

1 **REYATAZ™**

Rx only

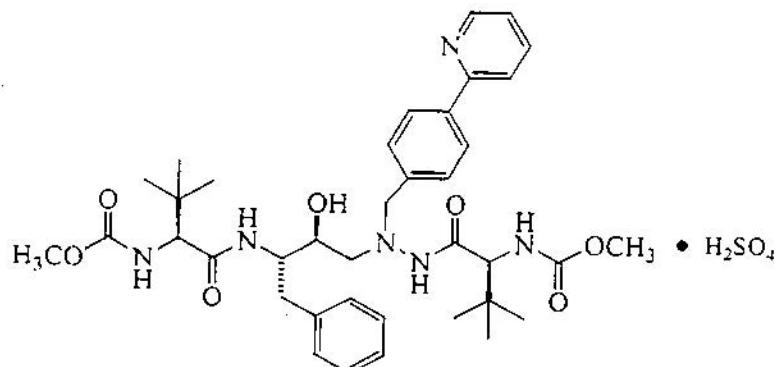
2 **(atazanavir sulfate) Capsules**

3 **(Patient Information Leaflet Included)**

4 **DESCRIPTION**

5 REYATAZ™ (atazanavir sulfate) is an azapeptide inhibitor of HIV-1 protease.

6 The chemical name for atazanavir sulfate is (3S,8S,9S,12S)-3,12-Bis(1,1-
7 dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-
8 2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate (1:1). Its molecular formula
9 is C₃₈H₅₂N₆O₇•H₂SO₄, which corresponds to a molecular weight of 802.9 (sulfuric acid
10 salt). The free base molecular weight is 704.9. Atazanavir sulfate has the following
11 structural formula:



13

14 Atazanavir sulfate is a white to pale yellow crystalline powder. It is slightly soluble in
15 water (4-5 mg/mL, free base equivalent) with the pH of a saturated solution in water being about
16 1.9 at 24 ± 3° C.

17 REYATAZ Capsules are available for oral administration in strengths containing the
18 equivalent of 100 mg, 150 mg, or 200 mg of atazanavir as atazanavir sulfate and the
19 following inactive ingredients: crospovidone, lactose monohydrate, and magnesium stearate.
20 The capsule shells contain the following inactive ingredients: gelatin, FD&C Blue #2, and
21 titanium dioxide. The capsules are printed with ink containing shellac, titanium dioxide,
22 FD&C Blue #2, isopropyl alcohol, ammonium hydroxide, propylene glycol, n-butyl alcohol,
23 simethicone, and dehydrated alcohol.

24 **CLINICAL PHARMACOLOGY**

25 **Microbiology**

26 **Mechanism of Action**

27 Atazanavir is an azapeptide HIV-1 protease inhibitor. The compound selectively inhibits the
28 virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus
29 preventing formation of mature virions.

30 **Antiviral Activity *In Vitro***

31 Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC_{50}) in
32 the absence of human serum of 2 to 5 nM against a variety of laboratory and clinical HIV-1
33 isolates grown in peripheral blood mononuclear cells, macrophages, CEM-SS cells, and
34 MT-2 cells. Two-drug combination studies with atazanavir showed additive to antagonistic
35 antiviral activity *in vitro* with abacavir and the NNRTIs (delavirdine, efavirenz, and
36 nevirapine) and additive antiviral activity *in vitro* with the protease inhibitors (amprenavir,
37 indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir) and NRTIs (didanosine,
38 lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine) without enhanced cytotoxicity.

39 **Resistance *In Vitro***

40 HIV-1 isolates with reduced susceptibility to atazanavir (93- to 183-fold resistant) from three
41 different viral strains were selected *in vitro* by 5 months. The mutations in these HIV-1
42 viruses that appeared to contribute to atazanavir resistance included N88S, I50L, I84V,
43 A71V, and M46I. Changes were also observed at the protease cleavage sites following drug
44 selection. The I50L substitution, with or without an A71V substitution, conferred atazanavir
45 resistance in recombinant viral clones in a variety of genetic backgrounds. Recombinant
46 viruses containing the I50L mutation were growth impaired and showed increased
47 susceptibility to other protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir,
48 ritonavir, and saquinavir).

49 **Cross-Resistance *In Vitro***

50 Atazanavir susceptibility was evaluated *in vitro* using a diverse panel of 551 clinical isolates
51 from patients without prior atazanavir exposure. These isolates exhibited resistance to at least
52 one approved protease inhibitor, with resistance defined as ≥ 2.5 -fold change in EC_{50} relative
53 to a reference strain. Greater than 80% of the isolates resistant to 1 or 2 protease inhibitors

54 (with the majority resistant to nelfinavir) retained susceptibility to atazanavir despite the
55 presence of key mutations (eg, D30N) associated with protease inhibitor resistance. Of 104
56 isolates displaying nelfinavir-specific resistance, 84 retained susceptibility to atazanavir.
57 There was a clear trend toward decreased atazanavir susceptibility as isolates exhibited
58 resistance to multiple protease inhibitors. Baseline phenotypic and genotypic analyses of
59 clinical isolates from atazanavir clinical trials of protease inhibitor-experienced subjects
60 showed that isolates cross-resistant to multiple protease inhibitors were also highly cross-
61 resistant (61%-95%) to atazanavir. Greater than 90% of the isolates containing mutations
62 I84V or G48V were resistant to atazanavir. Greater than 60% of isolates containing L90M,
63 A71V/T, M46I, or a change at V82 were resistant to atazanavir, and 38% of isolates
64 containing a D30N mutation in addition to other changes were resistant to atazanavir.
65 Atazanavir-resistant isolates were highly cross-resistant (51%-100%) to other protease
66 inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). The I50L
67 and I50V substitutions yielded selective resistance to atazanavir and amprenavir,
68 respectively, and did not appear to confer cross-resistance.

69 **Resistance *In Vivo***

70 Atazanavir-resistant isolates have been obtained from patients experiencing virologic failure
71 on atazanavir therapy. There were 14 atazanavir-resistant isolates from studies of treatment-
72 naive patients (n=96 evaluable isolates) that showed decreases in susceptibility levels from
73 baseline, and all had an I50L substitution emerge on atazanavir therapy (after an average of
74 50 weeks of therapy) often in combination with an A71V mutation. Phenotypic analysis of
75 the isolates containing the signature mutation I50L showed atazanavir-specific resistance,
76 which coincided with increased susceptibility to other protease inhibitors (amprenavir,
77 indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). In contrast, 89% (32 of 36) of
78 atazanavir-resistant isolates from studies of treatment-experienced patients (n=67 evaluable
79 isolates) treated with atazanavir (n=26) or atazanavir plus saquinavir (n=10) showed no
80 evidence of the emergence of the I50L substitution. Instead, these isolates displayed
81 decreased susceptibility to multiple protease inhibitors and contained mutations associated
82 with resistance to multiple protease inhibitors. These mutations included I84V, L90M,
83 A71V/T, N88S/D, and M46I, which conferred atazanavir resistance and reduced the clinical
84 response to atazanavir. Generally, if protease inhibitor mutations were present in the HIV-1
85 of the patient at baseline, atazanavir resistance developed through mutations associated with
86 resistance to other protease inhibitors instead of the I50L mutation. These mutations
87 conferred high cross-resistance to other protease inhibitors with 100% of the isolates resistant
88 to nelfinavir, >80% of the isolates resistant to indinavir, ritonavir, and saquinavir, and >35%
89 of the isolates resistant to amprenavir and lopinavir. Genotypic and/or phenotypic analysis of

90 baseline virus may aid in determining atazanavir susceptibility before initiation of atazanavir
91 therapy.

92 **Pharmacokinetics**

93 The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-
94 infected patients (see Table 1).

Table 1: Steady-State Pharmacokinetics of Atazanavir in Healthy Subjects or HIV-Infected Patients in the Fed State After Atazanavir 400 mg Once Daily

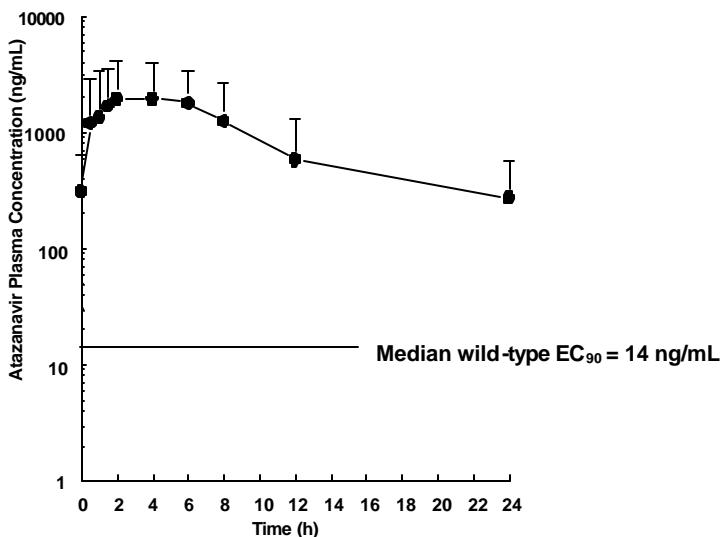
| Parameter | Healthy Subjects (n=14) | HIV-Infected Patients (n=13) |
|--------------------------|----------------------------|---------------------------------|
| C _{max} (ng/mL) | | |
| Geometric mean (CV%) | 5199 (26) | 2298 (71) |
| Mean (SD) | 5358 (1371) | 3152 (2231) |
| T _{max} (h) | | |
| Median | 2.5 | 2.0 |
| AUC (ng·h/mL) | | |
| Geometric mean (CV%) | 28132 (28) | 14874 (91) |
| Mean (SD) | 29303 (8263) | 22262 (20159) |
| T-half (h) | | |
| Mean (SD) | 7.9 (2.9) | 6.5 (2.6) |
| C _{min} (ng/mL) | | |
| Geometric mean (CV%) | 159 (88) | 120 (109) |
| Mean (SD) | 218 (191) | 273 (298) ^a |

^a n=12.

95

96 Figure 1 displays the mean plasma concentrations of atazanavir on Day 29 (steady
97 state) following REYATAZ 400 mg once daily (as two 200-mg capsules) with a light meal in
98 HIV-infected adult patients.

99 **Figure 1:** Mean (SD) Steady-State Plasma Concentrations of Atazanavir (400-mg
100 dose) for HIV-Infected Adult Patients (n=13)



101

102

103 **Absorption**

104 Atazanavir is rapidly absorbed with a T_{max} of approximately 2.5 hours. Atazanavir
105 demonstrates nonlinear pharmacokinetics with greater than dose-proportional increases in
106 AUC and C_{max} values over the dose range of 200-800 mg once daily. Steady-state is
107 achieved between Days 4 and 8, with an accumulation of approximately 2.3-fold.

108 **Food Effect**

109 Administration of REYATAZ with food enhances bioavailability and reduces
110 pharmacokinetic variability. Administration of a single 400-mg dose of REYATAZ with a
111 light meal (357 kcal, 8.2 g fat, 10.6 g protein) resulted in a 70% increase in AUC and 57%
112 increase in C_{max} relative to the fasting state. Administration of a single 400-mg dose of
113 REYATAZ with a high-fat meal (721 kcal, 37.3 g fat, 29.4 g protein) resulted in a mean
114 increase in AUC of 35% with no change in C_{max} relative to the fasting state. Administration
115 of REYATAZ with either a light meal or high-fat meal decreased the coefficient of variation
116 of AUC and C_{max} by approximately one half compared to the fasting state.

117 **Distribution**

118 Atazanavir is 86% bound to human serum proteins and protein binding is independent of
119 concentration. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a
120 similar extent (89% and 86%, respectively). In a multiple-dose study in HIV-infected patients
121 dosed with REYATAZ 400 mg once daily with a light meal for 12 weeks, atazanavir was
122 detected in the cerebrospinal fluid and semen. The cerebrospinal fluid/plasma ratio for
123 atazanavir (n=4) ranged between 0.0021 and 0.0226 and seminal fluid/plasma ratio (n=5)
124 ranged between 0.11 and 4.42.

125 **Metabolism**

126 Atazanavir is extensively metabolized in humans. The major biotransformation pathways of
127 atazanavir in humans consisted of monooxygenation and dioxygenation. Other minor
128 biotransformation pathways for atazanavir or its metabolites consisted of glucuronidation, N-
129 dealkylation, hydrolysis, and oxygenation with dehydrogenation. Two minor metabolites of
130 atazanavir in plasma have been characterized. Neither metabolite demonstrated *in vitro*
131 antiviral activity. *In vitro* studies using human liver microsomes suggested that atazanavir is
132 metabolized by CYP3A.

133 **Elimination**

134 Following a single 400-mg dose of ¹⁴C-atazanavir, 79% and 13% of the total radioactivity
135 was recovered in the feces and urine, respectively. Unchanged drug accounted for
136 approximately 20% and 7% of the administered dose in the feces and urine, respectively. The
137 mean elimination half-life of atazanavir in healthy volunteers (n=214) and HIV-infected
138 adult patients (n=13) was approximately 7 hours at steady state following a dose of 400 mg
139 daily with a light meal.

140 **Effects on Electrocardiogram**

141 Concentration- and dose-dependent prolongation of the PR interval in the electrocardiogram
142 has been observed in healthy volunteers receiving atazanavir. In a placebo-controlled study
143 (AI424-076), the mean (\pm SD) maximum change in PR interval from the predose value was
144 24 (\pm 15) msec following oral dosing with 400 mg of atazanavir (n=65) compared to 13 (\pm 11)
145 msec following dosing with placebo (n=67). The PR interval prolongations in this study were
146 asymptomatic. There is limited information on the potential for a pharmacodynamic
147 interaction in humans between atazanavir and other drugs that prolong the PR interval of the
148 electrocardiogram. (See **WARNINGS**.)

149 Electrocardiographic effects of atazanavir were determined in a clinical pharma-
150 cology study of 72 healthy subjects. Oral doses of 400 mg and 800 mg were compared with
151 placebo; there was no concentration-dependent effect of atazanavir on the QTc interval
152 (using Fridericia's correction). In 1793 HIV-infected patients receiving antiretroviral
153 regimens, QTc prolongation was comparable in the atazanavir and comparator regimens. No
154 atazanavir-treated healthy subject or HIV-infected patient had a QTc interval >500 msec.

155 **Special Populations**

156 **Age/Gender**

157 A study of the pharmacokinetics of atazanavir was performed in young (n=29; 18-40 years)
158 and elderly (n=30; ≥65 years) healthy subjects. There were no clinically important
159 pharmacokinetic differences observed due to age or gender.

160 **Race**

161 There are insufficient data to determine whether there are any effects of race on the
162 pharmacokinetics of atazanavir.

163 **Pediatrics**

164 The pharmacokinetics of atazanavir in pediatric patients are under investigation. There are
165 insufficient data at this time to recommend a dose.

166 **Impaired Renal Function**

167 In healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of
168 the administered dose. There are no pharmacokinetic data available on patients with
169 impaired renal function.

170 **Impaired Hepatic Function**

171 Atazanavir is metabolized and eliminated primarily by the liver. REYATAZ has been
172 studied in adult subjects with moderate to severe hepatic impairment (14 Child-Pugh B and 2
173 Child-Pugh C subjects) after a single 400-mg dose. The mean AUC(0-∞) was 42% greater in
174 subjects with impaired hepatic function than in healthy volunteers. The mean half-life of
175 atazanavir in hepatically impaired subjects was 12.1 hours compared to 6.4 hours in healthy
176 volunteers. Increased concentrations of atazanavir are expected in patients with moderately

177 or severely impaired hepatic function (see **PRECAUTIONS** and **DOSAGE AND**
178 **ADMINISTRATION**).

179 **Drug-Drug Interactions (see also CONTRAINDICATIONS,**
180 **WARNINGS, and PRECAUTIONS: Drug Interactions)**

181 Atazanavir is metabolized in the liver by CYP3A. Atazanavir inhibits CYP3A and UGT1A1
182 at clinically relevant concentrations with K_i of 2.35 μM (CYP3A4 isoform) and 1.9 μM ,
183 respectively. REYATAZ should not be administered concurrently with medications with
184 narrow therapeutic windows that are substrates of CYP3A or UGT1A1 (see
185 **CONTRAINDICATIONS**).

186 Atazanavir competitively inhibits CYP1A2 and CYP2C9 with K_i values of 12 μM
187 and a C_{\max}/K_i ratio of ~0.25. There is a potential drug-drug interaction between atazanavir
188 and CYP1A2 or CYP2C9 substrates. Atazanavir does not inhibit CYP2C19 or CYP2E1 at
189 clinically relevant concentrations.

190 Atazanavir has been shown *in vivo* not to induce its own metabolism, nor to increase
191 the biotransformation of some drugs metabolized by CYP3A. In a multiple-dose study,
192 REYATAZ decreased the urinary ratio of endogenous 6 β -OH cortisol to cortisol versus
193 baseline, indicating that CYP3A production was not induced.

194 Drugs that induce CYP3A activity may increase the clearance of atazanavir, resulting
195 in lowered plasma concentrations. Coadministration of REYATAZ and other drugs that
196 inhibit CYP3A may increase atazanavir plasma concentrations.

197 Drug interaction studies were performed with REYATAZ and other drugs likely to be
198 coadministered and some drugs commonly used as probes for pharmacokinetic interactions.
199 The effects of coadministration of REYATAZ on the AUC, C_{\max} , and C_{\min} are summarized
200 in Tables 2 and 3. For information regarding clinical recommendations, see
201 **PRECAUTIONS: Drug Interactions**, Tables 8 and 9.

202

Table 2: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs^a

| Coadministered Drug | Coadministered Drug Dose/Schedule | REYATAZ Dose/Schedule | n | Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00 | | |
|--|---|---|-----------------|---|-----------------------------------|-----------------------------------|
| | | | | C _{max} | AUC | C _{min} |
| atenolol | 50 mg QD, d 7-11 and d 19-23 | 400 mg QD, d 1-11 | 19 | 1.00 (0.89, 1.12) | 0.93 (0.85, 1.01) | 0.74 (0.65, 0.86) |
| clarithromycin | 500 mg QD, d 7-10 and d 18-21 | 400 mg QD, d 1-10 | 29 | 1.06 (0.93, 1.20) | 1.28 (1.16, 1.43) | 1.91 (1.66, 2.21) |
| didanosine (ddI) (buffered tablets) plus stavudine (d4T) ^b | ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose | 400 mg x 1 dose simultaneously with ddI and d4T | 32 ^c | 0.11 (0.06, 0.18) | 0.13 (0.08, 0.21) | 0.16 (0.10, 0.27) |
| diltiazem | ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose 180 mg QD, d 7-11 and d 19-23 | 400 mg x 1 dose 1 hour after ddI + d4T | 32 ^c | 1.12 (0.67, 1.18) | 1.03 (0.64, 1.67) | 1.03 (0.61, 1.73) |
| efavirenz | 600 mg QD, d 7-20 | 400 mg QD, d 1-20 | 27 | 0.41 (0.33, 0.51) | 0.26 (0.22, 0.32) | 0.07 (0.05, 0.10) |
| | 600 mg QD, d 7-20 | 400 mg QD, d 1-6 then 300 mg/ritonavir 100 mg QD, 2 h before efavirenz, d 7-20 | 13 | 1.14 (0.83, 1.58) | 1.39 (1.02, 1.88) | 1.48 (1.24, 1.76) |
| ketoconazole | 200 mg QD, d 7-13 | 400 mg QD, d 1-13 | 14 | 0.99 (0.77, 1.28) | 1.10 (0.89, 1.37) | 1.03 (0.53, 2.01) |
| rifabutin | 150 mg QD, d 15-28 | 400 mg QD, d 1-28 | 7 | 1.34 (1.14, 1.59) | 1.15 (0.98, 1.34) | 1.13 (0.68, 1.87) |
| ritonavir ^d | 100 mg QD, d 11-20 | 300 mg QD, d 1-20 | 28 | 1.86 (1.69, 2.05) | 3.38 (3.13, 3.63) | 11.89 (10.23, 13.82) |
| tenofovir ^e | 300 mg QD, d 9-16 | 400 mg QD, d 2-16 | 34 | 0.79 (0.73, 0.86) | 0.75 (0.70, 0.81) | 0.60 (0.52, 0.68) |
| | 300 mg QD, d 15-42 | 300 mg/ritonavir 100 mg QD, d 1-42 | 10 | 0.72 ^f (0.50, 1.05) | 0.75 ^f (0.58, 0.97) | 0.77 ^f (0.54, 1.10) |

^a Data provided are under fed conditions unless otherwise noted.

^b All drugs were given under fasted conditions.

^c One subject did not receive REYATAZ.

^d Compared with atazanavir 400 mg QD historical data, administration of atazanavir/ritonavir 300/100 mg QD increased the atazanavir geometric mean values of C_{max}, AUC, and C_{min} by 18%, 103%, and 671%, respectively. The geometric mean values of atazanavir pharmacokinetic parameters when coadministered with ritonavir were: C_{max} = 6129 ng/mL, AUC = 57039 ng·h/mL, and C_{min} = 1227 ng/mL.

^e tenofovir disoproxil fumarate.

^f Ratio of atazanavir plus ritonavir plus tenofovir to atazanavir plus ritonavir. Atazanavir 300 mg plus ritonavir 100 mg results in higher atazanavir exposure than atazanavir 400 mg (see footnote d). The geometric mean values of atazanavir pharmacokinetic parameters when coadministered with ritonavir and tenofovir were: C_{max} = 3190 ng/mL, AUC = 34459 ng·h/mL, and C_{min} = 491 ng/mL.

Table 3: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of REYATAZ^a

| Coadministered Drug | Coadministered Drug Dose/Schedule | REYATAZ Dose/Schedule | n | Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without REYATAZ; No effect = 1.00 | | |
|--|---|---|-----------------|--|--|--|
| | | | | C _{max} | AUC | C _{min} |
| atenolol | 50 mg QD, d 7-11 and d 19-23 | 400 mg QD, d 1-11 | 19 | 1.34 (1.26, 1.42) | 1.25 (1.16, 1.34) | 1.02 (0.88, 1.19) |
| clarithromycin | 500 mg QD, d 7-10 and d 18-21 | 400 mg QD, d 1-10 | 21 | 1.50 (1.32, 1.71) OH- clarithromycin: 0.28 (0.24, 0.33) | 1.94 (1.75, 2.16) OH- clarithromycin: 0.30 (0.26, 0.34) | 0.38 (0.35, 0.43) OH- clarithromycin: 2.64 (2.36, 2.94) |
| didanosine (ddI) (buffered tablets) plus stavudine (d4T) ^b | ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose | 400 mg x 1 dose simultaneous with ddI and d4T | 32 ^c | ddI: 0.92 (0.84, 1.02) d4T: 1.08 (0.96, 1.22) | ddI: 0.98 (0.92, 1.05) d4T: 1.00 (0.97, 1.03) | NA d4T: 1.04 (0.94, 1.16) |
| diltiazem | 180 mg QD, d 7-11 and d 19- 23 | 400 mg QD, d 1-11 | 28 | 1.98 (1.78, 2.19) desacetyl- diltiazem: 2.72 (2.44, 3.03) | 2.25 (2.09, 2.16) desacetyl- diltiazem: 2.65 (2.45, 2.87) | 0.41 (0.37, 0.47) desacetyl- diltiazem: 0.45 (0.41, 0.49) |
| ethinyl estradiol & norethindrone | Ortho-Novum® 7/7/7 QD, d 1-29 | 400 mg QD, d 16-29 | 19 | ethinyl estradiol: 1.15 (0.99, 1.32) norethindrone: 1.67 (1.42, 1.96) | ethinyl estradiol: 1.48 (1.31, 1.68) norethindrone: 2.10 (1.68, 2.62) | ethinyl estradiol: 1.91 (1.57, 2.33) norethindrone: 3.62 (2.57, 5.09) |
| rifabutin | 300 mg QD, d 1-10 then 150 mg QD, d 11-20 | 600 mg QD ^d , d 11-20 | 3 | 1.18 (0.94, 1.48) 25-O-desacetyl- rifabutin: 8.20 (5.90, 11.40) | 2.10 (1.57, 2.79) 25-O-desacetyl- rifabutin: 22.01 (15.97, 30.34) | 3.43 (1.98, 5.96) 25-O-desacetyl- rifabutin: 75.6 (30.1, 190.0) |
| saquinavir (soft gelatin capsules) ^e | 1200 mg QD, d 1-13 | 400 mg QD, d 7-13 | 7 | 4.39 (3.24, 5.95) | 5.49 (4.04, 7.47) | 6.86 (5.29, 8.91) |
| tenofovir ^f | 300 mg QD, d 9- 16 and d 24-30 | 400 mg QD, d 2-16 | 33 | 1.14 (1.08, 1.20) | 1.24 (1.21, 1.28) | 1.22 (1.15, 1.30) |
| lamivudine + zidovudine | 150 mg lamivudine + 300 mg zidovudine BID, d 1-12 | 400 mg QD, d 7-12 | 19 | lamivudine: 1.04 (0.92, 1.16) zidovudine: 1.05 (0.88, 1.24) zidovudine glucuronide: 0.95 (0.88, 1.02) | lamivudine: 1.03 (0.98, 1.08) zidovudine: 1.05 (0.96, 1.14) zidovudine glucuronide: 1.00 (0.97, 1.03) | lamivudine: 1.12 (1.04, 1.21) zidovudine: 0.69 (0.57, 0.84) zidovudine glucuronide: 0.82 (0.62, 1.08) |

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- ^a Data provided are under fed conditions unless otherwise noted.
 - ^b All drugs were given under fasted conditions.
 - ^c One subject did not receive REYATAZ.
 - ^d Not the recommended therapeutic dose of atazanavir.
 - ^e The combination of atazanavir and saquinavir 1200 mg QD produced daily saquinavir exposures similar to the values produced by the standard therapeutic dosing of saquinavir at 1200 mg TID. However, the C_{max} is about 79% higher than that for the standard dosing of saquinavir (soft gelatin capsules) alone at 1200 mg TID.
 - ^f tenofovir disoproxil fumarate.

NA = not available.

203

204 INDICATIONS AND USAGE

205 REYATAZ is indicated in combination with other antiretroviral agents for the treatment of
206 HIV–1 infection.

207 This indication is based on analyses of plasma HIV–1 RNA levels and CD4 cell
208 counts from controlled studies of 48 weeks duration in antiretroviral-naïve patients and a
209 controlled study of 24 weeks duration in antiretroviral-treatment-experienced patients.

210 In antiretroviral-treatment-experienced patients, the use of REYATAZ may be
211 considered for adults with HIV strains that are expected to be susceptible to REYATAZ as
212 assessed by genotypic and/or phenotypic testing. (See **CLINICAL PHARMACOLOGY:**
213 **Microbiology and Description of Clinical Studies.**)

214 Description of Clinical Studies

215 Patients Without Prior Antiretroviral Therapy

216 *Study AI424-034: REYATAZ once daily compared to efavirenz once daily, each in
217 combination with fixed-dose lamivudine + zidovudine twice daily.* Study AI424-034 was a
218 randomized, double-blind, multicenter trial comparing REYATAZ (400 mg once daily) to
219 efavirenz (600 mg once daily), each in combination with a fixed-dose combination of
220 lamivudine (3TC) (150 mg) and zidovudine (ZDV) (300 mg) given twice daily, in 810
221 antiretroviral treatment-naïve patients. Patients had a mean age of 34 years (range: 18 to 73),
222 36% were Hispanic, 33% were Caucasian, and 65% were male. The mean baseline CD4 cell
223 count was 321 cells/mm³ (range: 64 to 1424 cells/mm³) and the mean baseline plasma HIV–1
224 RNA level was 4.8 log₁₀ copies/mL (range: 2.2 to 5.9 log₁₀ copies/mL). Treatment response
225 and outcomes through Week 48 are presented in Table 4.

226

**Table 4: Outcomes of Randomized Treatment Through Week 48
(Study AI424-034)**

| Outcome | REYATAZ 400 mg once daily + lamivudine + zidovudine ^d (n=405) | efavirenz 600 mg once daily + lamivudine + zidovudine ^d (n=405) |
|---|--|--|
| Responder ^a | 67% (32%) | 62% (37%) |
| Virologic failure ^b | 20% | 21% |
| Rebound | 17% | 16% |
| Never suppressed through Week 48 | 3% | 5% |
| Death | — | <1% |
| Discontinued due to adverse event | 5% | 7% |
| Discontinued for other reasons ^c | 8% | 10% |

^a Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48. Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.0 or 1.5 as geographically appropriate.

^b Includes confirmed viral rebound and failure to achieve confirmed HIV RNA <400 copies/mL through Week 48.

^c Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.

^d As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

227

228 Through 48 weeks of therapy, the proportion of responders among patients with high viral
229 loads (ie, baseline HIV RNA \geq 100,000 copies/mL) was comparable for the REYATAZ and
230 efavirenz arms. The mean increase from baseline in CD4 cell count was 176 cells/mm³ for the
231 REYATAZ arm and 160 cells/mm³ for the efavirenz arm.

232 *Study AI424-008: REYATAZ 400 mg once daily compared to REYATAZ 600 mg once daily,
233 and compared to nelfinavir 1250 mg twice daily, each in combination with stavudine and
234 lamivudine twice daily.* Study AI424-008 was a 48-week, randomized, multicenter trial,
235 blinded to dose of REYATAZ, comparing REYATAZ at two dose levels (400 mg and 600
236 mg once daily) to nelfinavir (1250 mg twice daily), each in combination with stavudine (40
237 mg) and lamivudine (150 mg) given twice daily, in 467 antiretroviral treatment-naïve
238 patients. Patients had a mean age of 35 years (range: 18 to 69), 55% were Caucasian, and
239 63% were male. The mean baseline CD4 cell count was 295 cells/mm³ (range: 4 to 1003
240 cells/mm³) and the mean baseline plasma HIV-1 RNA level was 4.7 log₁₀ copies/mL (range:
241 1.8 to 5.9 log₁₀ copies/mL). Treatment response and outcomes through Week 48 are
242 presented in Table 5.

Table 5: Outcomes of Randomized Treatment Through Week 48 (Study AI424-008)

| Outcome | REYATAZ 400 mg once daily + lamivudine + stavudine (n=181) | nelfinavir 1250 mg twice daily + lamivudine + stavudine (n=91) |
|---|---|---|
| Responder ^a | 67% (33%) | 59% (38%) |
| Virologic failure ^b | 24% | 27% |
| Rebound | 14% | 14% |
| Never suppressed through Week 48 | 10% | 13% |
| Death | <1% | — |
| Discontinued due to adverse event | 1% | 3% |
| Discontinued for other reasons ^c | 7% | 10% |

^a Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48. Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.0 or 1.5 as geographically appropriate.

^b Includes confirmed viral rebound and failure to achieve confirmed HIV RNA <400 copies/mL through Week 48.

^c Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.

243

244 Through 48 weeks of therapy, the mean increase from baseline in CD4 cell count was
245 234 cells/mm³ for the REYATAZ 400-mg arm and 211 cells/mm³ for the nelfinavir arm.

246 **Patients With Prior Antiretroviral Therapy**

247 *Study AI424-043: REYATAZ once daily compared to lopinavir + ritonavir twice daily, each*
248 *in combination with two nucleosides.* Study AI424-043 is an ongoing, randomized, open-
249 label, multicenter trial comparing REYATAZ (400 mg once daily) to lopinavir + ritonavir
250 (400/100 mg twice daily), each in combination with two NRTIs, in 300 patients who
251 experienced virologic failure to only one prior PI-containing regimen. For the 229 patients
252 who have been assessed for efficacy, the mean time of prior exposure to antiretrovirals was
253 140 weeks for PIs, 180 weeks for NRTIs, and 85 weeks for NNRTIs (13% of patients). The
254 mean age was 38 years (range: 23 to 64); 53% were Hispanic, 41% were Caucasian, and 81%
255 were male. The mean baseline CD4 cell count was 318 cells/mm³ (range: 18 to 1118
256 cells/mm³) and the mean baseline plasma HIV-1 RNA level was 4.17 log₁₀ copies/mL
257 (range: 2.60 to 5.87 log₁₀ copies/mL). Treatment response and outcomes through Week 24
258 are presented in Table 6.

259

Table 6: Outcomes of Treatment Through 24 Weeks in Study AI424-043 (Patients with Prior Antiretroviral Experience)

| Outcome | REYATAZ 400 mg once daily + 2 NRTIs (n=114) | lopinavir + ritonavir (400/100 mg) twice daily + 2 NRTIs (n=115) |
|---|--|---|
| Percent of Randomized Patients Responding | | |
| HIV RNA <400 copies/mL ^{a,b} | 54% | 75% |
| HIV RNA <50 copies/mL ^{a,b} | 34% | 50% |
| HIV RNA Mean Change from Baseline (log ₁₀ copies/mL) ^{b,c} | -1.73 | -2.16 |
| CD4 Mean Change from Baseline (cells/mm ³) ^d | 101 | 121 |

^a Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 24.

^b Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.5.

^c Protocol-defined co-primary efficacy outcome measure: time -averaged difference = 0.31. Based on patients with baseline and Week 24 HIV RNA measurements (REYATAZ, n=95; lopinavir + ritonavir, n=102).

^d Based on patients with baseline and Week 24 CD4 cell count measurements (REYATAZ, n=92; lopinavir + ritonavir, n=100).

260

261 Study AI424-043 also compared changes from baseline in LDL-cholesterol (see
262 **ADVERSE REACTIONS**, Table 14).

263 **CONTRAINDICATIONS**

264 REYATAZ is contraindicated in patients with known hypersensitivity to any of its
265 ingredients, including atazanavir.

266 Coadministration of REYATAZ is contraindicated with drugs that are highly
267 dependent on CYP3A for clearance and for which elevated plasma concentrations are
268 associated with serious and/or life-threatening events. These drugs are listed in Table 7.

Table 7: Drugs That Are Contraindicated with REYATAZ Due to Potential CYP450-Mediated Interactions*

| Drug class | Drugs within class that are contraindicated with REYATAZ |
|-------------------|---|
| Benzodiazepines | midazolam, triazolam |
| Ergot Derivatives | dihydroergotamine, ergotamine, ergonovine, methylergonovine |
| GI Motility Agent | cisapride |
| Neuroleptic | pimozide |

*Please see Table 8 for additional drugs that should not be coadministered with REYATAZ.

269

270 **WARNINGS**

271 **ALERT: Find out about medicines that should NOT be taken with REYATAZ.** This
272 statement is included on the product's bottle label. (See **CONTRAINDICATIONS**,
273 **WARNINGS: Drug Interactions**, and **PRECAUTIONS: Drug Interactions**.)

274 **Drug Interactions**

275 Atazanavir is an inhibitor of CYP3A and UGT1A1. Coadministration of REYATAZ and
276 drugs primarily metabolized by CYP3A [eg, calcium channel blockers, HMG-CoA reductase
277 inhibitors, immunosuppressants, and phosphodiesterase (PDE5) inhibitors] or UGT1A1 (eg,
278 irinotecan) may result in increased plasma concentrations of the other drug that could
279 increase or prolong its therapeutic and adverse effects. (Also see **PRECAUTIONS: Drug**
280 **Interactions**, Tables 8 and 9.)

281 Particular caution should be used when prescribing PDE5 inhibitors for erectile
282 dysfunction (eg, sildenafil, tadalafil, or vardenafil) for patients receiving protease inhibitors,
283 including REYATAZ. Coadministration of a protease inhibitor with a PDE5 inhibitor is
284 expected to substantially increase the PDE5 inhibitor concentration and may result in an
285 increase in PDE5 inhibitor-associated adverse events, including hypotension, visual changes,
286 and priapism. (See **PRECAUTIONS: Drug Interactions** and **Information for Patients**,
287 and the complete prescribing information for the PDE5 inhibitor.)

288 Concomitant use of REYATAZ with lovastatin or simvastatin is not recommended.
289 Caution should be exercised if HIV protease inhibitors, including REYATAZ, are used
290 concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the
291 CYP3A pathway (eg, atorvastatin). The risk of myopathy, including rhabdomyolysis, may
292 be increased when HIV protease inhibitors, including REYATAZ, are used in combination
293 with these drugs.

294 Concomitant use of REYATAZ and St. John's wort (*Hypericum perforatum*), or
295 products containing St. John's wort, is not recommended. Coadministration of protease
296 inhibitors, including REYATAZ, with St. John's wort is expected to substantially decrease
297 concentrations of the protease inhibitor and may result in suboptimal levels of atazanavir and
298 lead to loss of virologic response and possible resistance to atazanavir or to the class of
299 protease inhibitors.

300 **PR Interval Prolongation**

301 Atazanavir has been shown to prolong the PR interval of the electrocardiogram in some
302 patients. In healthy volunteers and in patients, abnormalities in atrioventricular (AV)
303 conduction were asymptomatic and limited to first-degree AV block with rare exceptions
304 (see **OVERDOSAGE**). In clinical trials, asymptomatic first-degree AV block was observed
305 in 5.9% of atazanavir-treated patients (n=920), 5.2% of lopinavir/ritonavir-treated patients
306 (n=252), 10.4% of nelfinavir-treated patients (n=48), and in 3.0% of efavirenz-treated
307 patients (n=329). There has been no second- or third-degree AV block. Because of limited
308 clinical experience, atazanavir should be used with caution in patients with preexisting
309 conduction system disease (eg, marked first-degree AV block or second- or third-degree AV
310 block). (See **CLINICAL PHARMACOLOGY: Effects on Electrocardiogram**.)

311 In a pharmacokinetic study between atazanavir 400 mg once daily and diltiazem 180
312 mg once daily, a CYP3A substrate, there was a 2-fold increase in the diltiazem plasma
313 concentration and an additive effect on the PR interval. When used in combination with
314 atazanavir, a dose reduction of diltiazem by one half should be considered and ECG
315 monitoring is recommended. In a pharmacokinetic study between atazanavir 400 mg once
316 daily and atenolol 50 mg once daily, there was no substantial additive effect of atazanavir
317 and atenolol on the PR interval. When used in combination with atazanavir, there is no need
318 to adjust the dose of atenolol. (See **PRECAUTIONS: Drug Interactions**.)

319 Pharmacokinetic studies between atazanavir and other drugs that prolong the PR
320 interval including beta blockers (other than atenolol), verapamil, and digoxin have not been
321 performed. An additive effect of atazanavir and these drugs cannot be excluded; therefore,
322 caution should be exercised when atazanavir is given concurrently with these drugs,
323 especially those that are metabolized by CYP3A (eg, verapamil). (See **PRECAUTIONS:**
324 **Drug Interactions**.)

325 **Diabetes Mellitus/Hyperglycemia**

326 New-onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, and
327 hyperglycemia have been reported during postmarketing surveillance in HIV-infected
328 patients receiving protease inhibitor therapy. Some patients required either initiation or dose
329 adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some
330 cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease
331 inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been
332 reported voluntarily during clinical practice, estimates of frequency cannot be made and a

333 causal relationship between protease inhibitor therapy and these events has not been
334 established.

335 **PRECAUTIONS**

336 **General**

337 **Hyperbilirubinemia**

338 Most patients taking REYATAZ experience asymptomatic elevations in indirect
339 (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT). This
340 hyperbilirubinemia is reversible upon discontinuation of REYATAZ. Hepatic transaminase
341 elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies.
342 No long-term safety data are available for patients experiencing persistent elevations in total
343 bilirubin >5 times ULN. Alternative antiretroviral therapy to REYATAZ may be considered
344 if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns
345 for patients. Dose reduction of atazanavir is not recommended since long-term efficacy of
346 reduced doses has not been established. (See **ADVERSE REACTIONS: Laboratory**
347 **Abnormalities**, Tables 11 and 13.)

348 **Hepatic Impairment and Toxicity**

349 Atazanavir is principally metabolized by the liver; caution should be exercised when
350 administering this drug to patients with hepatic impairment because atazanavir
351 concentrations may be increased (see **DOSAGE AND ADMINISTRATION**). Patients with
352 underlying hepatitis B or C viral infections or marked elevations in transaminases prior to
353 treatment may be at increased risk for developing further transaminase elevations or hepatic
354 decompensation.

355 **Resistance/Cross-Resistance**

356 Various degrees of cross-resistance among protease inhibitors have been observed.
357 Resistance to atazanavir may not preclude the subsequent use of other protease inhibitors.
358 (See **CLINICAL PHARMACOLOGY: Microbiology**.)

359 **Hemophilia**

360 There have been reports of increased bleeding, including spontaneous skin hematomas and
361 hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In

362 some patients additional factor VIII was given. In more than half of the reported cases,
363 treatment with protease inhibitors was continued or reintroduced. A causal relationship
364 between protease inhibitor therapy and these events has not been established.

365 **Lactic Acidosis Syndrome**

366 Cases of lactic acidosis syndrome (LAS), sometimes fatal, and symptomatic hyperlactatemia
367 have been reported in patients receiving REYATAZ in combination with nucleoside
368 analogues, which are known to be associated with increased risk of LAS. Female gender and
369 obesity are also known risk factors for LAS. The contribution of REYATAZ to the risk of
370 development of LAS has not been established.

371 **Fat Redistribution**

372 Redistribution/accumulation of body fat including central obesity, dorsocervical fat
373 enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and
374 "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The
375 mechanism and long-term consequences of these events are currently unknown. A causal
376 relationship has not been established.

377 **Information for Patients**

378 A statement to patients and healthcare providers is included on the product's bottle label:
379 **ALERT: Find out about medicines that should NOT be taken with REYATAZ** A
380 Patient Package Insert (PPI) for REYATAZ is available for patient information.

381 Patients should be told that sustained decreases in plasma HIV RNA have been
382 associated with a reduced risk of progression to AIDS and death. Patients should remain
383 under the care of a physician while using REYATAZ. Patients should be advised to take
384 REYATAZ with food every day and take other concomitant antiretroviral therapy as
385 prescribed. REYATAZ must always be used in combination with other antiretroviral drugs.
386 Patients should not alter the dose or discontinue therapy without consulting with their doctor.
387 If a dose of REYATAZ is missed, patients should take the dose as soon as possible and then
388 return to their normal schedule. However, if a dose is skipped the patient should not double
389 the next dose.

390 Patients should be informed that REYATAZ is not a cure for HIV infection and that
391 they may continue to develop opportunistic infections and other complications associated
392 with HIV disease. Patients should be told that there are currently no data demonstrating that

393 therapy with REYATAZ can reduce the risk of transmitting HIV to others through sexual
394 contact.

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

398 Patients receiving a PDE5 inhibitor and atazanavir should be advised that they may
399 be at an increased risk of a PDE5 inhibitor-associated adverse events including hypotension,
400 visual changes, and prolonged penile erection, and should promptly report any symptoms to
401 their doctor.

402 Patients should be informed that atazanavir may produce changes in the
403 electrocardiogram (PR prolongation). Patients should consult their physician if they are
404 experiencing symptoms such as dizziness or lightheadedness.

405 REYATAZ should be taken with food to enhance absorption.

406 Patients should be informed that asymptomatic elevations in indirect bilirubin have
407 occurred in patients receiving REYATAZ. This may be accompanied by yellowing of the
408 skin or whites of the eyes and alternative antiretroviral therapy may be considered if the
409 patient has cosmetic concerns.

410 Patients should be informed that redistribution or accumulation of body fat may occur
411 in patients receiving antiretroviral therapy including protease inhibitors and that the cause
412 and long-term health effects of these conditions are not known at this time. It is unknown
413 whether long-term use of REYATAZ will result in a lower incidence of lipodystrophy than
414 with other protease inhibitors.

415 **Drug Interactions**

416 Atazanavir is an inhibitor of CYP3A and UGT1A1. Coadministration of REYATAZ and
417 drugs primarily metabolized by CYP3A (eg, calcium channel blockers, HMG-CoA reductase
418 inhibitors, immunosuppressants, and PDE5 inhibitors) or UGT1A1 (eg, irinotecan) may
419 result in increased plasma concentrations of the other drug that could increase or prolong
420 both its therapeutic and adverse effects (see Tables 8 and 9). Atazanavir is metabolized in the
421 liver by the cytochrome P450 enzyme system. Coadministration of REYATAZ and drugs
422 that induce CYP3A, such as rifampin, may decrease atazanavir plasma concentrations and

423 reduce its therapeutic effect. Coadministration of REYATAZ and drugs that inhibit CYP3A
424 may increase atazanavir plasma concentrations.

425 Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of
426 atazanavir are expected if antacids, buffered medications, H₂-receptor antagonists, and
427 proton-pump inhibitors are administrated with atazanavir.

428 Atazanavir has the potential to prolong the PR interval of the electrocardiogram in
429 some patients. Caution should be used when coadministering REYATAZ with medicinal
430 products known to induce PR interval prolongation (eg, atenolol, diltiazem [see Table 9]).

431 Drugs that are contraindicated or not recommended for coadministration with
432 REYATAZ are included in Table 8. These recommendations are based on either drug
433 interaction studies or predicted interactions due to the expected magnitude of interaction and
434 potential for serious events or loss of efficacy.

Table 8: Drugs That Should Not Be Administered with REYATAZ

| Drug class: Specific Drugs | Clinical Comment |
|---|---|
| Antimycobacterials: rifampin | Decreases plasma concentrations and AUC of most protease inhibitors by about 90%. This may result in loss of therapeutic effect and development of resistance. |
| Antineoplastics: irinotecan | Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities. |
| Benzodiazepines: midazolam, triazolam | CONTRAINDED due to potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression. |
| Calcium Channel Blockers: bepridil | Potential for serious and/or life-threatening adverse events. |
| Ergot Derivatives: dihydroergotamine, ergotamine, ergonovine, methylergonovine | CONTRAINDED due to potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues. |
| GI Motility Agent: cisapride | CONTRAINDED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias. |
| HMG-CoA Reductase Inhibitors: lovastatin, simvastatin | Potential for serious reactions such as myopathy including rhabdomyolysis. |
| Neuroleptic: pimozide | CONTRAINDED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias. |
| Protease Inhibitors: indinavir | Both REYATAZ and indinavir are associated with indirect (unconjugated) hyperbilirubinemia. Combinations of these drugs have not been studied and coadministration of REYATAZ and indinavir is not recommended. |
| Proton-Pump Inhibitors | Concomitant use of REYATAZ and proton-pump inhibitors is not recommended. Coadministration of REYATAZ with proton-pump inhibitors is expected to substantially decrease REYATAZ plasma concentrations and reduce its therapeutic effect. |
| Herbal Products: St. John's wort (<i>Hypericum perforatum</i>) | Patients taking REYATAZ should not use products containing St. John's wort (<i>Hypericum perforatum</i>) because coadministration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance. |

**Table 9: Established and Other Potentially Significant Drug Interactions:
Alteration in Dose or Regimen May Be Recommended Based on Drug
Interaction Studies or Predicted Interactions^a**

| Concomitant Drug Class: Specific Drugs | Effect on Concentration of Atazanavir or Concomitant Drug | Clinical Comment |
|---|--|---|
| HIV Antiviral Agents | | |
| Nucleoside Reverse Transcriptase Inhibitors (NRTIs): didanosine buffered formulations | ↓ atazanavir | Coadministration of REYATAZ with didanosine buffered tablets did not alter exposure to didanosine; however, exposure to atazanavir was markedly decreased (presumably due to the increase in gastric pH caused by buffers in the didanosine tablets). In addition, it is recommended that didanosine be administered on an empty stomach; therefore, REYATAZ should be given (with food) 2 h before or 1 h after didanosine buffered formulations (see CLINICAL PHARMACOLOGY: Drug-Drug Interactions). Because didanosine EC capsules are to be given on an empty stomach and REYATAZ is to be given with food, they should be administered at different times. |
| Nucleotide Reverse Transcriptase Inhibitors: tenofovir disoproxil fumarate | ↓ atazanavir ↑ tenofovir | Tenofovir may decrease the AUC and C _{max} of atazanavir. When coadministered with tenofovir, it is recommended that REYATAZ 300 mg be given with ritonavir 100 mg and tenofovir 300 mg (all as a single daily dose with food). REYATAZ without ritonavir should not be coadministered with tenofovir. REYATAZ increases tenofovir concentrations. The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving REYATAZ and tenofovir should be monitored for tenofovir-associated adverse events. |
| Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs): efavirenz | ↓ atazanavir | If REYATAZ is to be coadministered with efavirenz, which decreases atazanavir exposure, it is recommended that REYATAZ 300 mg with ritonavir 100 mg be coadministered with efavirenz 600 mg (all as a single daily dose with food), as this combination results in atazanavir exposure that approximates the mean exposure to atazanavir produced by 400 mg of REYATAZ alone. REYATAZ without ritonavir should not be coadministered with efavirenz. |
| Protease Inhibitors: saquinavir (soft gelatin capsules) | ↑ saquinavir | Appropriate dosing recommendations for this combination, with respect to efficacy and safety, have not been established. |
| Protease Inhibitors: ritonavir | ↑ atazanavir | Coadministration of REYATAZ and ritonavir is currently under clinical investigation. If REYATAZ is coadministered with ritonavir, it is recommended that REYATAZ 300 mg once daily be given with ritonavir 100 mg once daily with food. |
| Other Agents | | |
| Antacids and buffered medications | ↓ atazanavir | Reduced plasma concentrations of atazanavir are expected if antacids, including buffered medications, are administered with REYATAZ. REYATAZ should be administered 2 h before or 1 h after these medications. |
| Antiarrhythmics: amiodarone, lidocaine (systemic), quinidine | ↑ amiodarone, lidocaine (systemic), quinidine | Coadministration with REYATAZ has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with REYATAZ. |
| Anticoagulants: warfarin | ↑ warfarin | Coadministration with REYATAZ has the potential to produce serious and/or life-threatening bleeding and has not been studied. It is recommended that INR (International Normalized Ratio) be monitored. |
| Antidepressants: tricyclic antidepressants | ↑ tricyclic antidepressants | Coadministration with REYATAZ has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with REYATAZ. |
| Antimycobacterials: rifabutin | ↑ rifabutin | A rifabutin dose reduction of up to 75% (eg, 150 mg every other day or 3 times per week) is recommended. |
| Calcium channel blockers: diltiazem | ↑ diltiazem and desacetyl-diltiazem | Caution is warranted. A dose reduction of diltiazem by 50% should be considered. ECG monitoring is recommended. |
| eg, felodipine, nifedipine, nicardipine, and verapamil | ↑ calcium channel blocker | Caution is warranted. Dose titration of the calcium channel blocker should be considered. ECG monitoring is recommended. |

| | | |
|--|--|---|
| HMG-CoA reductase inhibitors: atorvastatin | ↑ atorvastatin | The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including REYATAZ, are used in combination with atorvastatin. Caution should be exercised. |
| H ₂ -Receptor antagonists | ↓ atazanavir | Reduced plasma concentrations of atazanavir are expected if H ₂ -receptor antagonists are administered with REYATAZ. This may result in loss of therapeutic effect and development of resistance. To lessen the effect of H ₂ -receptor antagonists on atazanavir exposure, it is recommended that an H ₂ -receptor antagonist and REYATAZ be administered as far apart as possible, preferably 12 hours apart. |
| Immunosuppressants: cyclosporin, sirolimus, tacrolimus | ↑ immunosuppressants | Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with REYATAZ. |
| Macrolide antibiotics: clarithromycin | ↑ clarithromycin ↓ 14-OH clarithromycin ↑ atazanavir | Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a dose reduction of clarithromycin by 50% should be considered when it is coadministered with REYATAZ. In addition, concentrations of the active metabolite 14-OH clarithromycin are significantly reduced; consider alternative therapy for indications other than infections due to <i>Mycobacterium avium</i> complex. |
| Oral contraceptives: ethinyl estradiol and norethindrone | ↑ ethinyl estradiol ↑ norethindrone | Mean concentrations of ethinyl estradiol, when coadministered as a 35-µg dose with REYATAZ, are increased to a level between mean concentrations produced by a 35-µg and a 50-µg ethinyl estradiol dose. Decreased HDL or increased insulin resistance may be associated with increased mean concentrations of norethindrone, when coadministered with REYATAZ, particularly in diabetic women. Caution should be exercised. It is recommended that the lowest effective dose of each oral contraceptive component be used. |
| PDE5 inhibitors: sildenafil tadalafil vardenafil | ↑ sildenafil ↑ tadalafil ↑ vardenafil | Coadministration with REYATAZ has not been studied but may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, visual changes, and priapism. Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Use tadalafil with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events. |

^a For magnitude of interactions see CLINICAL PHARMACOLOGY: Tables 2 and 3.

436

437 Based on known metabolic profiles, clinically significant drug interactions are not
 438 expected between REYATAZ and fluvastatin, pravastatin, dapsone, trimethoprim/sulfa-
 439 methoxazole, azithromycin, erythromycin, itraconazole, or fluconazole. REYATAZ does not
 440 interact with substrates of CYP2D6 (eg, nortriptyline, desipramine, metoprolol).

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

442 Long-term carcinogenicity studies of atazanavir in animals have not been completed.
 443 Atazanavir tested positive in an *in vitro* clastogenicity test using primary human
 444 lymphocytes, in the absence and presence of metabolic activation. Atazanavir tested
 445 negative in the *in vitro* Ames reverse-mutation assay, *in vivo* micronucleus and DNA repair
 446 tests in rats, and *in vivo* DNA damage test in rat duodenum (comet assay).

447 At the systemic drug exposure levels (AUC) equal to (in male rats) or two times (in
 448 female rats) those at the human clinical dose (400 mg once daily), atazanavir did not produce
 449 significant effects on mating, fertility, or early embryonic development.

450 **Pregnancy**

451 **Pregnancy Category B**

452 At maternal doses producing the systemic drug exposure levels equal to (in rabbits) or two
453 times (in rats) those at the human clinical dose (400 mg once daily), atazanavir did not
454 produce teratogenic effects. In the pre- and post-natal development assessment in rats,
455 atazanavir, at maternally toxic drug exposure levels two times those at the human clinical
456 dose, caused body weight loss or weight gain suppression in the offspring. Offspring were
457 unaffected at a lower dose that produced maternal exposure equivalent to that observed in
458 humans given 400 mg once daily.

459 Hyperbilirubinemia occurred frequently during treatment with REYATAZ. It is not
460 known whether REYATAZ administered to the mother during pregnancy will exacerbate
461 physiological hyperbilirubinemia and lead to kernicterus in neonates and young infants. In
462 the prepartum period, additional monitoring and alternative therapy to REYATAZ should be
463 considered.

464 There are no adequate and well-controlled studies in pregnant women. Cases of lactic
465 acidosis syndrome, sometimes fatal, and symptomatic hyperlactatemia have been reported in
466 patients (including pregnant women) receiving REYATAZ in combination with nucleoside
467 analogues, which are known to be associated with increased risk of lactic acidosis syndrome.
468 REYATAZ should be used during pregnancy only if the potential benefit justifies the
469 potential risk to the fetus. (See **PRECAUTIONS: Lactic Acidosis Syndrome**.)

470 ***Antiretroviral Pregnancy Registry:*** To monitor maternal-fetal outcomes of pregnant
471 women exposed to REYATAZ, an Antiretroviral Pregnancy Registry has been established.
472 Physicians are encouraged to register patients by calling 1-800-258-4263.

473 **Nursing Mothers**

474 **The Centers for Disease Control and Prevention recommend that HIV-infected mothers
475 not breast-feed their infants to avoid risking postnatal transmission of HIV.** It is not
476 known whether atazanavir is secreted in human milk. A study in lactating rats has
477 demonstrated that atazanavir is secreted in milk. Because of both the potential for HIV
478 transmission and the potential for serious adverse reactions in nursing infants, **mothers
479 should be instructed not to breast-feed if they are receiving REYATAZ.**

480 **Pediatric Use**

481 The optimal dosing regimen for use of REYATAZ in pediatric patients has not been
482 established. REYATAZ should not be administered to pediatric patients below the age of 3
483 months due to the risk of kernicterus.

484 **Geriatric Use**

485 Clinical studies of REYATAZ did not include sufficient numbers of patients aged 65 and
486 over to determine whether they respond differently from younger patients. Based on a
487 comparison of mean single-dose pharmacokinetic values for C_{max} and AUC, a dose
488 adjustment based upon age is not recommended. In general, appropriate caution should be
489 exercised in the administration and monitoring of REYATAZ in elderly patients reflecting
490 the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant
491 disease or other drug therapy.

492 **ADVERSE REACTIONS**

493 **Adult Patients**

494 **Treatment-Emergent Adverse Events in Treatment-Naive Patients**

495 Selected clinical adverse events of moderate or severe intensity in $\geq 3\%$ of treatment-naive
496 patients receiving combination therapy including REYATAZ are presented in Table 10. For
497 other information regarding observed or potentially serious adverse events, see **WARNINGS**
498 and **PRECAUTIONS**.

Table 10: Selected Treatment-Emergent Adverse Events of Moderate or Severe Intensity Reported in $\geq 3\%$ of Adult Treatment-Naive Patients^a

| | Phase III Study AI424-034 64 weeks ^b | Phase II Studies AI424-007, -008 120 weeks ^{b,c} | Phase II Studies AI424-007, -008 73 weeks ^{b,c} | |
|---|--|--|---|---------|
| | (n=404) | (n=401) | (n=279) | (n=191) |
| Body as a Whole | | | | |
| Headache | 14% | 13% | 10% | 8% |
| Fever | 4% | 6% | 5% | 5% |
| Pain | 3% | 2% | 1% | 2% |
| Fatigue | 2% | 2% | 3% | 2% |
| Back pain | 2% | 5% | 6% | 3% |
| Digestive System | | | | |
| Nausea | 16% | 13% | 10% | 6% |
| Jaundice/scleral icterus | 7% | <1% | 8% | * |
| Abdominal pain | 6% | 5% | 10% | 8% |
| Vomiting | 6% | 8% | 8% | 7% |
| Diarrhea | 6% | 7% | 8% | 25% |
| Metabolic and Nutritional System | | | | |
| Lipodystrophy | 1% | 1% | 8% | 3% |
| Musculoskeletal System | | | | |
| Arthralgia | <1% | 2% | 4% | 4% |
| Nervous System | | | | |
| Depression | 4% | 5% | 8% | 3% |
| Insomnia | 3% | 5% | 1% | <1% |
| Dizziness | 3% | 8% | 1% | * |
| Peripheral neurologic symptoms | 1% | 2% | 8% | 7% |
| Respiratory System | | | | |
| Increased cough | 3% | 4% | 5% | 1% |
| Skin and Appendages | | | | |
| Rash | 9% | 13% | 10% | 3% |

* None reported in this treatment arm.

^a Based on regimen(s) containing REYATAZ.

^b Median time on therapy.

^c Includes long-term follow-up.

^d As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

500 **Treatment-Emergent Adverse Events in Treatment-Experienced Patients**

501 In Phase III clinical trials, REYATAZ has been studied in 144 treatment-experienced patients
502 in combination with two NRTIs (AI424-043) and in 229 treatment-experienced patients in
503 combination with either ritonavir, tenofovir, and one NRTI or saquinavir, tenofovir, and one
504 NRTI (AI424-045). Treatment-emergent adverse events of moderate or severe intensity were
505 comparable between these patients and treatment-naive patients (Table 10).

506 **Treatment-Emergent Adverse Events in All REYATAZ-Treated Patients**

507 Treatment-emergent adverse events of at least moderate intensity occurring in less than 3%
508 of adult patients receiving REYATAZ in all Phase II/III clinical trials (n=1597) and
509 considered of possible, probable, certain, or unknown relationship to treatment with
510 REYATAZ-containing regimens, and not listed in Table 10 are listed below by body system.

511 *Body as a whole:* allergic reaction, angioedema, asthenia, burning sensation, chest
512 pain, dysplasia, edema, facial atrophy, generalized edema, heat sensitivity, infection, malaise,
513 overdose, pallor, peripheral edema, photosensitivity, substernal chest pain, sweating.

514 *Cardiovascular system:* heart arrest, heart block, hypertension, myocarditis,
515 palpitation, syncope, vasodilatation.

516 *Digestive system:* acholia, anorexia, aphthous stomatitis, colitis, constipation, dental
517 pain, dyspepsia, enlarged abdomen, esophageal ulcer, esophagitis, flatulence, gastritis,
518 gastroenteritis, gastrointestinal disorder, hepatitis, hepatomegaly, hepatosplenomegaly,
519 increased appetite, liver damage, liver fatty deposit, mouth ulcer, pancreatitis, peptic ulcer.

520 *Endocrine system:* decreased male fertility.

521 *Hemic and lymphatic system:* ecchymosis, purpura.

522 *Metabolic and nutritional disorders:* buffalo hump, dehydration, diabetes mellitus,
523 dyslipidemia, gout, lactic acidosis, lipohypertrophy, obesity, weight decrease, weight gain.

524 *Musculoskeletal system:* bone pain, extremity pain, muscle atrophy, myalgia,
525 myasthenia, myopathy.

526 *Nervous system:* abnormal dream, abnormal gait, agitation, amnesia, anxiety,
527 confusion, convulsion, decreased libido, emotional lability, hallucination, hostility,

528 hyperkinesia, hypesthesia, increased reflexes, nervousness, psychosis, sleep disorder,
529 somnolence, suicide attempt, twitch.

530 *Respiratory system:* dyspnea, hiccup, hypoxia.

531 *Skin and appendages:* alopecia, cellulitis, dermatophytosis, dry skin, eczema, nail
532 disorder, pruritus, seborrhea, urticaria, vesiculobullous rash.

533 *Special senses:* otitis, taste perversion, tinnitus.

534 *Urogenital system:* abnormal urine, amenorrhea, crystalluria, gynecomastia,
535 hematuria, impotence, kidney calculus, kidney failure, kidney pain, menstrual disorder,
536 oliguria, pelvic pain, polyuria, proteinuria, urinary frequency, urinary tract infection.

537 **Laboratory Abnormalities**

538 The percentages of adult treatment-naive patients treated with combination therapy including
539 REYATAZ with Grade 3-4 laboratory abnormalities are presented in Table 11.

540

Table 11: Selected Grade 3-4 Laboratory Abnormalities Reported in $\geq 2\%$ of Adult Treatment-Naive Patients^a

| Variable | Limit ^d | Phase III Study AI424-034 | | Phase II Studies AI424-007, -008 | |
|-----------------|----------------------------|---|---|---|--|
| | | 64 weeks ^b REYATAZ 400 mg once daily + lamivudine + zidovudine ^e | 64 weeks ^b efavirenz 600 mg once daily + lamivudine + zidovudine ^e | 120 weeks ^{b,c} REYATAZ 400 mg once daily + stavudine + lamivudine or + stavudine + didanosine | 73 weeks ^{b,c} nelfinavir 750 mg TID or 1250 mg BID + stavudine + lamivudine or + stavudine + didanosine |
| Chemistry | <u>High</u> | | | | |
| SGOT/AST | $\geq 5.1 \times$ ULN | 2% | 2% | 7% | 5% |
| SGPT/ALT | $\geq 5.1 \times$ ULN | 4% | 3% | 9% | 7% |
| Total Bilirubin | $\geq 2.6 \times$ ULN | 35% | <1% | 47% | 3% |
| Amylase | $\geq 2.1 \times$ ULN | * | * | 14% | 10% |
| Lipase | $\geq 2.1 \times$ ULN | <1% | 1% | 4% | 5% |
| Hematology | <u>Low</u> | | | | |
| Hemoglobin | <8.0 g/dL | 5% | 3% | <1% | 4% |
| Neutrophils | <750 cells/mm ³ | 7% | 9% | 3% | 7% |

* None reported in this treatment arm.

^a Based on regimen(s) containing REYATAZ.

^b Median time on therapy.

^c Includes long-term follow-up.

^d ULN=upper limit of normal.

^e As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

541

542 **Patients Co-infected With Hepatitis B and/or Hepatitis C Virus**

543 Liver function tests should be monitored in patients with a history of hepatitis B or C. In
544 studies AI424-008 and AI424-034, 74 patients treated with 400 mg of REYATAZ once
545 daily, 58 who received efavirenz, and 12 who received nelfinavir were seropositive for
546 hepatitis B and/or C at study entry. AST levels >5 times the upper limit of normal (ULN)
547 developed in 9% of the REYATAZ-treated patients, 5% of the efavirenz-treated patients, and
548 17% of the nelfinavir-treated patients. ALT levels >5 times ULN developed in 15% of the
549 REYATAZ-treated patients, 14% of the efavirenz-treated patients, and 17% of the nelfinavir-
550 treated patients. Within atazanavir and control regimens, no difference in frequency of
551 bilirubin elevations was noted between seropositive and seronegative patients (see
552 **PRECAUTIONS: General**).

553 **Lipids**

554 For Study AI424-034, changes from baseline in fasting LDL-cholesterol, HDL-cholesterol,
555 total cholesterol, and fasting triglycerides are shown in Table 12.

Table 12: Lipid Values, Mean Change from Baseline, Study AI424-034

| | REYATAZ ^a | | | efavirenz ^b | | |
|------------------------------|---|--------------------------------|--|---|--------------------------------|--|
| | <u>Baseline</u> mg/dL (n=383 ^d) | Week 48 | | <u>Baseline</u> mg/dL (n=378 ^d) | Week 48 | |
| | | mg/dL (n=283 ^d) | Change ^c (n=272 ^d) | | mg/dL (n=264 ^d) | Change ^c (n=253 ^d) |
| LDL-Cholesterol ^e | 98 | 98 | +1% | 98 | 114 | +18% |
| HDL-Cholesterol | 39 | 43 | +13% | 38 | 46 | +24% |
| Total Cholesterol | 164 | 168 | +2% | 162 | 195 | +21% |
| Triglycerides ^e | 138 | 124 | -9% | 129 | 168 | +23% |

^a REYATAZ 400 mg once daily with the fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

^b Efavirenz 600 mg once daily with the fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

^c The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values and is not a simple difference of the baseline and Week 48 mean values.

^d Number of patients with LDL-cholesterol measured.

^e Fasting.

556 The percentages of adult treatment-experienced patients treated with combination
557 therapy including REYATAZ with Grade 3-4 laboratory abnormalities are presented in Table
558 13.

Table 13: Selected Grade 3-4 Laboratory Abnormalities Reported in $\geq 2\%$ of Adult Treatment-Experienced Patients^a

| Variable | Limit ^c | Phase III Study AI424-043 | | Phase III Study AI424-045 | | |
|-----------------|------------------------------|---|--|--|---|--|
| | | 24 weeks ^b REYATAZ 400 mg once daily + 2 NRTIs | 24 weeks ^b lopinavir + ritonavir (400/100 mg) BID ^d + 2 NRTIs | 15 weeks ^b REYATAZ 300 mg once daily + ritonavir 100 mg once daily + tenofovir + NRTI | 12 weeks ^b REYATAZ 400 mg once daily + saquinavir ^e 1200 mg once daily + tenofovir + NRTI | 13 weeks ^b lopinavir + ritonavir (400/100 mg) BID ^d + tenofovir + NRTI |
| Chemistry | <u>High</u> | | | | | |
| SGOT/AST | $\geq 5.1 \times \text{ULN}$ | 3% | 1% | <1% | 2% | <1% |
| SGPT/ALT | $\geq 5.1 \times \text{ULN}$ | 6% | 1% | 3% | 3% | 3% |
| Total Bilirubin | $\geq 2.6 \times \text{ULN}$ | 22% | * | 40% | 13% | * |
| Lipase | $\geq 2.1 \times \text{ULN}$ | 4% | 3% | 4% | <1% | 6% |
| Hematology | <u>Low</u> | | | | | |
| Platelets | $<50,000/\text{mm}^3$ | * | * | <1% | 4% | <1% |
| Neutrophils | $<750 \text{ cells/mm}^3$ | 5% | 3% | 4% | 5% | 4% |

* None reported in this treatment arm.

^a Based on regimen(s) containing REYATAZ.

^b Median time on therapy.

^c ULN=upper limit of normal.

^d As a fixed-dose combination.

^e Soft gelatin capsules.

559

560 Lipids

561 For Study AI424-043, changes from baseline in fasting LDL-cholesterol, HDL-cholesterol,
562 total cholesterol, and fasting triglycerides are shown in Table 14.

Table 14: Lipid Values, Mean Change from Baseline, Study AI424-043

| | REYATAZ ^a | | | lopinavir + ritonavir ^b | | |
|--------------------------------|---|--------------------------------|--|---|--------------------------------|--|
| | <u>Baseline</u> mg/dL (n=143 ^d) | Week 24 | | <u>Baseline</u> mg/dL (n=144 ^d) | Week 24 | |
| | | mg/dL (n=123 ^d) | Change ^c (n=123 ^d) | | mg/dL (n=107 ^d) | Change ^c (n=106 ^d) |
| LDL-Cholesterol ^{e,f} | 106 | 95 | -6% | 103 | 107 | +5% |
| HDL-Cholesterol | 39 | 41 | +12% | 37 | 45 | +18% |
| Total Cholesterol | 181 | 170 | -2% | 175 | 201 | +17% |
| Triglycerides ^f | 192 | 193 | -2% | 192 | 262 | +55% |

^a REYATAZ 400 mg once daily + 2 NRTIs.

^b Lopinavir + ritonavir (400/100 mg) BID + 2 NRTIs.

^c The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 24 values and is not a simple difference of the baseline and Week 24 mean values.

^d Number of patients with LDL-cholesterol measured.

^e Protocol-defined co-primary safety outcome measure.

^f Fasting.

563

564 **OVERDOSAGE**

565 Human experience of acute overdose with REYATAZ is limited. Single doses up to 1200 mg
566 have been taken by healthy volunteers without symptomatic untoward effects. A single self-
567 administered overdose of 29.2 g of REYATAZ in an HIV-infected patient (73 times the 400-mg
568 recommended dose) was associated with asymptomatic bifascicular block and PR interval
569 prolongation. These events resolved spontaneously. At high doses that lead to high drug
570 exposures, jaundice due to indirect (unconjugated) hyperbilirubinemia (without associated liver
571 function test changes) or PR interval prolongation may be observed. (See **WARNINGS,**
572 **PRECAUTIONS**, and **CLINICAL PHARMACOLOGY: Effects on Electrocardiogram.**)

573 Treatment of overdosage with REYATAZ should consist of general supportive
574 measures, including monitoring of vital signs and ECG, and observations of the patient's
575 clinical status. If indicated, elimination of unabsorbed atazanavir should be achieved by
576 emesis or gastric lavage. Administration of activated charcoal may also be used to aid
577 removal of unabsorbed drug. There is no specific antidote for overdose with REYATAZ.
578 Since atazanavir is extensively metabolized by the liver and is highly protein bound, dialysis
579 is unlikely to be beneficial in significant removal of this medicine.

580 **DOSAGE AND ADMINISTRATION**

581 **Adults**

582 The recommended dose of REYATAZ is 400 mg (two 200-mg capsules) once daily taken
583 with food.

584 Important dosing information:

585 Efavirenz. When coadministered with efavirenz, it is recommended that
586 REYATAZ 300 mg and ritonavir 100 mg be given with efavirenz 600 mg
587 (all as a single daily dose with food). REYATAZ without ritonavir should
588 not be coadministered with efavirenz.

589 Didanosine. When coadministered with didanosine buffered formulations,
590 REYATAZ should be given (with food) 2 hours before or 1 hour after
591 didanosine.

592 Tenofovir disoproxil fumarate. When coadministered with tenofovir, it is
593 recommended that REYATAZ 300 mg be given with ritonavir 100 mg and

594 tenofovir 300 mg (all as a single daily dose with food). **REYATAZ without**
595 **ritonavir should not be coadministered with tenofovir.**

596 For these drugs and other antiretroviral agents (eg, ritonavir, saquinavir) for which
597 dosing modification may be appropriate, see **CLINICAL PHARMACOLOGY: Drug-**
598 **Drug Interactions** and **PRECAUTIONS**, Table 9.

599 **Patients with Renal Impairment**

600 There are insufficient data to recommend a dosage adjustment for patients with renal
601 impairment (see **CLINICAL PHARMACOLOGY: Pharmacokinetics, Impaired Renal**
602 **Function**).

603 **Patients with Hepatic Impairment**

604 REYATAZ should be used with caution in patients with mild to moderate hepatic
605 insufficiency. A dose reduction to 300 mg once daily should be considered for patients with
606 moderate hepatic insufficiency (Child-Pugh Class B). REYATAZ should not be used in
607 patients with severe hepatic insufficiency (Child-Pugh Class C). (See **PRECAUTIONS** and
608 **CLINICAL PHARMACOLOGY: Pharmacokinetics, Impaired Hepatic Function**)

609 **HOW SUPPLIED**

610 REYATAZ™ (atazanavir sulfate) Capsules are available in the following strengths and
611 configurations of plastic bottles with child-resistant closures.

| Product Strength* | Capsule Shell Color (cap/body) | Markings on Capsule (ink color) | | Capsules per Bottle | NDC Number |
|-------------------|--------------------------------|---------------------------------|--------------|---------------------|--------------|
| | | cap | body | | |
| 100 mg | blue/white | BMS 100 mg (white) | 3623 (blue) | 60 | 0003-3623-12 |
| 150 mg | blue/powder blue | BMS 150 mg (white) | 3624 (blue) | 60 | 0003-3624-12 |
| 200 mg | blue/blue | BMS 200 mg (white) | 3631 (white) | 60 | 0003-3631-12 |

* atazanavir equivalent as atazanavir sulfate.

612 REYATAZ (atazanavir sulfate) Capsules should be stored at 25° C (77° F);
613 excursions permitted to 15–30° C (59–86° F) [see USP Controlled Room Temperature].

615 US Patent Nos: 5,849,911 and 6,087,383.

616

617

618 Bristol-Myers Squibb Virology

619 Bristol-Myers Squibb Company

620 Princeton, NJ 08543 USA

621

Revised _____

622

Patient Information

623

REYATAZ™ (RAY-ah-taz)

Rx only

624

(generic name = atazanavir sulfate)

625

Capsules

626 **ALERT: Find out about medicines that should NOT be taken with REYATAZ.** Read
627 the section "What important information should I know about taking REYATAZ with other
628 medicines?"

629 Read the Patient Information that comes with REYATAZ before you start using it and each
630 time you get a refill. There may be new information. This leaflet provides a summary about
631 REYATAZ and does not include everything there is to know about your medicine. This
632 information does not take the place of talking with your healthcare provider about your
633 medical condition or treatment.

634 What is REYATAZ?

635 REYATAZ is a prescription medicine used with other anti-HIV medicines to treat people
636 who are infected with the human immunodeficiency virus (HIV). HIV is the virus that causes
637 acquired immune deficiency syndrome (AIDS). REYATAZ is a type of anti-HIV medicine
638 called a protease inhibitor. HIV infection destroys CD4 (T) cells, which are important to the
639 immune system. The immune system helps fight infection. After a large number of T cells
640 are destroyed, AIDS develops. REYATAZ helps to block HIV protease, an enzyme that is
641 needed for the HIV virus to multiply. REYATAZ may lower the amount of HIV in your
642 blood, help your body keep its supply of CD4 (T) cells, and reduce the risk of death and
643 illness associated with HIV.

644 Does REYATAZ cure HIV or AIDS?

645 **REYATAZ does not cure HIV infection or AIDS.** At present there is no cure for HIV
646 infection. People taking REYATAZ may still get opportunistic infections or other conditions
647 that happen with HIV infection. Opportunistic infections are infections that develop because
648 the immune system is weak. Some of these conditions are pneumonia, herpes virus
649 infections, and *Mycobacterium avium* complex (MAC) infections. **It is very important that**
650 **you see your healthcare provider regularly while taking REYATAZ.**

651 **REYATAZ does not lower your chance of passing HIV to other people through**
652 **sexual contact, sharing needles, or being exposed to your blood.** For your health and the
653 health of others, it is important to always practice safer sex by using a latex or polyurethane
654 condom or other barrier to lower the chance of sexual contact with semen, vaginal secretions,
655 or blood. Never use or share dirty needles.

656 **Who should not take REYATAZ?**

657 **Do not take REYATAZ if you:**

- 658 • **are taking certain medicines.** (See "What important information should I know about
659 taking REYATAZ with other medicines?") Serious life-threatening side effects or death
660 may happen. Before you take REYATAZ, tell your healthcare provider about all
661 medicines you are taking or planning to take. These include other prescription and
662 nonprescription medicines, vitamins, and herbal supplements.
- 663 • **are allergic to REYATAZ or to any of its ingredients.** The active ingredient is
664 atazanavir sulfate. See the end of this leaflet for a complete list of ingredients in
665 REYATAZ. Tell your healthcare provider if you think you have had an allergic reaction
666 to any of these ingredients.

667 **What should I tell my healthcare provider before I take REYATAZ?**

668 **Tell your healthcare provider:**

- 669 • **If you are pregnant or planning to become pregnant.** It is not known if REYATAZ
670 can harm your unborn baby. Pregnant women have experienced serious side effects when
671 taking REYATAZ with other HIV medicines called nucleoside analogues. You and your
672 healthcare provider will need to decide if REYATAZ is right for you. If you use
673 REYATAZ while you are pregnant, talk to your healthcare provider about the
674 Antiretroviral Pregnancy Registry.
- 675 • **If you are breast-feeding.** You should not breast-feed if you are HIV-positive because
676 of the chance of passing HIV to your baby. Also, it is not known if REYATAZ can pass
677 into your breast milk and if it can harm your baby. If you are a woman who has or will
678 have a baby, talk with your healthcare provider about the best way to feed your baby.
- 679 • **If you have liver problems or are infected with the hepatitis B or C virus.** See "What
680 are the possible side effects of REYATAZ?"
- 681 • **If you have diabetes.** See "What are the possible side effects of REYATAZ?"
- 682 • **If you have hemophilia.** See "What are the possible side effects of REYATAZ?"

- 683 • **About all the medicines you take** including prescription and nonprescription medicines,
684 vitamins, and herbal supplements. Keep a list of your medicines with you to show your
685 healthcare provider. For more information, see "What important information I should
686 know about taking REYATAZ with other medicines?" and "Who should not take
687 REYATAZ?" Some medicines can cause serious side effects if you also take
688 REYATAZ.

689 **How should I take REYATAZ?**

- 690 • **Take REYATAZ once every day exactly as instructed by your healthcare provider.**
691 Your healthcare provider will prescribe the amount of REYATAZ that is right for you.
692 Your dose will depend on your liver function and on the other anti-HIV medicines that
693 you are taking. REYATAZ is always used with other anti-HIV medicines. If you are
694 taking REYATAZ with SUSTIVA® (efavirenz) or with VIREAD® (tenofovir disoproxil
695 fumarate), you should also be taking NORVIR® (ritonavir).
- 696 • **Always take REYATAZ with food** (a meal or snack) to help it work better. Swallow the
697 capsules whole. **Do not open the capsules.** Try to take REYATAZ at the same time
698 each day.
- 699 • **If you are taking antacids or Videx® (didanosine) Chewable/Dispersible Buffered
700 Tablets,** take REYATAZ 2 hours before or 1 hour after these medicines.
- 701 • **Do not change your dose or stop taking REYATAZ without first talking with your
702 healthcare provider.** It is important to stay under a healthcare provider's care while taking
703 REYATAZ.
- 704 • **When your supply of REYATAZ starts to run low,** get more from your healthcare
705 provider or pharmacy. It is important not to run out of REYATAZ. The amount of HIV
706 in your blood may increase if the medicine is stopped for even a short time.
- 707 • **If you miss a dose of REYATAZ,** take it as soon as possible and then take your next
708 scheduled dose at its regular time. If, however, it is within 6 hours of your next dose, do
709 not take the missed dose. Wait and take the next dose at the regular time. Do not double
710 the next dose. **It is important that you do not miss any doses of REYATAZ or your
711 other anti-HIV medicines.**
- 712 • **If you take more than the prescribed dose of REYATAZ,** call your healthcare
713 provider or poison control center right away.

714 **Can children take REYATAZ?**

715 REYATAZ has not been fully studied in children under 16 years of age. REYATAZ should
716 not be used in babies under the age of 3 months.

717 **What are the possible side effects of REYATAZ?**

718 The following list of side effects is **not** complete. Report any new or continuing symptoms to
719 your healthcare provider. If you have questions about side effects, ask your healthcare
720 provider. Your healthcare provider may be able to help you manage these side effects.

721 **REYATAZ can cause the following side effects:**

- 722 • **yellowing of the skin or eyes.** These effects may be due to increases in bilirubin levels in
723 the blood (bilirubin is made by the liver). Call your healthcare provider if your skin or
724 the white part of your eyes turn yellow. Although these effects may not be damaging to
725 your liver, skin, or eyes, it is important to tell your healthcare provider promptly if they
726 occur.
- 727 • **a change in the way your heart beats (heart rhythm change).** Call your healthcare
728 provider right away if you get dizzy or lightheaded. These could be symptoms of a heart
729 problem.
- 730 • **diabetes and high blood sugar (hyperglycemia)** sometimes happen in patients taking
731 protease inhibitor medicines like REYATAZ. Some patients had diabetes before taking
732 protease inhibitors while others did not. Some patients may need changes in their diabetes
733 medicine.
- 734 • **if you have liver disease** including hepatitis B or C, your liver disease may get worse
735 when you take anti-HIV medicines like REYATAZ.
- 736 • **some patients with hemophilia** have increased bleeding problems with protease
737 inhibitors like REYATAZ.
- 738 • **a serious condition called lactic acidosis syndrome** (a severe buildup of an acid in the
739 blood that sometimes causes death). Some people who have taken REYATAZ with anti-
740 HIV medicines called nucleoside analogues have developed lactic acidosis syndrome.
741 Lactic acidosis syndrome has happened more in people who are female or obese (very
742 overweight). Lactic acidosis syndrome is a medical emergency and must be treated in the
743 hospital. **Call your healthcare provider right away and do not continue to take**

744 **REYATAZ and your other anti-HIV medicines unless instructed to by your**
745 **healthcare provider if you get any of the following signs of lactic acidosis syndrome:**

- 746 • You have persistent nausea, vomiting, or unusual or unexpected stomach discomfort,
- 747 • You feel very weak and tired,
- 748 • You have trouble breathing,
- 749 • You have weakness, especially in your arms and legs.
- 750 • **changes in body fat.** These changes may include an increased amount of fat in the upper
751 back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs,
752 arms, and face may also happen. The cause and long-term health effects of these
753 conditions are not known at this time.

754 Other common side effects of REYATAZ taken with other anti-HIV medicines include
755 nausea; headache; rash; stomach pain; vomiting; diarrhea; depression; fever; increased
756 cough; dizziness; trouble sleeping; pain; tiredness; back pain; numbness, tingling, or burning
757 of hands or feet; and joint pain.

758 **What important information should I know about taking REYATAZ
759 with other medicines*?**

760 **Do not take REYATAZ if you take the following medicines (not all brands may be
761 listed; tell your healthcare provider about all the medicines you take). REYATAZ may
762 cause serious, life-threatening side effects or death when used with these medicines.**

- 763 • Ergot medicines: dihydroergotamine, ergonovine, ergotamine, and methylergonovine
764 such as Cafergot[®], Migranal[®], D.H.E. 45[®], ergotrate maleate, Methergine[®], and others
765 (used for migraine headaches).
- 766 • Halcion[®] (triazolam, used for insomnia).
- 767 • Versed[®] (midazolam, used for sedation).
- 768 • Orap[®] (pimozide, used for Tourette's disorder).
- 769 • Propulsid[®] (cisapride, used for certain stomach problems).

770 **Do not take the following medicines with REYATAZ because of possible serious side
771 effects:**

- 772 • Camptosar[®] (irinotecan, used for cancer),
- 773 • Vascor[®] (bepridil, used for high blood pressure),

- 774 • Crixivan[®] (indinavir, used for HIV infection). Both REYATAZ and Crixivan sometimes
775 cause increased levels of bilirubin in the blood.
- 776 • Cholesterol-lowering medicines Mevacor[®] (lovastatin) or Zocor[®] (simvastatin).

777 **Do not take the following medicines with REYATAZ because they may lower the
778 amount of REYATAZ in your blood.** This may lead to an increased HIV viral load.
779 Resistance to REYATAZ or cross-resistance to other HIV medicines may develop:

- 780 • Rifampin (also known as Rimactane[®], Rifadin[®], Rifater[®], or Rifamate[®], used for
781 tuberculosis).
- 782 • St. John's wort (*Hypericum perforatum*), an herbal product sold as a dietary supplement,
783 or products containing St. John's wort.
- 784 • "Proton-pump inhibitors" used for indigestion, heartburn, or ulcers such as AcipHex[®]
785 (rabeprazole), Nexium[®] (esomeprazole), Prevacid[®] (lansoprazole), Prilosec[®]
786 (omeprazole), or Protonix[®] (pantoprazole).

787 **The following medicines may require your healthcare provider to monitor your therapy
788 more closely:**

- 789 • Cialis[®] (tadalafil), Levitra[®] (vardenafil), or Viagra[®] (sildenafil). REYATAZ may
790 increase the chances of serious side effects that can happen with Cialis, Levitra, or
791 Viagra. Do not use Cialis, Levitra, or Viagra while you are taking REYATAZ unless
792 your healthcare provider tells you it is okay.
- 793 • Lipitor[®] (atorvastatin). There is an increased chance of serious side effects if you take
794 REYATAZ with this cholesterol-lowering medicine.
- 795 • Medicines for abnormal heart rhythm: Cordarone[®] (amiodarone), lidocaine, quinidine
796 (also known as Cardioquin[®], Quinidex[®], and others).
- 797 • Coumadin[®] (warfarin).
- 798 • Tricyclic antidepressants such as Elavil[®] (amitriptyline), Norpramin[®] (desipramine),
799 Sinequan[®] (doxepin), Surmontil[®] (trimipramine), Tofranil[®] (imipramine), or Vivactil[®]
800 (protriptyline).
- 801 • Medicines to prevent organ transplant rejection: Sandimmune[®] or Neoral[®] (cyclosporin),
802 Rapamune[®] (sirolimus), or Prograf[®] (tacrolimus).

803 **The following medicines may require a change in the dose or dose schedule of either
804 REYATAZ or the other medicine:**

- Fortovase[®], Invirase[®] (saquinavir).
- Norvir[®] (ritonavir).
- Sustiva[®] (efavirenz).
- Videx[®] (didanosine) or antacids.
- Viread[®] (tenofovir disoproxil fumarate).
- Mycobutin[®] (rifabutin).
- Calcium channel blockers such as Cardizem[®] or Tiazac[®] (diltiazem), Covera-HS[®] or Isoptin SR[®] (verapamil) and others.
- Biaxin[®] (clarithromycin).
- Oral contraceptives ("the pill").
- Medicines for indigestion, heartburn, or ulcers such as Axid[®] (nizatidine), Pepcid AC[®] (famotidine), Tagamet[®] (cimetidine), or Zantac[®] (ranitidine).

817 **Remember:**

- 1. Know all the medicines you take.**
- 2. Tell your healthcare provider about all the medicines you take.**
- 3. Do not start a new medicine without talking to your healthcare provider.**

821 **How should I store REYATAZ?**

- Store REYATAZ Capsules at room temperature, 59° to 86° F (15° to 30° C). Do **not** store this medicine in a damp place such as a bathroom medicine cabinet or near the kitchen sink.
- Keep your medicine in a tightly closed container.
- Throw away REYATAZ when it is outdated or no longer needed by flushing it down the toilet or pouring it down the sink.

828 **General information about REYATAZ**

829 This medicine was prescribed for your particular condition. Do not use REYATAZ for
830 another condition. Do not give REYATAZ to other people, even if they have the same

831 symptoms you have. It may harm them. **Keep REYATAZ and all medicines out of the**
832 **reach of children and pets.**

833 This summary does not include everything there is to know about REYATAZ. Medicines are
834 sometimes prescribed for conditions that are not mentioned in patient information leaflets.
835 Remember no written summary can replace careful discussion with your healthcare provider.
836 If you would like more information, talk with your healthcare provider or you can call 1-800-
837 426-7644.

838 **What are the ingredients in REYATAZ?**

839 **Active Ingredient:** atazanavir sulfate

840 **Inactive Ingredients:** Crospovidone, lactose monohydrate (milk sugar), magnesium stearate,
841 gelatin, FD&C Blue #2, and titanium dioxide.

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844 Sustiva® are registered trademarks of Bristol-Myers Squibb Pharma Company. Other
845 brands listed are the trademarks of their respective owners and are not trademarks of
846 Bristol-Myers Squibb Company.

847

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852 This Patient Information Leaflet has been approved by the U.S. Food and Drug
853 Administration.

854 Revised _____

855 Based on package insert dated _____

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