resistance to INVIRASE or to the class of protease inhibitors (see

Concomitant Drug Class: Drug Name	Effect on Concentration of Saquinavir or Concomitant Drug	Clinical Comment
		WARNINGS).
Garlic Capsules ^b	↓ Saquinavir	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.

407 ^aSee **CLINICAL PHARMACOLOGY: Pharmacokinetics, Table 2 and Table 3** for
408 magnitude of interactions.

409 ^bINVIRASE/ritonavir interaction has not been evaluated.

410 Drugs That Are Mainly Metabolized by CYP3A4

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

419 Inducers of CYP3A4

420 Coadministration with compounds that are potent inducers of CYP3A4 (e.g.,
421 phenobarbital, phenytoin, dexamethasone, carbamazepine) may result in decreased
422 plasma levels of saquinavir.

423 Carcinogenesis, Mutagenesis and Impairment of Fertility

424 Carcinogenesis

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

430 Mutagenesis

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

437 **Impairment of Fertility**

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

442 **Pregnancy**

443 **Teratogenic Effects: Category B**

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

451 **Antiretroviral Pregnancy Registry**

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

455 **Nursing Mothers**

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

462 **Pediatric Use**

463 Safety and effectiveness of INVIRASE in HIV-infected pediatric patients younger than
464 16 years of age have not been established.

465 **Geriatric Use**

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

471 **ADVERSE REACTIONS**

472 **Clinical Trials Experience**

473 Because clinical trials are conducted under widely varying conditions, adverse reaction
474 rates observed in the clinical trials of a drug cannot be directly compared to rates in the
475 clinical trials of another drug and may not reflect the rates observed in clinical practice.

476 **Concomitant Therapy with Ritonavir Adverse Reactions**

477 In combination with ritonavir the recommended dose of INVIRASE is 1000 mg two
 478 times daily with ritonavir 100 mg two times daily in combination with other antiretroviral
 479 agents. **Table 6** lists grade 2, 3 and 4 adverse events that occurred in $\geq 2\%$ of patients
 480 receiving saquinavir soft gel capsules with ritonavir (1000/100 mg bid).

481 **Table 6** **Grade 2, 3 and 4 Adverse Events (All Causality^a) Reported in**
 482 **$\geq 2\%$ of Adult Patients in the MaxCmin 1 Study of saquinavir**
 483 **soft gel capsules in Combination with Ritonavir 1000/100 mg**
 484 **bid**

Adverse Events	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)

485 ^aIncludes events with unknown relationship to study drug

486 Limited experience is available from three studies investigating the pharmacokinetics of
 487 the INVIRASE 500 mg film-coated tablet compared to the INVIRASE 200 mg capsule in
 488 healthy volunteers (n=140). In two of these studies saquinavir was boosted with ritonavir;

489 in the other study, saquinavir was administered as single drug. The INVIRASE tablet and
490 the capsule formulations were similarly tolerated. The most common adverse events were
491 gastrointestinal disorders (such as diarrhea). Similar bioavailability was demonstrated and
492 no clinically significant differences in saquinavir exposures were seen. Thus, similar
493 safety profiles are expected between the two INVIRASE formulations.

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

503 **Additional Adverse Reactions Reported with Saquinavir**

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

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

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

513 **Endocrine/Metabolic:** appetite decrease, appetite disturbance, dehydration, diabetes
514 mellitus, dry eye syndrome, hypercalcemia, hyperglycemia, hyperkalemia,
515 hypernatremia, hyperphosphatemia, hypertriglyceridemia, hypocalcemia, hypokalemia,
516 hyponatremia, hypophosphatemia, weight increase, xerophthalmia

517 **Gastrointestinal:** ascites, abdominal discomfort, buccal mucosa ulceration, cheilitis,
518 colic abdominal, constipation, dyspepsia, dysphagia, esophagitis, eructation, exacerbation
519 of chronic liver disease with grade 4 LFT, feces bloodstained, feces discolored,
520 flatulence, gastralgia, gastritis, gastrointestinal inflammation, intestinal obstruction,
521 gingivitis, glossitis, hemorrhage rectum, hemorrhoids, hepatitis, hepatomegaly,
522 hepatosplenomegaly, hyperbilirubinemia, infectious diarrhea, jaundice, liver enzyme
523 disorder, melena, pain pelvic, painful defecation, pancreatitis, parotid disorder, portal
524 hypertension, right and left upper quadrant abdominal pain, salivary glands disorder,
525 stomach upset, stomatitis, toothache, tooth disorder, vomiting, frequent bowel
526 movements

527 **Hematologic:** anemia, bleeding dermal, hemolytic anemia, leukopenia,
528 microhemorrhages, neutropenia, pancytopenia, splenomegaly, thrombocytopenia,
529 lymphadenopathy

- 530 Infections and Infestations: abscess, angina tonsillaris, candidiasis, cellulitis, herpes
531 simplex, herpes zoster, infection bacterial, infection mycotic, infection staphylococcal,
532 influenza, moniliasis
- 533 Investigations: ALT increase, AST increase, GGT increase, increased alkaline
534 phosphatase, increased creatine phosphokinase, increased gamma GT, isolated increase in
535 transaminase, raised amylase, raised LDH, TSH increase
- 536 Musculoskeletal: arthralgia, arthritis, back pain, cramps leg, cramps muscle, creatine
537 phosphokinase increased, musculoskeletal disorders, musculoskeletal pain, myalgia,
538 stiffness, tissue changes, trauma
- 539 Neoplasms benign, malignant and unspecified: acute myeloblastic leukemia
- 540 Neurological: ataxia, confusion, convulsions, dizziness, dysarthria, dysesthesia,
541 extremity numbness, headache, heart rate disorder, hyperesthesia, hyperreflexia,
542 hyporeflexia, light-headed feeling, mouth dry, myelopolyradiculoneuritis, numbness face,
543 pain facial, paresis, paresthesia, peripheral neuropathy, poliomyelitis, prickly sensation,
544 progressive multifocal leukoencephalopathy, seizures, spasms, intracranial hemorrhage
545 leading to death, tremor, unconsciousness
- 546 Psychological: agitation, amnesia, anxiety, anxiety attack, depression, dreaming
547 excessive, euphoria, hallucination, insomnia, intellectual ability reduced, irritability,
548 lethargy, libido disorder, overdose effect, psychic disorder, psychosis, somnolence,
549 speech disorder, suicide attempt
- 550 Reproductive System: impotence, prostate enlarged, vaginal discharge
- 551 Respiratory: bronchitis, cough, dyspnea, epistaxis, hemoptysis, laryngitis, pharyngitis,
552 pneumonia, pulmonary disease, respiratory disorder, rhinitis, sinusitis, upper respiratory
553 tract infection
- 554 Skin and Appendages: acne, alopecia, bullous skin eruption and polyarthritis,
555 chalazion, dermatitis, dermatitis seborrheic, eczema, erythema, folliculitis, furunculosis,
556 hair changes, hot flushes, nail disorder, night sweats, papillomatosis, photosensitivity
557 reaction, pigment changes skin, rash maculopapular, severe cutaneous reaction associated
558 with increased liver function tests, skin disorder, skin nodule, skin ulceration, Stevens-
559 Johnson syndrome, sweating increased, urticaria, verruca, xeroderma
- 560 Special Senses: blepharitis, earache, ear pressure, eye irritation, hearing decreased,
561 otitis, taste alteration, tinnitus, visual disturbance
- 562 Urinary System: micturition disorder, nephrolithiasis, renal calculus, urinary tract
563 bleeding, urinary tract infection
- 564 **Postmarketing Experience**
- 565 Additional adverse events that have been observed during the postmarketing period are
566 similar to those seen in clinical trials with INVIRASE and saquinavir soft gel capsules
567 alone or in combination with ritonavir.

568 **OVERDOSAGE**

569 There is limited experience of overdose with saquinavir.

570 No acute toxicities or sequelae were noted in 1 patient who ingested 8 grams of
571 INVIRASE as a single dose. The patient was treated with induction of emesis within 2 to
572 4 hours after ingestion. A second patient ingested 2.4 grams of INVIRASE in
573 combination with 600 mg of ritonavir and experienced pain in the throat that lasted for 6
574 hours and then resolved. In an exploratory Phase II study of oral dosing with INVIRASE
575 at 7200 mg/day (1200 mg q4h), there were no serious toxicities reported through the first
576 25 weeks of treatment.

577 Treatment of overdose with saquinavir should consist of general supportive measures
578 including monitoring of vital signs and ECG and observations of the patient's clinical
579 status. Since saquinavir is highly protein bound, dialysis is unlikely to be beneficial in
580 significant removal of the active substance.

581 **DOSAGE AND ADMINISTRATION**

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

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

- 585 • INVIRASE 1000-mg twice daily (5 x 200-mg capsules or 2 x 500-mg tablets) in
586 combination with ritonavir 100-mg twice daily.
587 • Ritonavir should be taken at the same time as INVIRASE.
588 • INVIRASE and ritonavir should be taken within 2 hours after a meal.

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

590 When administered with lopinavir/ritonavir 400/100 mg twice daily, the appropriate dose
591 of INVIRASE is 1000 mg twice daily (with no additional ritonavir).

592 **Monitoring of Patients**

593 Clinical chemistry tests, viral load, and CD4 count should be performed prior to initiating
594 INVIRASE therapy and at appropriate intervals thereafter.

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

596 For serious toxicities that may be associated with INVIRASE, the drug should be
597 interrupted. INVIRASE at doses less than 1000 mg with 100 mg ritonavir twice daily are
598 not recommended since lower doses have not shown antiviral activity. For recipients of
599 combination therapy with INVIRASE and ritonavir, dose adjustments may be necessary.
600 These adjustments should be based on the known toxicity profile of the individual agent
601 and the pharmacokinetic interaction between saquinavir and the coadministered drug (see
602 **PRECAUTIONS: Drug Interactions**). Physicians should refer to the complete product
603 information for these drugs for comprehensive dose adjustment recommendations and
604 drug-associated adverse reactions of nucleoside analogues.

605 **HOW SUPPLIED**

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

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

611 The capsules and tablets should be stored at 25°C (77°F); excursions permitted to 15° to
612 30°C (59° to 86°F) [see USP Controlled Room Temperature] in tightly closed bottles.

613 Capsules Manufactured by:

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

615 Tablets Manufactured by:

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

Distributed by:



Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

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620 Revised: January/2010

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Patient Information About INVIRASE (in-ver-ase)

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INVIRASE[®]

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(saquinavir mesylate)

641

CAPSULES and TABLETS

642

Generic Name: Saquinavir mesylate (sa-KWIN-a-veer mes-il-late)

643

Rx only

644

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

645

Please read this product information carefully before you start taking INVIRASE and each time you renew your prescription. There may be new information. Reading this information can help you take this medicine correctly. However, it is not a substitute for your doctor's advice about the safety and benefits of INVIRASE. You should talk to your doctor about INVIRASE as part of your long-term treatment plan for HIV before you start taking your medication and ask any questions you may have at regular checkups. Remember, you should remain under a doctor's care when using INVIRASE and should not change or stop your therapy without talking to your doctor first.

652

653

What is INVIRASE?

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INVIRASE belongs to a class of anti-HIV medicines called protease (PRO-tee-ase) inhibitors. INVIRASE Capsules and Tablets in combination with other anti-HIV drugs are used for the treatment of HIV, the virus that causes AIDS (acquired immunodeficiency syndrome).

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How does INVIRASE work?

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INVIRASE fights HIV as it grows inside cells by blocking an enzyme (protease) that HIV needs to reproduce.

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Who should not take INVIRASE?

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Anyone who has had a severe allergic reaction (e.g. trouble breathing or severe rash) to INVIRASE or any of the ingredients in the capsule or tablet should not take it. The use of INVIRASE in patients under 16 years of age, over 65 years of age, or patients with severe liver problems has not been fully investigated.

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How should INVIRASE/NORVIR[®] (ritonavir) be taken?

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- The recommended dosage of INVIRASE in combination with NORVIR (ritonavir) is INVIRASE 5 capsules or 2 tablets twice a day taken with 1 capsule of NORVIR twice a day. Your doctor may change the dose of other medications you may be taking for other illnesses.

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- INVIRASE must be taken along with NORVIR (ritonavir).

- 672 • INVIRASE must be taken with meals or up to 2 hours after a meal—but it is easiest
673 to remember if you take it with your meals. When INVIRASE is taken without food,
674 the amount of INVIRASE in the blood is lower and may not fight HIV as well.
- 675 • When taking INVIRASE and other anti-HIV medicines, it is very important to follow
676 the directions exactly and take your medication every day. If you skip doses—or take
677 less than the prescribed dose—the medicine will not work as well, and your disease
678 could get worse.
- 679 – If you miss a dose, you should take the next dose as soon as possible. However,
680 do not double the dose.

681 **What results have been seen with INVIRASE?**

682 INVIRASE with NORVIR has been shown to reduce the amount of virus in the blood
683 (“viral load”) and increase CD4 (T) cells when taken with other HIV therapy.

684 **What are the side effects of INVIRASE?**

685 People treated with INVIRASE in combination with NORVIR may have side effects. The
686 majority of these have been described as mild. In clinical studies of patients who received
687 saquinavir in combination with NORVIR and other HIV drugs, the side effects seen most
688 often were: body fat change (5.4%), nausea (10.8%), vomiting (7.4%), diarrhea (8.1%),
689 stomach pain (6.1%), tiredness (6.1%), and pneumonia (5.4%).

690 Diabetes (new onset or worsening) and increased blood sugar levels have been reported
691 with the use of protease inhibitors. In addition, increased bleeding in patients with
692 hemophilia has also been associated with these drugs.

693 When INVIRASE is taken with NORVIR, some patients may experience large increases
694 in triglyceride and lipid levels. The long-term chance of getting complications such as
695 heart attack and stroke due to increases in triglyceride and cholesterol levels caused by
696 protease inhibitors is not known at this time.

697 Changes in body fat have been seen in some patients taking anti-HIV medications. These
698 changes may include increased amount of fat in the upper back and neck (“buffalo
699 hump”), breasts, and around the trunk. Loss of fat from the legs and arms may also
700 happen. The cause and long-term health effects of these conditions are not known at this
701 time.

702 These are not the only side effects that can occur with INVIRASE. Your doctor can
703 discuss with you a more complete list of side effects and laboratory abnormalities that
704 may accompany this medication.

705 If any side effects or unusual symptoms do occur, contact your doctor immediately. Do
706 not stop or decrease your dose on your own. Lowering the dose may make INVIRASE
707 less effective in fighting HIV.

708 **Are there other medications that I should not take with INVIRASE/NORVIR**
709 **(ritonavir)?**

710 There are some drugs that should not be taken with INVIRASE/NORVIR. Before starting
711 therapy with INVIRASE/NORVIR, be sure to tell your doctor all of the medicines—
712 prescription medications, as well as over-the-counter drugs and nutritional supplements—
713 that you are now taking or plan to take.

714 **Medicines you should not take with INVIRASE/NORVIR**

Drug Class	Drugs Within Class Not to Be Taken with INVIRASE/NORVIR (ritonavir)
Antiarrhythmics	PACERONE [®] (amiodarone), TAMBOCOR [®] (flecainide), RHYTHMOL [®] (propafenone), bepridil, quinidine
Antimigraines	Ergot medications (e.g. WIGRAINE [®] and CAFERGOT [®])
GI motility agents	PROPULSID [®] (cisapride)*
Sedatives, hypnotics	VERSED [®] (orally administered midazolam), Halcion [®] (triazolam)
Antimycobacterial agents	Rifampin
Neuroleptics	ORAP [®] (Pimozide)
HMG-CoA Reductase Inhibitors	MEVACOR [®] ALTOPREV [®] , ADVICOR [®] (lovastatin), ZOCOR [®] , VYTORIN [®] , SIMCOR [®] (simvastatin)

715 * No longer sold in the US.

716 INVIRASE causes increased blood levels of some of these compounds. This can lead to
717 serious or life-threatening reactions such as irregular heartbeat or prolonged sedation.

718 **The following medicines may increase blood levels and side effects of INVIRASE**
719 **when taken with INVIRASE/NORVIR:**

- 720 • REYATAZ[®] (atazanavir, used for HIV infection)
- 721 • PRILOSEC[®] (omeprazole, for treatment of gastrointestinal conditions such as ulcers
722 or GERD)
- 723 • BIAXIN[®] (clarithromycin, for treatment of infections)
- 724 • CRIXIVAN[®] (indinavir, used for HIV infection)
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726 **INVIRASE/NORVIR may not work as well when taken together with the following**
727 **medicines, herbal products, or dietary supplements:**

- 728 • SUSTIVA[®] (efavirenz, used for HIV infection)
- 729 • VIRAMUNE[®] (nevirapine, used for HIV infection)

- 730 • APTIVUS[®] ([tipranavir]/NORVIR [ritonavir] used for HIV infection)
- 731 • Anticonvulsants such as CARBATROL[®] (carbamazepine), phenobarbital, and
732 DILANTIN[®] (phenytoin)
- 733 • MYCOBUTIN[®] (rifabutin, an antimycobacterial agent)
- 734 • Corticosteroids such as dexamethasone
- 735 • Garlic capsules, an herbal product sold as a dietary supplement
- 736 • St. John's wort (*Hypericum perforatum*) or products containing St. John's wort, an
737 herbal product sold as a dietary supplement
- 738 **Your healthcare provider may need to monitor your therapy more closely if you**
739 **take INVIRASE/NORVIR with the following medicines:**
- 740 • CIALIS[®] (tadalafil), LEVITRA[®] (vardenafil), or VIAGRA[®] (sildenafil citrate) used
741 for erectile dysfunction. INVIRASE may increase the chances of serious side effects
742 that can happen with CIALIS, LEVITRA, or VIAGRA
- 743 • COUMADIN[®] (warfarin) (a blood thinner)
- 744 • Antidepressants such as DESYREL[®] (trazodone), ELAVIL[®] (amitriptyline), or
745 TOFRANIL[®] (imipramine)
- 746 • Benzodiazepines used as sedatives or sleeping pills such as XANAX[®] (alprazolam),
747 TRANXENE[®] (clorazepate), VALIUM[®] (diazepam), and DALMANE[®] (flurazepam)
- 748 • LIPITOR[®] (atorvastatin) and CRESTOR[®] (rosuvastatin) used for lowering
749 cholesterol
- 750 • Calcium channel blockers used for treatment of high blood pressure or heart disease,
751 such as diltiazem (also known as CARDIZEM[®], CARTIA XT[®], DILACOR XR[®],
752 DILTZAC[®], TAZTIA XT[®], TIAZAC[®]), PLENDIL[®] (felodipine), PROCARDIA[®]
753 (nifedipine), CARDENE[®] (nicardipine), NIMOTOP[®] (nimodipine), verapamil-
754 containing medications (such as CALAN[®], VERELAN[®]), amlodipine-containing
755 medications (such as CADUET[®], NORVASC[®]), SULAR[®] (nisoldipine), and
756 DYNACIRC[®] (isradipine)
- 757 • NIZORAL[®] (ketoconazole) and SPORANOX[®] (itraconazole) used to treat fungal
758 infections
- 759 • Medicines to prevent organ transplant rejection: SANDIMMUNE[®] (cyclosporine),
760 NEORAL[®] (cyclosporine), RAPAMUNE[®] (sirolimus), or PROGRAF[®] (tacrolimus)
- 761 • FLONASE[®], FLOVENT[®], ADVAIR[®] (fluticasone propionate), given by nose or
762 inhaled to treat allergic symptoms or asthma
- 763 • LANOXIN[®] (digoxin) used to treat heart rhythm problems or other heart conditions
- 764 • Oral contraceptives containing ethinyl estradiol used for preventing pregnancy

- 765 • Methadone used for the treatment of opioid addiction

766 **Does INVIRASE cure HIV/AIDS?**

767 INVIRASE does not cure AIDS, and it does not prevent you from getting other illnesses
768 that result from advanced HIV infection. In addition, INVIRASE has not been shown to
769 reduce the risk that you may transmit HIV to others through sexual contact or infected
770 blood. You must continue to follow all of your doctor's recommendations for managing
771 your illness.

772 **What else should I discuss with my doctor?**

773 Inform your doctor:

- 774 • If you are pregnant or become pregnant while taking INVIRASE. The effects of
775 INVIRASE on pregnant women or unborn babies are not yet fully known. In
776 addition, experts advise against breast-feeding if you are HIV positive, to reduce the
777 risk of passing the virus to your baby.
- 778 • If you are taking anti-HIV medications. Your doctor may want to change one or more
779 of your anti-HIV drugs in order to achieve the best results when you start treatment with
780 INVIRASE.
- 781 • If you have diabetes or a family history of diabetes, or if you have hemophilia,
782 hepatitis or other liver disease, your doctor should decide if INVIRASE is right for
783 you.
- 784 • If you have ever taken FORTOVASE, discuss with your doctor whether INVIRASE
785 is right for you.

786 **How is INVIRASE supplied?**

787 INVIRASE is available as light brown and green capsules in a 200-mg strength.
788 INVIRASE comes in bottles of 270 capsules.

789 INVIRASE is also available as light orange to greyish- or brownish-orange tablets in a
790 500-mg strength. INVIRASE comes in bottles of 120 tablets.

791 **How should I store INVIRASE?**

792 INVIRASE capsules and tablets should be stored at room temperature. The bottles should be
793 kept tightly closed.

794 INVIRASE has been prescribed specifically for you, and only for a particular condition.
795 Do not use it for anything else. Do not give it to anyone else. If you think you have taken
796 more than your prescribed dose, seek medical attention.

797 **Keep this medication and all other medications out of the reach of children.** Do not
798 keep medicine that is out of date or that you no longer need. Be sure that if you throw any
799 medicine away, it is out of the reach of children.

800 This provides only a brief summary of product information about INVIRASE. If you
801 have any questions about INVIRASE or HIV, talk to your doctor.

802 The brands listed are trademarks of their respective owners and are not trademarks of
803 Roche Laboratories, Inc. The makers of these brands are not affiliated with and do not
804 endorse Roche Laboratories, Inc. or its products.

805 *If you have any questions about INVIRASE, call toll free at 1-800-910-4687.*

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