

1 **REYATAZ<sup>®</sup>**

**Rx only**

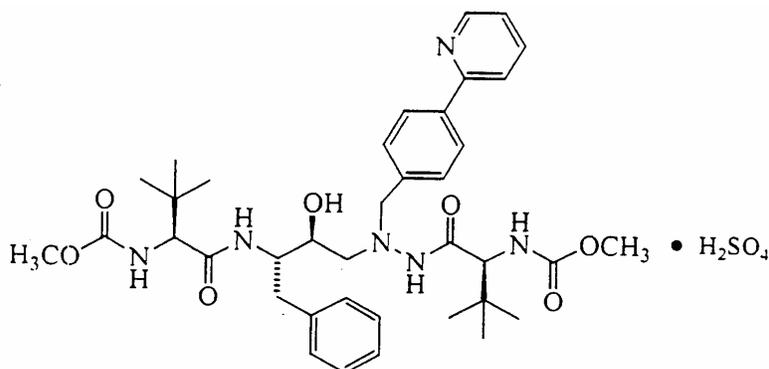
2 **(atazanavir sulfate) Capsules**

3 **(Patient Information Leaflet Included)**

4 **DESCRIPTION**

5 REYATAZ<sup>®</sup> (atazanavir sulfate) is an azapeptide inhibitor of HIV-1 protease.

6 The chemical name for atazanavir sulfate is (3*S*,8*S*,9*S*,12*S*)-3,12-Bis(1,1-  
7 dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-  
8 pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester,  
9 sulfate (1:1). Its molecular formula is C<sub>38</sub>H<sub>52</sub>N<sub>6</sub>O<sub>7</sub>•H<sub>2</sub>SO<sub>4</sub>, which corresponds to a  
10 molecular weight of 802.9 (sulfuric acid salt). The free base molecular weight is 704.9.  
11 Atazanavir sulfate has the following structural formula:



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

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

## 23 **CLINICAL PHARMACOLOGY**

### 24 **Microbiology**

#### 25 **Mechanism of Action**

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

#### 29 **Antiviral Activity *In Vitro***

30 Atazanavir exhibits anti-HIV-1 activity with a mean 50% inhibitory concentration (IC<sub>50</sub>)  
31 in the absence of human serum of 2 to 5 nM against a variety of laboratory and clinical  
32 HIV-1 isolates grown in peripheral blood mononuclear cells, macrophages, CEM-SS  
33 cells, and MT-2 cells. Two-drug combination studies with ATV showed additive to  
34 antagonistic antiviral activity *in vitro* with abacavir and the NNRTIs (delavirdine,  
35 efavirenz, and nevirapine) and additive antiviral activity *in vitro* with the PIs  
36 (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), NRTIs  
37 (didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine),  
38 the HIV-1 fusion inhibitor enfuvirtide, and two compounds used in the treatment of viral  
39 hepatitis, adefovir and ribavirin, without enhanced cytotoxicity.

#### 40 **Resistance**

41 *In vitro*: HIV-1 isolates with a decreased susceptibility to ATV have been selected  
42 *in vitro* and obtained from patients treated with ATV or atazanavir/ritonavir (ATV/RTV).  
43 HIV-1 isolates that were 93- to 183-fold resistant to ATV from three different viral  
44 strains were selected *in vitro* by 5 months. The mutations in these HIV-1 viruses that  
45 contributed to ATV resistance included I50L, N88S, I84V, A71V, and M46I. Changes  
46 were also observed at the protease cleavage sites following drug selection. Recombinant  
47 viruses containing the I50L mutation were growth impaired and displayed increased  
48 *in vitro* susceptibility to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir,  
49 and saquinavir). The I50L and I50V substitutions yielded selective resistance to ATV and  
50 amprenavir, respectively, and did not appear to be cross-resistant.

51 *Clinical Studies of Treatment-Naive Patients*: ATV-resistant clinical isolates from  
52 treatment-naive patients who experienced virologic failure developed an I50L mutation

53 (after an average of 50 weeks of ATV therapy), often in combination with an A71V  
54 mutation. In treatment-naïve patients, viral isolates that developed the I50L mutation  
55 showed phenotypic resistance to ATV but retained *in vitro* susceptibility to other PIs  
56 (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir); however, there  
57 are no clinical data available to demonstrate the effect of the I50L mutation on the  
58 efficacy of subsequently administered PIs.

59 *Clinical Studies of Treatment-Experienced Patients:* In contrast, from studies of  
60 treatment-experienced patients treated with ATV or ATV/RTV, most ATV-resistant  
61 isolates from patients who experienced virologic failure developed mutations that were  
62 associated with resistance to multiple PIs and displayed decreased susceptibility to  
63 multiple PIs. The most common protease mutations to develop in the viral isolates of  
64 patients who failed treatment with ATV 300 mg once daily and RTV 100 mg once daily  
65 (together with tenofovir and an NRTI) included V32I, L33F/V/I, E35D/G, M46I/L, I50L,  
66 F53L/V, I54V, A71V/T/I, G73S/T/C, V82A/T/L, I85V, and L89V/Q/M/T. Other  
67 mutations that developed on ATV/RTV treatment including E34K/A/Q, G48V, I84V,  
68 N88S/D/T, and L90M occurred in less than 10% of patient isolates. Generally, if  
69 multiple PI resistance mutations were present in the HIV-1 of the patient at baseline,  
70 ATV resistance developed through mutations associated with resistance to other PIs and  
71 could include the development of the I50L mutation.

## 72 **Cross-Resistance**

73 Cross-resistance among PIs has been observed. Baseline phenotypic and genotypic  
74 analyses of clinical isolates from ATV clinical trials of PI-experienced subjects showed  
75 that isolates cross-resistant to multiple PIs were cross-resistant to ATV. Greater than  
76 90% of the isolates with mutations that included I84V or G48V were resistant to ATV.  
77 Greater than 60% of isolates containing L90M, G73S/T/C, A71V/T, I54V, M46I/L, or a  
78 change at V82 were resistant to ATV, and 38% of isolates containing a D30N mutation in  
79 addition to other changes were resistant to ATV. Isolates resistant to ATV were also  
80 cross-resistant to other PIs with >90% of the isolates resistant to indinavir, lopinavir,  
81 nelfinavir, ritonavir, and saquinavir, and 80% resistant to amprenavir. In treatment-  
82 experienced patients, PI-resistant viral isolates that developed the I50L mutation in  
83 addition to other PI resistance-associated mutations were also cross-resistant to other PIs.

84 Genotypic and/or phenotypic analysis of baseline virus may aid in determining  
85 ATV susceptibility before initiation of ATV/RTV therapy. An association between  
86 virologic response at 48 weeks and the number and type of primary PI-resistance-

87 associated mutations detected in baseline HIV-1 isolates from antiretroviral-experienced  
88 patients receiving ATV/RTV once daily or lopinavir (LPV)/RTV twice daily in Study  
89 AI424-045 is shown in Table 1.

90 Overall, both the number and type of baseline PI mutations affected response  
91 rates in treatment-experienced patients. In the ATV/RTV group, patients had lower  
92 response rates when 3 or more baseline PI mutations including a mutation at position 36,  
93 71, 77, 82, or 90 were present compared to patients with 1-2 PI mutations including one  
94 of these mutations.

**Table 1: HIV RNA Response by Number and Type of Baseline PI Mutation, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis**

Number and Type of Baseline PI Mutations <sup>a</sup>	Virologic Response = HIV RNA <400 copies/mL <sup>b</sup>	
	ATV/RTV (n=110)	LPV/RTV (n=113)
<b>3 or more primary PI mutations including:<sup>c</sup></b>		
D30N	75% (6/8)	50% (3/6)
M36I/V	19% (3/16)	33% (6/18)
M46I/L/T	24% (4/17)	23% (5/22)
I54V/L/T/M/A	31% (5/16)	31% (5/16)
A71V/T/I/G	34% (10/29)	39% (12/31)
G73S/A/C/T	14% (1/7)	38% (3/8)
V77I	47% (7/15)	44% (7/16)
V82A/F/T/S/I	29% (6/21)	27% (7/26)
I84V/A	11% (1/9)	33% (2/6)
N88D	63% (5/8)	67% (4/6)
L90M	10% (2/21)	44% (11/25)
<b>Number of baseline primary PI mutations<sup>a</sup></b>		
All patients, as-treated	58% (64/110)	59% (67/113)
0-2 PI mutations	75% (50/67)	75% (50/67)
3-4 PI mutations	41% (14/34)	43% (12/28)
5 or more PI mutations	0% (0/9)	28% (5/18)

<sup>a</sup> Primary mutations include any change at D30, V32, M36, M46, I47, G48, I50, I54, A71, G73, V77, V82, I84, N88, and L90.

<sup>b</sup> Results should be interpreted with caution because the subgroups were small.

<sup>c</sup> There were insufficient data (n<3) for PI mutations V32I, I47V, G48V, I50V, and F53L.

95

96 The response rates of antiretroviral-experienced patients in Study AI424-045 were  
97 analyzed by baseline phenotype (shift in *in vitro* susceptibility relative to reference,  
98 Table 2). The analyses are based on a select patient population with 62% of patients  
99 receiving an NNRTI-based regimen before study entry compared to 35% receiving a PI-  
100 based regimen. Additional data are needed to determine clinically relevant break points  
101 for REYATAZ.

**Table 2: Baseline Phenotype by Outcome, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis**

Baseline Phenotype <sup>a</sup>	Virologic Response = HIV RNA <400 copies/mL <sup>b</sup>	
	ATV/RTV (n=111)	LPV/RTV (n=111)
0-2	71% (55/78)	70% (56/80)
>2-5	53% (8/15)	44% (4/9)
>5-10	13% (1/8)	33% (3/9)
>10	10% (1/10)	23% (3/13)

<sup>a</sup> Fold change in *in vitro* susceptibility relative to the wild-type reference.

<sup>b</sup> Results should be interpreted with caution because the subgroups were small.

102

## 103 Pharmacokinetics

104 The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in  
105 HIV-infected patients after administration of REYATAZ 400 mg once daily and after  
106 administration of REYATAZ 300 mg with ritonavir 100 mg once daily (see Table 3).

**Table 3: Steady-State Pharmacokinetics of Atazanavir in Healthy Subjects or HIV-Infected Patients in the Fed State**

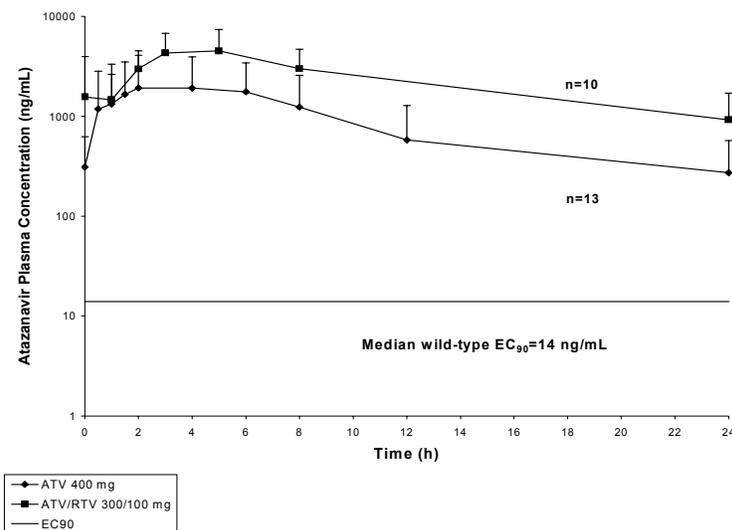
Parameter	400 mg once daily		300 mg with ritonavir 100 mg once daily	
	Healthy Subjects (n=14)	HIV-Infected Patients (n=13)	Healthy Subjects (n=28)	HIV-Infected Patients (n=10)
$C_{max}$ (ng/mL)				
Geometric mean (CV%)	5199 (26)	2298 (71)	6129 (31)	4422 (58)
Mean (SD)	5358 (1371)	3152 (2231)	6450 (2031)	5233 (3033)
$T_{max}$ (h)				
Median	2.5	2.0	2.7	3.0
AUC (ng•h/mL)				
Geometric mean (CV%)	28132 (28)	14874 (91)	57039 (37)	46073 (66)
Mean (SD)	29303 (8263)	22262 (20159)	61435 (22911)	53761 (35294)
T-half (h)				
Mean (SD)	7.9 (2.9)	6.5 (2.6)	18.1 (6.2) <sup>a</sup>	8.6 (2.3)
$C_{min}$ (ng/mL)				
Geometric mean (CV%)	159 (88)	120 (109)	1227 (53)	636 (97)
Mean (SD)	218 (191)	273 (298) <sup>b</sup>	1441 (757)	862 (838)

<sup>a</sup> n=26.

<sup>b</sup> n=12.

107           Figure 1 displays the mean plasma concentrations of atazanavir at steady state  
108 after REYATAZ 400 mg once daily (as two 200-mg capsules) with a light meal and after  
109 REYATAZ 300 mg (as two 150-mg capsules) with ritonavir 100 mg once daily with a  
110 light meal in HIV-infected adult patients.

111 **Figure 1:** Mean (SD) Steady-State Plasma Concentrations of Atazanavir  
112 **400 mg (n=13) and 300 mg with Ritonavir (n=10) for HIV-**  
113 **Infected Adult Patients**



#### 114 **Absorption**

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

#### 119 **Food Effect**

120 Administration of REYATAZ with food enhances bioavailability and reduces  
121 pharmacokinetic variability. Administration of a single 400-mg dose of REYATAZ with  
122 a light meal (357 kcal, 8.2 g fat, 10.6 g protein) resulted in a 70% increase in AUC and  
123 57% increase in  $C_{max}$  relative to the fasting state. Administration of a single 400-mg dose  
124 of REYATAZ with a high-fat meal (721 kcal, 37.3 g fat, 29.4 g protein) resulted in a  
125 mean increase in AUC of 35% with no change in  $C_{max}$  relative to the fasting state.  
126 Administration of REYATAZ with either a light meal or high-fat meal decreased the  
127 coefficient of variation of AUC and  $C_{max}$  by approximately one half compared to the  
128 fasting state.

129 **Distribution**

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

137 **Metabolism**

138 Atazanavir is extensively metabolized in humans. The major biotransformation pathways  
139 of atazanavir in humans consisted of monooxygenation and dioxygenation. Other minor  
140 biotransformation pathways for atazanavir or its metabolites consisted of glucuronidation,  
141 N-dealkylation, hydrolysis, and oxygenation with dehydrogenation. Two minor  
142 metabolites of atazanavir in plasma have been characterized. Neither metabolite  
143 demonstrated *in vitro* antiviral activity. *In vitro* studies using human liver microsomes  
144 suggested that atazanavir is metabolized by CYP3A.

145 **Elimination**

146 Following a single 400-mg dose of <sup>14</sup>C-atazanavir, 79% and 13% of the total  
147 radioactivity was recovered in the feces and urine, respectively. Unchanged drug  
148 accounted for approximately 20% and 7% of the administered dose in the feces and urine,  
149 respectively. The mean elimination half-life of atazanavir in healthy volunteers (n=214)  
150 and HIV-infected adult patients (n=13) was approximately 7 hours at steady state  
151 following a dose of 400 mg daily with a light meal.

152 **Effects on Electrocardiogram**

153 Concentration- and dose-dependent prolongation of the PR interval in the  
154 electrocardiogram has been observed in healthy volunteers receiving atazanavir. In a  
155 placebo-controlled study (AI424-076), the mean ( $\pm$ SD) maximum change in PR interval  
156 from the predose value was 24 ( $\pm$ 15) msec following oral dosing with 400 mg of  
157 atazanavir (n=65) compared to 13 ( $\pm$ 11) msec following dosing with placebo (n=67). The  
158 PR interval prolongations in this study were asymptomatic. There is limited information

159 on the potential for a pharmacodynamic interaction in humans between atazanavir and  
160 other drugs that prolong the PR interval of the electrocardiogram. (See **WARNINGS**.)

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

## 168 **Special Populations**

### 169 **Age/Gender**

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

### 173 **Race**

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

### 176 **Pediatrics**

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

### 179 **Impaired Renal Function**

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

### 183 **Impaired Hepatic Function**

184 Atazanavir is metabolized and eliminated primarily by the liver. REYATAZ (atazanavir  
185 sulfate) has been studied in adult subjects with moderate to severe hepatic impairment

186 (14 Child-Pugh B and 2 Child-Pugh C subjects) after a single 400-mg dose. The mean  
187  $AUC_{(0-\infty)}$  was 42% greater in subjects with impaired hepatic function than in healthy  
188 volunteers. The mean half-life of atazanavir in hepatically impaired subjects was  
189 12.1 hours compared to 6.4 hours in healthy volunteers. Increased concentrations of  
190 atazanavir are expected in patients with moderately or severely impaired hepatic function  
191 (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). The  
192 pharmacokinetics of REYATAZ in combination with ritonavir have not been studied in  
193 subjects with hepatic impairment.

194 **Drug-Drug Interactions** (see also **CONTRAINDICATIONS**,  
195 **WARNINGS**, and **PRECAUTIONS: Drug Interactions**)

196 Atazanavir is metabolized in the liver by CYP3A. Atazanavir is a metabolism-dependent  
197 CYP3A inhibitor, with a  $K_{inact}$  value of 0.05 to 0.06  $\text{min}^{-1}$  and  $K_i$  value of 0.84 to  
198 1.0  $\mu\text{M}$ . Atazanavir is also a direct inhibitor for UGT1A1 ( $K_i=1.9 \mu\text{M}$ ) and CYP2C8  
199 ( $K_i=2.1 \mu\text{M}$ ). REYATAZ should not be administered concurrently with medications with  
200 narrow therapeutic windows that are substrates of CYP3A, UGT1A1, or CYP2C8 (see  
201 **CONTRAINDICATIONS**).

202 Clinically significant interactions are not expected between atazanavir and  
203 substrates of CYP2C19, CYP2C9, CYP2D6, CYP2B6, CYP2A6, CYP1A2, or CYP2E1.

204 Atazanavir has been shown *in vivo* not to induce its own metabolism, nor to  
205 increase the biotransformation of some drugs metabolized by CYP3A. In a multiple-dose  
206 study, REYATAZ decreased the urinary ratio of endogenous  $6\beta\text{-OH}$  cortisol to cortisol  
207 versus baseline, indicating that CYP3A production was not induced.

208 Drugs that induce CYP3A activity may increase the clearance of atazanavir,  
209 resulting in lowered plasma concentrations. Coadministration of REYATAZ (atazanavir  
210 sulfate) and other drugs that inhibit CYP3A may increase atazanavir plasma  
211 concentrations.

212 Drug interaction studies were performed with REYATAZ and other drugs likely  
213 to be coadministered and some drugs commonly used as probes for pharmacokinetic  
214 interactions. The effects of coadministration of REYATAZ on the AUC,  $C_{max}$ , and  $C_{min}$   
215 are summarized in Tables 4 and 5. For information regarding clinical recommendations,  
216 see **PRECAUTIONS: Drug Interactions**, Tables 10 and 11.

**Table 4: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs<sup>a</sup>**

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 <sub>max</sub>	AUC	C <sub>min</sub>
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 BID, 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) <sup>b</sup>	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose simultaneously with ddI and d4T	31	0.11 (0.06, 0.18)	0.13 (0.08, 0.21)	0.16 (0.10, 0.27)
	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose 1 hour after ddI + d4T	31	1.12 (0.67, 1.18)	1.03 (0.64, 1.67)	1.03 (0.61, 1.73)
ddI (enteric-coated [EC] capsules) <sup>c</sup>	400 mg QD d 8 (fed)	400 mg QD d 2-8	34	1.03 (0.93, 1.14)	0.99 (0.91, 1.08)	0.98 (0.89, 1.08)
	400 mg QD d 19 (fed)	300 mg/ritonavir 100 mg QD d 9-19	31	1.04 (1.01, 1.07)	1.00 (0.96, 1.03)	0.87 (0.82, 0.92)
diltiazem	180 mg QD, d 7-11 and d 19-23	400 mg QD, d 1-11	30	1.04 (0.96, 1.11)	1.00 (0.95, 1.05)	0.98 (0.90, 1.07)
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)
famotidine	40 mg BID d 7-12	400 mg QD d 1-12 (simultaneous administration)	15	0.53 (0.34, 0.82)	0.59 (0.40, 0.87)	0.58 (0.37, 0.89)
	40 mg BID d 7-12	400 mg QD d 1-6, d 7-12 (10 hr after, 2 hr before famotidine)	14	1.08 (0.82, 1.41)	0.95 (0.74, 1.21)	0.79 (0.60, 1.04)
	40 mg BID d 11-20 <sup>d</sup>	300 mg QD/ritonavir 100 mg QD d 1-20 <sup>d</sup> (simultaneous administration)	14	0.86 (0.79, 0.94)	0.82 (0.75, 0.89)	0.72 (0.64, 0.81)
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)

omeprazole	40 mg QD d 7-12 <sup>e</sup>	400 mg QD d 1-12	16	0.04 (0.04, 0.05)	0.06 (0.05, 0.07)	0.05 (0.03, 0.07)
	40 mg QD d 11-20 <sup>e</sup>	300 mg QD/ ritonavir 100 mg QD d 1-20	15	0.28 (0.24, 0.32)	0.24 (0.21, 0.27)	0.22 (0.19, 0.26)
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)
rifampin	600 mg QD d 17-26	300 mg QD/ ritonavir 100 mg QD d 7-26	16	0.47 (0.41, 0.53)	0.28 (0.25, 0.32)	0.02 (0.02, 0.03)
ritonavir <sup>f</sup>	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 <sup>g</sup>	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 <sup>h</sup> (0.50, 1.05)	0.75 <sup>h</sup> (0.58, 0.97)	0.77 <sup>h</sup> (0.54, 1.10)

<sup>a</sup> Data provided are under fed conditions unless otherwise noted.

<sup>b</sup> All drugs were given under fasted conditions.

<sup>c</sup> 400 mg ddI EC and REYATAZ were administered together with food on Days 8 and 19.

<sup>d</sup> REYATAZ 300 mg plus ritonavir 100 mg once daily coadministered with famotidine 40 mg twice daily resulted in atazanavir geometric mean  $C_{max}$  that was similar and AUC and  $C_{min}$  values that were 1.79- and 4.46-fold higher relative to REYATAZ 400 mg once daily alone.

<sup>e</sup> Omeprazole was administered on an empty stomach 2 hours before REYATAZ.

<sup>f</sup> 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.

<sup>g</sup> Note that similar results were observed in studies where administration of tenofovir and REYATAZ was separated by 12 hours.

<sup>h</sup> 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 <sup>f</sup>). 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. Study was conducted in HIV-infected individuals.

**Table 5: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of REYATAZ<sup>a</sup>**

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 <sub>max</sub>	AUC	C <sub>min</sub>
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 BID, d 7-10 and d 18-21	400 mg QD, d 1-10	21	1.50 (1.32, 1.71)	1.94 (1.75, 2.16)	2.60 (2.35, 2.88)
				OH-clarithromycin: 0.28 (0.24, 0.33)	OH-clarithromycin: 0.30 (0.26, 0.34)	OH-clarithromycin: 0.38 (0.34, 0.42)
didanosine (ddI) (buffered tablets) plus stavudine (d4T) <sup>b</sup>	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose simultaneous with ddI and d4T	31	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)
ddI (enteric-coated [EC] capsules) <sup>c</sup>	400 mg QD d 1 (fasted), 8 (fed)	400 mg QD, d 2-8	34	0.64 (0.55, 0.74)	0.66 (0.60, 0.74)	1.13 (0.91, 1.41)
	400 mg QD d 1 (fasted), 19 (fed)	300 mg QD/ritonavir 100 mg QD, d 9-19	31	0.62 (0.52, 0.74)	0.66 (0.59, 0.73)	1.25 (0.92, 1.70)
diltiazem	180 mg QD, d 7-11 and d 19-23	400 mg QD, d 1-11	28	1.98 (1.78, 2.19)	2.25 (2.09, 2.16)	2.42 (2.14, 2.73)
				desacetyl-diltiazem: 2.72 (2.44, 3.03)	desacetyl-diltiazem: 2.65 (2.45, 2.87)	desacetyl-diltiazem: 2.21 (2.02, 2.42)
ethinyl estradiol & norethindrone	Ortho-Novum <sup>®</sup> 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)
methadone	stable maintenance dose, d 1-15	400 mg QD, d 2-15	16	(R)-methadone <sup>d</sup> 0.91 (0.84, 1.0) total:0.85 (0.78, 0.93)	(R)-methadone <sup>d</sup> 1.03 (0.95, 1.10) total:0.94 (0.87, 1.02)	(R)-methadone <sup>d</sup> 1.11 (1.02, 1.20) total:1.02 (0.93, 1.12)
omeprazole <sup>e</sup>	40 mg single dose d 7 and d 20	400 mg QD d 1-12	16	1.24 (1.04, 1.47)	1.45 (1.20, 1.76)	NA

rifabutin	300 mg QD, d 1-10 then 150 mg QD, d 11-20	600 mg QD, <sup>f</sup> 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 <sup>g</sup> (soft gelatin capsules)	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 <sup>h</sup>	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)
	300 mg QD d 1-7 (pm) d 25-34 (pm) <sup>i</sup>	300 mg QD/ritonavir 100 mg QD d 25-34 (am) <sup>i</sup>	12	1.34 (1.20, 1.51)	1.37 (1.30, 1.45)	1.29 (1.21, 1.36)
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)

<sup>a</sup> Data provided are under fed conditions unless otherwise noted.

<sup>b</sup> All drugs were given under fasted conditions.

<sup>c</sup> 400 mg ddi EC and REYATAZ were administered together with food on Days 8 and 19.

<sup>d</sup> (R)-methadone is the active isomer of methadone.

<sup>e</sup> Omeprazole was used as a metabolic probe for CYP2C19. Omeprazole was given 2 hours after REYATAZ on Day 7; and was given alone 2 hours after a light meal on Day 20.

<sup>f</sup> Not the recommended therapeutic dose of atazanavir.

<sup>g</sup> 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<sub>max</sub> is about 79% higher than that for the standard dosing of saquinavir (soft gelatin capsules) alone at 1200 mg TID.

<sup>h</sup> Note that similar results were observed in a study where administration of tenofovir and REYATAZ was separated by 12 hours.

<sup>i</sup> Administration of tenofovir and REYATAZ was temporally separated by 12 hours.

NA = not available.

217

## 218 INDICATIONS AND USAGE

219 REYATAZ (atazanavir sulfate) is indicated in combination with other antiretroviral  
220 agents for the treatment of HIV-1 infection.

221 This indication is based on analyses of plasma HIV-1 RNA levels and CD4+ cell  
222 counts from controlled studies of 48 weeks duration in antiretroviral-naive and  
223 antiretroviral-treatment-experienced patients.

224 The following points should be considered when initiating therapy with  
225 REYATAZ:

- 226 • In antiretroviral-experienced patients with prior virologic failure,  
227 coadministration of REYATAZ/ritonavir is recommended.
  
- 228 • In Study AI424-045 REYATAZ/ritonavir and lopinavir/ritonavir were similar  
229 for the primary efficacy outcome measure of time-averaged difference in  
230 change from baseline in HIV RNA level. This study was not large enough to  
231 reach a definitive conclusion that REYATAZ/ritonavir and lopinavir/ritonavir  
232 are equivalent on the secondary efficacy outcome measure of proportions  
233 below the HIV RNA lower limit of detection (see **Description of Clinical  
234 Studies**).
  
- 235 • The number of baseline primary protease inhibitor mutations affects the  
236 virologic response to REYATAZ/ritonavir (see **CLINICAL  
237 PHARMACOLOGY: Microbiology**).
  
- 238 • There are no data regarding the use of REYATAZ/ritonavir in therapy-naive  
239 patients.

## 240 **Description of Clinical Studies**

### 241 **Patients Without Prior Antiretroviral Therapy**

242 *Study AI424-034: REYATAZ once daily compared to efavirenz once daily, each in*  
243 *combination with fixed-dose lamivudine + zidovudine twice daily.* Study AI424-034 was  
244 a randomized, double-blind, multicenter trial comparing REYATAZ (400 mg once daily)  
245 to efavirenz (600 mg once daily), each in combination with a fixed-dose combination of  
246 lamivudine (3TC) (150 mg) and zidovudine (ZDV) (300 mg) given twice daily, in 810  
247 antiretroviral treatment-naive patients. Patients had a mean age of 34 years (range: 18 to  
248 73), 36% were Hispanic, 33% were Caucasian, and 65% were male. The mean baseline  
249 CD4+ cell count was 321 cells/mm<sup>3</sup> (range: 64 to 1424 cells/mm<sup>3</sup>) and the mean baseline  
250 plasma HIV-1 RNA level was 4.8 log<sub>10</sub> copies/mL (range: 2.2 to 5.9 log<sub>10</sub> copies/mL).  
251 Treatment response and outcomes through Week 48 are presented in Table 6.

**Table 6: Outcomes of Randomized Treatment Through Week 48 (Study AI424-034)**

Outcome	REYATAZ 400 mg once daily + lamivudine + zidovudine <sup>d</sup> (n=405)	efavirenz 600 mg once daily + lamivudine + zidovudine <sup>d</sup> (n=405)
Responder <sup>a</sup>	67% (32%)	62% (37%)
Virologic failure <sup>b</sup>	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 <sup>c</sup>	8%	10%

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

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

<sup>c</sup> Includes lost to follow-up, patient’s withdrawal, noncompliance, protocol violation, and other reasons.

<sup>d</sup> As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

252 Through 48 weeks of therapy, the proportion of responders among patients with  
253 high viral loads (ie, baseline HIV RNA  $\geq 100,000$  copies/mL) was comparable for the  
254 REYATAZ and efavirenz arms. The mean increase from baseline in CD4+ cell count was  
255 176 cells/mm<sup>3</sup> for the REYATAZ arm and 160 cells/mm<sup>3</sup> for the efavirenz arm.

256 *Study AI424-008: REYATAZ 400 mg once daily compared to REYATAZ 600 mg once*  
257 *daily, and compared to nelfinavir 1250 mg twice daily, each in combination with*  
258 *stavudine and lamivudine twice daily.* Study AI424-008 was a 48-week, randomized,  
259 multicenter trial, blinded to dose of REYATAZ, comparing REYATAZ at two dose  
260 levels (400 mg and 600 mg once daily) to nelfinavir (1250 mg twice daily), each in  
261 combination with stavudine (40 mg) and lamivudine (150 mg) given twice daily, in 467  
262 antiretroviral treatment-naïve patients. Patients had a mean age of 35 years (range: 18 to  
263 69), 55% were Caucasian, and 63% were male. The mean baseline CD4+ cell count was  
264 295 cells/mm<sup>3</sup> (range: 4 to 1003 cells/mm<sup>3</sup>) and the mean baseline plasma HIV-1 RNA  
265 level was 4.7 log<sub>10</sub> copies/mL (range: 1.8 to 5.9 log<sub>10</sub> copies/mL). Treatment response  
266 and outcomes through Week 48 are presented in Table 7.

**Table 7: 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 <sup>a</sup>	67% (33%)	59% (38%)
Virologic failure <sup>b</sup>	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 <sup>c</sup>	7%	10%

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

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

<sup>c</sup> Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.

267 Through 48 weeks of therapy, the mean increase from baseline in CD4+ cell  
268 count was 234 cells/mm<sup>3</sup> for the REYATAZ 400-mg arm and 211 cells/mm<sup>3</sup> for the  
269 nelfinavir arm.

### 270 **Patients With Prior Antiretroviral Therapy**

271 *Study AI424-045: REYATAZ once daily + ritonavir once daily compared to REYATAZ*  
272 *once daily + saquinavir (soft gelatin capsules) once daily, and compared to lopinavir +*  
273 *ritonavir twice daily, each in combination with tenofovir + one NRTI.* Study AI424-045  
274 is an ongoing, randomized, multicenter trial comparing REYATAZ (300 mg once daily)  
275 with ritonavir (100 mg once daily) to REYATAZ (400 mg once daily) with saquinavir  
276 soft gelatin capsules (1200 mg once daily), and to lopinavir + ritonavir (400/100 mg  
277 twice daily), each in combination with tenofovir and one NRTI, in 347 (of 358  
278 randomized) patients who experienced virologic failure on HAART regimens containing  
279 PIs, NRTIs, and NNRTIs. The mean time of prior exposure to antiretrovirals was 139  
280 weeks for PIs, 283 weeks for NRTIs, and 85 weeks for NNRTIs. The mean age was 41  
281 years (range: 24 to 74); 60% were Caucasian, and 78% were male. The mean baseline  
282 CD4+ cell count was 338 cells/mm<sup>3</sup> (range: 14 to 1543 cells/mm<sup>3</sup>) and the mean baseline  
283 plasma HIV-1 RNA level was 4.4 log<sub>10</sub> copies/mL (range: 2.6 to 5.88 log<sub>10</sub> copies/mL).

284 Treatment outcomes through Week 48 for the REYATAZ/ritonavir and  
285 lopinavir/ritonavir treatment arms are presented in Table 8. **REYATAZ/ritonavir and**  
286 **lopinavir/ritonavir were similar for the primary efficacy outcome measure of time-**  
287 **averaged difference in change from baseline in HIV RNA level. Study AI424-045**  
288 **was not large enough to reach a definitive conclusion that REYATAZ/ritonavir and**  
289 **lopinavir/ritonavir are equivalent on the secondary efficacy outcome measure of**  
290 **proportions below the HIV RNA lower limit of detection.** See also Tables 1 and 2 in  
291 **CLINICAL PHARMACOLOGY: Microbiology.**

**Table 8: Outcomes of Treatment Through Week 48 in Study AI424-045 (Patients with Prior Antiretroviral Experience)**

Outcome	REYATAZ 300 mg + ritonavir 100 mg once daily + tenofovir + 1 NRTI (n=119)	lopinavir/ritonavir (400/100 mg) twice daily + tenofovir + 1 NRTI (n=118)	Difference <sup>a</sup> (REYATAZ- lopinavir/ritonavir) (CI)
HIV RNA Change from Baseline (log <sub>10</sub> copies/mL) <sup>b</sup>	-1.58	-1.70	+0.12 <sup>c</sup> (-0.17, 0.41)
CD4+ Change from Baseline (cells/mm <sup>3</sup> ) <sup>d</sup>	116	123	-7 (-67, 52)
Percent of Patients Responding <sup>e</sup>			
HIV RNA <400 copies/mL <sup>b</sup>	55%	57%	-2.2% (-14.8%, 10.5%)
HIV RNA <50 copies/mL <sup>b</sup>	38%	45%	-7.1% (-19.6%, 5.4%)

<sup>a</sup> Time-averaged difference through Week 48 for HIV RNA; Week 48 difference in HIV RNA percentages and CD4+ mean changes, REYATAZ/ritonavir vs lopinavir/ritonavir; CI = 97.5% confidence interval for change in HIV RNA; 95% confidence interval otherwise.

<sup>b</sup> Roche Amplicor<sup>®</sup> HIV-1 Monitor<sup>™</sup> Assay, test version 1.5.

<sup>c</sup> Protocol-defined primary efficacy outcome measure.

<sup>d</sup> Based on patients with baseline and Week 48 CD4+ cell count measurements (REYATAZ/ritonavir, n=85 ; lopinavir/ritonavir, n=93).

<sup>e</sup> Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL (<50 copies/mL) through Week 48.

292 No patients in the REYATAZ/ritonavir treatment arm and three patients in the  
293 lopinavir/ritonavir treatment arm experienced a new-onset CDC Category C event during  
294 the study.

295 In Study AI424-045, the mean change from baseline in plasma HIV-1 RNA for  
296 REYATAZ 400 mg with saquinavir (n=115) was -1.55 log<sub>10</sub> copies/mL, and the time-  
297 averaged difference in change in HIV-1 RNA levels versus lopinavir/ritonavir was 0.33.

298 The corresponding mean increase in CD4+ cell count was 72 cells/mm<sup>3</sup>. Through 48  
299 weeks of treatment, the proportion of patients in this treatment arm with plasma HIV-1  
300 RNA <400 (<50) copies/mL was 38% (26%). In this study, coadministration of  
301 REYATAZ and saquinavir did not provide adequate efficacy (see **PRECAUTIONS:**  
302 **Drug Interactions**, Table 11).

303 Study AI424-045 also compared changes from baseline in lipid values (see  
304 **ADVERSE REACTIONS**, Table 17).

305 *Study AI424-043:* Study AI424-043 was a randomized, open-label, multicenter trial  
306 comparing REYATAZ (400 mg once daily) to lopinavir/ritonavir (400/100 mg twice  
307 daily), each in combination with two NRTIs, in 300 patients who experienced virologic  
308 failure to only one prior PI-containing regimen. Through 48 weeks, the proportion of  
309 patients with plasma HIV-1 RNA <400 (<50) copies/mL was 49% (35%) for patients  
310 randomized to REYATAZ (n=144) and 69% (53%) for patients randomized to  
311 lopinavir/ritonavir (n=146). The mean change from baseline was -1.59 log<sub>10</sub> copies/mL  
312 in the REYATAZ treatment arm and -2.02 log<sub>10</sub> copies/mL in the lopinavir/ritonavir  
313 arm. Based on the results of this study, REYATAZ without ritonavir is inferior to  
314 lopinavir/ritonavir in PI-experienced patients with prior virologic failure and is not  
315 recommended for such patients.

## 316 **CONTRAINDICATIONS**

317 REYATAZ (atazanavir sulfate) is contraindicated in patients with known hypersensitivity  
318 to any of its ingredients, including atazanavir.

319 Coadministration of REYATAZ is contraindicated with drugs that are highly  
320 dependent on CYP3A for clearance and for which elevated plasma concentrations are  
321 associated with serious and/or life-threatening events. These drugs are listed in Table 9.

**Table 9: Drugs That Are Contraindicated with REYATAZ Due to Potential CYP450-Mediated Interactions\***

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

\*Please see Table 10 for additional drugs that should not be coadministered with REYATAZ.

322 **WARNINGS**

323 **ALERT: Find out about medicines that should NOT be taken with REYATAZ.**

324 This statement is included on the product's bottle label. (See

325 **CONTRAINDICATIONS, WARNINGS: Drug Interactions, and PRECAUTIONS:**

326 **Drug Interactions.**)

327 **Drug Interactions**

328 Atazanavir is an inhibitor of CYP3A, CYP2C8, and UGT1A1. Coadministration of  
329 REYATAZ and drugs primarily metabolized by CYP3A [eg, calcium channel blockers,  
330 HMG-CoA reductase inhibitors, immunosuppressants, and phosphodiesterase (PDE5)  
331 inhibitors], CYP2C8, or UGT1A1 (eg, irinotecan) may result in increased plasma  
332 concentrations of the other drug that could increase or prolong its therapeutic and adverse  
333 effects. (Also see **PRECAUTIONS: Drug Interactions**, Tables 10 and 11.)

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

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

348 A drug interaction study in healthy subjects has shown that ritonavir significantly  
349 increases plasma fluticasone propionate exposures, resulting in significantly decreased  
350 serum cortisol concentrations. Concomitant use of REYATAZ with ritonavir and  
351 fluticasone propionate is expected to produce the same effects. Systemic corticosteroid  
352 effects including Cushing's syndrome and adrenal suppression have been reported during  
353 postmarketing use in patients receiving ritonavir and inhaled or intranasally administered

354 fluticasone propionate. Therefore, coadministration of fluticasone propionate and  
355 REYATAZ/ritonavir is not recommended unless the potential benefit to the patient  
356 outweighs the risk of systemic corticosteroid side effects (see **PRECAUTIONS: Drug**  
357 **Interactions**).

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

### 364 **PR Interval Prolongation**

365 Atazanavir has been shown to prolong the PR interval of the electrocardiogram in some  
366 patients. In healthy volunteers and in patients, abnormalities in atrioventricular (AV)  
367 conduction were asymptomatic and generally limited to first-degree AV block. There  
368 have been rare reports of second-degree AV block and other conduction abnormalities  
369 and no reports of third-degree AV block (see **OVERDOSAGE**). In clinical trials,  
370 asymptomatic first-degree AV block was observed in 5.9% of atazanavir-treated patients  
371 (n=920), 5.2% of lopinavir/ritonavir-treated patients (n=252), 10.4% of nelfinavir-treated  
372 patients (n=48), and 3.0% of efavirenz-treated patients (n=329). In Study AI424-045,  
373 asymptomatic first-degree AV block was observed in 5% (6/118) of atazanavir/ritonavir-  
374 treated patients and 5% (6/116) of lopinavir/ritonavir-treated patients who had on-study  
375 electrocardiogram measurements. Because of limited clinical experience, atazanavir  
376 should be used with caution in patients with preexisting conduction system disease (eg,  
377 marked first-degree AV block or second- or third-degree AV block). (See **CLINICAL**  
378 **PHARMACOLOGY: Effects on Electrocardiogram**.)

379 In a pharmacokinetic study between atazanavir 400 mg once daily and diltiazem  
380 180 mg once daily, a CYP3A substrate, there was a 2-fold increase in the diltiazem  
381 plasma concentration and an additive effect on the PR interval. When used in  
382 combination with atazanavir, a dose reduction of diltiazem by one half should be  
383 considered and ECG monitoring is recommended. In a pharmacokinetic study between  
384 atazanavir 400 mg once daily and atenolol 50 mg once daily, there was no substantial  
385 additive effect of atazanavir and atenolol on the PR interval. When used in combination  
386 with atazanavir, there is no need to adjust the dose of atenolol. (See **PRECAUTIONS:**  
387 **Drug Interactions**.)

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

## 394 **Diabetes Mellitus/Hyperglycemia**

395 New-onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, and  
396 hyperglycemia have been reported during postmarketing surveillance in HIV-infected  
397 patients receiving protease inhibitor therapy. Some patients required either initiation or  
398 dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In  
399 some cases, diabetic ketoacidosis has occurred. In those patients who discontinued  
400 protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events  
401 have been reported voluntarily during clinical practice, estimates of frequency cannot be  
402 made and a causal relationship between protease inhibitor therapy and these events has  
403 not been established.

## 404 **PRECAUTIONS**

### 405 **General**

### 406 **Hyperbilirubinemia**

407 Most patients taking REYATAZ experience asymptomatic elevations in indirect  
408 (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT).  
409 This hyperbilirubinemia is reversible upon discontinuation of REYATAZ. Hepatic  
410 transaminase elevations that occur with hyperbilirubinemia should be evaluated for  
411 alternative etiologies. No long-term safety data are available for patients experiencing  
412 persistent elevations in total bilirubin >5 times ULN. Alternative antiretroviral therapy to  
413 REYATAZ may be considered if jaundice or scleral icterus associated with bilirubin  
414 elevations presents cosmetic concerns for patients. Dose reduction of atazanavir is not  
415 recommended since long-term efficacy of reduced doses has not been established. (See  
416 **ADVERSE REACTIONS: Laboratory Abnormalities**, Tables 14 and 16.)

417 **Rash**

418 In controlled clinical trials (n=1597), rash (all grades, regardless of causality) occurred in  
419 21% of patients treated with REYATAZ. The median time to onset of rash was 8 weeks  
420 after initiation of REYATAZ and the median duration of rash was 1.3 weeks. Rashes  
421 were generally mild-to-moderate maculopapular skin eruptions. Dosing with REYATAZ  
422 was often continued without interruption in patients who developed rash. The  
423 discontinuation rate for rash in clinical trials was 0.4%. REYATAZ should be  
424 discontinued if severe rash develops. Cases of Stevens-Johnson syndrome and erythema  
425 multiforme have been reported in patients receiving REYATAZ.

426 **Hepatic Impairment and Toxicity**

427 Atazanavir is principally metabolized by the liver; caution should be exercised when  
428 administering this drug to patients with hepatic impairment because atazanavir  
429 concentrations may be increased (see **DOSAGE AND ADMINISTRATION**). Patients  
430 with underlying hepatitis B or C viral infections or marked elevations in transaminases  
431 prior to treatment may be at increased risk for developing further transaminase elevations  
432 or hepatic decompensation. There are no clinical trial data on the use of  
433 REYATAZ/ritonavir in patients with any degree of hepatic impairment.

434 **Resistance/Cross-Resistance**

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

438 **Hemophilia**

439 There have been reports of increased bleeding, including spontaneous skin hematomas  
440 and hemarthrosis, in patients with hemophilia type A and B treated with protease  
441 inhibitors. In some patients additional factor VIII was given. In more than half of the  
442 reported cases, treatment with protease inhibitors was continued or reintroduced. A  
443 causal relationship between protease inhibitor therapy and these events has not been  
444 established.

445 **Fat Redistribution**

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

451 **Immune Reconstitution Syndrome**

452 Immune reconstitution syndrome has been reported in patients treated with combination  
453 antiretroviral therapy, including REYATAZ. During the initial phase of combination  
454 antiretroviral treatment, patients whose immune system responds may develop an  
455 inflammatory response to indolent or residual opportunistic infections (such as  
456 *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis carinii* pneumonia, or  
457 tuberculosis), which may necessitate further evaluation and treatment.

458 **Information for Patients**

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

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

471 Patients should be informed that REYATAZ is not a cure for HIV infection and  
472 that they may continue to develop opportunistic infections and other complications  
473 associated with HIV disease. Patients should be told that there are currently no data  
474 demonstrating that therapy with REYATAZ can reduce the risk of transmitting HIV to  
475 others through sexual contact.

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

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

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

486 REYATAZ (atazanavir sulfate) should be taken with food to enhance absorption.

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

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

## 496 **Drug Interactions**

497 Atazanavir is an inhibitor of CYP3A, CYP2C8, and UGT1A1. Coadministration of  
498 REYATAZ and drugs primarily metabolized by CYP3A (eg, calcium channel blockers,  
499 HMG-CoA reductase inhibitors, immunosuppressants, and PDE5 inhibitors), CYP2C8, or  
500 UGT1A1 (eg, irinotecan) may result in increased plasma concentrations of the other drug  
501 that could increase or prolong both its therapeutic and adverse effects (see Tables 10 and  
502 11). Atazanavir is metabolized in the liver by the cytochrome P450 enzyme system.  
503 Coadministration of REYATAZ and drugs that induce CYP3A, such as rifampin, may  
504 decrease atazanavir plasma concentrations and reduce its therapeutic effect.  
505 Coadministration of REYATAZ and drugs that inhibit CYP3A may increase atazanavir  
506 plasma concentrations.

507           The potential for drug interactions with REYATAZ changes when REYATAZ is  
508 coadministered with the potent CYP3A inhibitor ritonavir. The magnitude of CYP3A-  
509 mediated drug interactions (effect on atazanavir or effect on coadministered drug) may  
510 change when REYATAZ is coadministered with ritonavir. See the complete prescribing  
511 information for Norvir<sup>®</sup> (ritonavir) for information on drug interactions with ritonavir.

512           Atazanavir solubility decreases as pH increases. Reduced plasma concentrations  
513 of atazanavir are expected if proton-pump inhibitors (see Table 10), antacids, buffered  
514 medications, or H<sub>2</sub>-receptor antagonists (see Table 11) are administered with atazanavir.

515           Atazanavir has the potential to prolong the PR interval of the electrocardiogram in  
516 some patients. Caution should be used when coadministering REYATAZ with medicinal  
517 products known to induce PR interval prolongation (eg, atenolol, diltiazem [see Table  
518 11]).

519           Drugs that are contraindicated or not recommended for coadministration with  
520 REYATAZ are included in Table 10. These recommendations are based on either drug  
521 interaction studies or predicted interactions due to the expected magnitude of interaction  
522 and potential for serious events or loss of efficacy.

**Table 10: Drugs That Should Not Be Administered with REYATAZ**

<b>Drug class: Specific Drugs</b>	<b>Clinical Comment</b>
<i>Antimycobacterials:</i> rifampin	Rifampin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect and development of resistance.
<i>Antineoplastics:</i> irinotecan	Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.
<i>Benzodiazepines:</i> midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
<i>Ergot Derivatives:</i> dihydrorergotamine, ergotamine, ergonovine, methylergonovine	CONTRAINDICATED 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.
<i>GI Motility Agent:</i> cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<i>HMG-CoA Reductase Inhibitors:</i> lovastatin, simvastatin	Potential for serious reactions such as myopathy including rhabdomyolysis.
<i>Neuroleptic:</i> pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<i>Protease Inhibitors:</i> 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.
<i>Proton-Pump Inhibitors</i>	Omeprazole substantially decreases plasma concentrations of atazanavir. Concomitant use of proton-pump inhibitors and REYATAZ may result in loss of therapeutic effect and development of resistance.
<i>Herbal Products:</i> 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.

523

**Table 11: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies<sup>a</sup> or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)**

<b>Concomitant Drug Class: Specific Drugs</b>	<b>Effect on Concentration of Atazanavir or Concomitant Drug</b>	<b>Clinical Comment</b>
<b><i>HIV Antiviral Agents</i></b>		
<i>Nucleoside Reverse Transcriptase Inhibitors (NRTIs):</i> didanosine buffered formulations enteric-coated (EC) capsules	↓ atazanavir ↓ didanosine	Coadministration of REYATAZ with didanosine buffered tablets results in a marked decrease in atazanavir exposure. It is recommended that REYATAZ be given (with food) 2 h before or 1 hr after didanosine buffered formulations. Simultaneous administration of didanosine EC and REYATAZ with food results in a decrease in didanosine exposure. Thus, REYATAZ and didanosine EC should be administered at different times.

**Table 11: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies<sup>a</sup> or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)**

<i>Concomitant Drug Class: Specific Drugs</i>	Effect on Concentration of Atazanavir or Concomitant Drug	Clinical Comment
<i>Nucleotide Reverse Transcriptase Inhibitors:</i> tenofovir disoproxil fumarate	↓ atazanavir ↑ tenofovir	Tenofovir may decrease the AUC and C <sub>min</sub> 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). <b>REYATAZ without ritonavir should not be coadministered with tenofovir.</b> 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.
<i>Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs):</i> efavirenz	↓ atazanavir	In treatment-naïve patients who receive efavirenz and REYATAZ, the recommended dose is REYATAZ 300 mg with ritonavir 100 mg and efavirenz 600 mg (all once daily), as this combination results in atazanavir exposure that approximates the mean exposure to atazanavir produced by 400 mg of REYATAZ alone. Dosing recommendations for efavirenz and REYATAZ in treatment-experienced patients have not been established.
<i>Non-nucleoside Reverse Transcriptase Inhibitors:</i> nevirapine	↓ atazanavir	<b>REYATAZ/ritonavir:</b> The effects of coadministration have not been studied. Nevirapine, an inducer of CYP3A, is expected to decrease atazanavir exposure. In the absence of data, coadministration is not recommended.
<i>Protease Inhibitors:</i> saquinavir (soft gelatin capsules)	↑ saquinavir	Appropriate dosing recommendations for this combination, with or without ritonavir, with respect to efficacy and safety have not been established. In a clinical study, saquinavir 1200 mg coadministered with REYATAZ 400 mg and tenofovir 300 mg (all given once daily) plus nucleoside analogue reverse transcriptase inhibitors did not provide adequate efficacy (see <b>Description of Clinical Studies</b> ).
<i>Protease Inhibitors:</i> ritonavir	↑ atazanavir	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. See the complete prescribing information for Norvir <sup>®</sup> (ritonavir) for information on drug interactions with ritonavir.
<i>Protease Inhibitors:</i> others	↑ other protease inhibitor	<b>REYATAZ/ritonavir:</b> Although not studied, the coadministration of REYATAZ/ ritonavir and other protease inhibitors would be expected to increase exposure to the other protease inhibitor. Such coadministration is not recommended.
<b>Other Agents</b>		
<i>Antacids and buffered medications</i>	↓ 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.
<i>Antiarrhythmics:</i> amiodarone, bepridil, lidocaine (systemic), quinidine	↑ amiodarone, bepridil, lidocaine (systemic), quinidine	Coadministration with REYATAZ has the potential to produce serious and/or life-threatening adverse events and has not been studied. Caution is warranted and therapeutic concentration monitoring of these drugs is recommended if they are used concomitantly with REYATAZ.
<i>Anticoagulants:</i> 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.
<i>Antidepressants:</i> 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.

**Table 11: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies<sup>a</sup> or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)**

<i>Concomitant Drug Class: Specific Drugs</i>	Effect on Concentration of Atazanavir or Concomitant Drug	Clinical Comment
trazodone	↑ trazodone	Concomitant use of trazodone and REYATAZ with or without ritonavir may increase plasma concentrations 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 REYATAZ, the combination should be used with caution and a lower dose of trazodone should be considered.
<i>Antifungals:</i> ketoconazole itraconazole	<b>REYATAZ/ ritonavir:</b> ↑ ketoconazole ↑ itraconazole	Coadministration of ketoconazole has only been studied with REYATAZ without ritonavir (negligible increase in atazanavir AUC and C <sub>max</sub> ). Due to the effect of ritonavir on ketoconazole, high doses of ketoconazole and itraconazole (>200 mg/day) should be used cautiously with REYATAZ/ritonavir.
<i>Antifungals:</i> voriconazole	Effect is unknown	Coadministration of voriconazole with REYATAZ, with or without ritonavir, has not been studied. Administration of voriconazole with ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%. Voriconazole should not be administered to patients receiving REYATAZ/ritonavir, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Coadministration of voriconazole with REYATAZ (without ritonavir) may increase atazanavir concentrations; however, no data are available.
<i>Antimycobacterials:</i> rifabutin	↑ rifabutin	A rifabutin dose reduction of up to 75% (eg, 150 mg every other day or 3 times per week) is recommended.
<i>Calcium channel blockers:</i> diltiazem	↑ diltiazem and desacetyl-diltiazem	Caution is warranted. A dose reduction of diltiazem by 50% should be considered. ECG monitoring is recommended. Coadministration of REYATAZ/ritonavir with diltiazem has not been studied.
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.
<i>HMG-CoA reductase inhibitors:</i> 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.
<i>H<sub>2</sub>-Receptor antagonists</i>	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when REYATAZ 400 mg once daily was administered simultaneously with famotidine 40 mg twice daily, which may result in loss of therapeutic effect and development of resistance.  In treatment-naïve patients taking an H <sub>2</sub> -receptor antagonist, either of the following regimens may be used: REYATAZ 400 mg once daily with food at least 2 hours before and at least 10 hours after the H <sub>2</sub> -receptor antagonist OR REYATAZ 300 mg with ritonavir 100 mg once daily with food, without the need for separation from the H <sub>2</sub> -receptor antagonist.  In treatment-experienced patients, the following regimen should be used: REYATAZ 300 mg with ritonavir 100 mg once daily with food at least 2 hours before and at least 10 hours after the H <sub>2</sub> -receptor antagonist.
<i>Immunosuppressants:</i> cyclosporin, sirolimus, tacrolimus	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with REYATAZ.
<i>Inhaled/nasal steroid:</i> fluticasone	<b>REYATAZ</b> ↑ fluticasone	Concomitant use of fluticasone propionate and REYATAZ (without ritonavir) may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.

**Table 11: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies<sup>a</sup> or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)**

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir or Concomitant Drug	Clinical Comment
	<i>REYATAZ/ritonavir</i> ↑ fluticasone	Concomitant use of fluticasone propionate and REYATAZ/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Coadministration of fluticasone propionate and REYATAZ/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see <b>WARNINGS</b> ).
<i>Macrolide antibiotics:</i> 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. Coadministration of REYATAZ/ritonavir with clarithromycin has not been studied.
<i>Hormonal contraceptives:</i> ethinyl estradiol and norethindrone	↑ ethinyl estradiol ↑ norethindrone	Coadministration of REYATAZ/ritonavir with hormonal contraceptives has not been studied. However, higher doses of ritonavir, without REYATAZ, decrease contraceptive steroid concentrations. Because contraceptive steroid concentrations may be altered when REYATAZ or REYATAZ/ritonavir is coadministered with oral contraceptives or with the contraceptive patch, alternate methods of nonhormonal contraception are recommended.
<i>PDE5 inhibitors:</i> 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.

<sup>a</sup> For magnitude of interactions see **CLINICAL PHARMACOLOGY**: Tables 4 and 5.

524 Based on known metabolic profiles, clinically significant drug interactions are not  
525 expected between REYATAZ and fluvastatin, pravastatin, dapsone, trimethoprim/sulfa-  
526 methoxazole, azithromycin, erythromycin, or fluconazole. REYATAZ does not interact  
527 with substrates of CYP2D6 (eg, nortriptyline, desipramine, metoprolol). Additionally, no  
528 clinically significant drug interaction was observed when REYATAZ was coadministered  
529 with methadone.

### 530 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

531 Two-year carcinogenicity studies in mice and rats were conducted with atazanavir. At  
532 the high dose in female mice, the incidence of benign hepatocellular adenomas was  
533 increased at systemic exposures 7.2-fold higher than those in humans at the

534 recommended 400-mg clinical dose. There were no increases in the incidence of tumors  
535 in male mice at any dose in the study. In rats, no significant positive trends in the  
536 incidence of neoplasms occurred at systemic exposures up to 5.7-fold higher than those  
537 in humans at the recommended 400-mg clinical dose. The clinical relevance of the  
538 carcinogenic findings in female mice is unknown.

539 Atazanavir tested positive in an *in vitro* clastogenicity test using primary human  
540 lymphocytes, in the absence and presence of metabolic activation. Atazanavir tested  
541 negative in the *in vitro* Ames reverse-mutation assay, *in vivo* micronucleus and DNA  
542 repair tests in rats, and *in vivo* DNA damage test in rat duodenum (comet assay).

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

## 546 **Pregnancy**

### 547 **Pregnancy Category B**

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

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

560 There are no adequate and well-controlled studies in pregnant women. Cases of  
561 lactic acidosis syndrome, sometimes fatal, and symptomatic hyperlactatemia have been  
562 reported in patients (including pregnant women) receiving REYATAZ in combination  
563 with nucleoside analogues, which are known to be associated with increased risk of lactic

564 acidosis syndrome. REYATAZ should be used during pregnancy only if the potential  
565 benefit justifies the potential risk to the fetus.

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

## 569 **Nursing Mothers**

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

## 576 **Pediatric Use**

577 The optimal dosing regimen for use of REYATAZ (atazanavir sulfate) in pediatric  
578 patients has not been established. REYATAZ should not be administered to pediatric  
579 patients below the age of 3 months due to the risk of kernicterus.

## 580 **Geriatric Use**

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

588 **ADVERSE REACTIONS**

589 **Adult Patients**

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

591 Selected drug-related clinical adverse events of moderate or severe intensity reported in  
592  $\geq 2\%$  of treatment-naive patients receiving combination therapy including REYATAZ are  
593 presented in Table 12. For other information regarding observed or potentially serious  
594 adverse events, see **WARNINGS** and **PRECAUTIONS**.

**Table 12: Selected Treatment-Emergent Adverse Events<sup>a</sup> of Moderate or Severe Intensity Reported in  $\geq 2\%$  of Adult Treatment-Naive Patients<sup>b</sup>**

	Phase III Study AI424-034		Phase II Studies AI424-007, -008	
	64 weeks <sup>c</sup> REYATAZ 400 mg once daily + lamivudine + zidovudine <sup>e</sup> (n=404)	64 weeks <sup>c</sup> efavirenz 600 mg once daily + lamivudine + zidovudine <sup>e</sup> (n=401)	120 weeks <sup>c,d</sup> REYATAZ 400 mg once daily + stavudine + lamivudine or didanosine (n=279)	73 weeks <sup>c,d</sup> nelfinavir 750 mg TID or 1250 mg BID + stavudine + lamivudine or didanosine (n=191)
<b>Body as a Whole</b>				
Headache	6%	6%	1%	2%
<b>Digestive System</b>				
Nausea	14%	12%	6%	4%
Jaundice/scleral icterus	7%	*	7%	*
Vomiting	4%	7%	3%	3%
Diarrhea	1%	2%	3%	16%
Abdominal pain	4%	4%	4%	2%
<b>Nervous System</b>				
Dizziness	2%	7%	<1%	*
Insomnia	3%	3%	<1%	*
Peripheral neurologic symptoms	<1%	1%	4%	3%
<b>Skin and Appendages</b>				
Rash	7%	10%	5%	1%

\* None reported in this treatment arm.

<sup>a</sup> Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

<sup>b</sup> Based on regimens containing REYATAZ.

<sup>c</sup> Median time on therapy.

<sup>d</sup> Includes long-term follow-up.

<sup>e</sup> As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

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

596 Selected drug-related clinical adverse events of moderate-severe intensity in  $\geq 2\%$  of  
597 treatment-experienced patients receiving REYATAZ/ritonavir are presented in Table 13.

598 For other information regarding observed or potentially serious adverse events, see  
599 **WARNINGS** and **PRECAUTIONS**.

**Table 13: Selected Treatment-Emergent Adverse Events<sup>a</sup> of Moderate or Severe Intensity Reported in  $\geq 2\%$  of Adult Treatment-Experienced Patients,<sup>b</sup> Study AI424-045**

	48 weeks <sup>c</sup> REYATAZ/ritonavir 300/100 mg once daily + tenofovir + NRTI (n=119)	48 weeks <sup>c</sup> lopinavir/ritonavir 400/100 mg twice daily <sup>d</sup> + tenofovir + NRTI (n=118)
<b>Body as a Whole</b>		
Fever	2%	*
<b>Digestive System</b>		
Jaundice/scleral icterus	9%	*
Diarrhea	3%	11%
Nausea	3%	2%
<b>Nervous System</b>		
Depression	2%	<1%
<b>Musculoskeletal System</b>		
Myalgia	4%	*

\* None reported in this treatment arm.

<sup>a</sup> Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

<sup>b</sup> Based on the regimen containing REYATAZ.

<sup>c</sup> Median time on therapy.

<sup>d</sup> As a fixed-dose combination.

600 **Laboratory Abnormalities**

601 **Treatment-Naive Patients**

602 The percentages of adult treatment-naive patients treated with combination therapy  
603 including REYATAZ with Grade 3-4 laboratory abnormalities are presented in Table 14.  
604

**Table 14: Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Naive Patients<sup>a</sup>**

Variable	Limit <sup>d</sup>	Phase III Study AI424-034		Phase II Studies AI424-007, -008	
		64 weeks <sup>b</sup> REYATAZ 400 mg once daily + lamivudine + zidovudine <sup>e</sup> (n=404)	64 weeks <sup>b</sup> efavirenz 600 mg once daily + lamivudine + zidovudine <sup>e</sup> (n=401)	120 weeks <sup>b,c</sup> REYATAZ 400 mg once daily + stavudine + lamivudine or + stavudine + didanosine (n=279)	73 weeks <sup>b,c</sup> nelfinavir 750 mg TID or 1250 mg BID + stavudine + lamivudine or + stavudine + didanosine (n=191)
Chemistry	<u>High</u>				
SGOT/AST	≥5.1 x ULN	2%	2%	7%	5%
SGPT/ALT	≥5.1 x ULN	4%	3%	9%	7%
Total Bilirubin	≥2.6 x ULN	35%	<1%	47%	3%
Amylase	≥2.1 x ULN	*	*	14%	10%
Lipase	≥2.1 x ULN	<1%	1%	4%	5%
Creatine Kinase	≥5.1 x ULN	6%	6%	11%	9%
Total Cholesterol	≥240 mg/dL	6%	24%	19%	48%
Triglycerides	≥751 mg/dL	<1%	3%	4%	2%
Hematology	<u>Low</u>				
Hemoglobin	<8.0 g/dL	5%	3%	<1%	4%
Neutrophils	<750 cells/mm <sup>3</sup>	7%	9%	3%	7%

\* None reported in this treatment arm.

<sup>a</sup> Based on regimen(s) containing REYATAZ.

<sup>b</sup> Median time on therapy.

<sup>c</sup> Includes long-term follow-up.

<sup>d</sup> ULN = upper limit of normal.

<sup>e</sup> As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

605 ***Lipids, Change from Baseline***

606 For Study AI424-034, changes from baseline in fasting LDL-cholesterol, HDL-  
607 cholesterol, total cholesterol, and fasting triglycerides are shown in Table 15.

**Table 15: Lipid Values, Mean Change from Baseline, Study AI424-034**

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

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

<sup>b</sup> Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. Use of serum lipid-reducing agents was more common in the efavirenz treatment arm (3%) than in the REYATAZ arm (1%).

<sup>c</sup> Efavirenz 600 mg once daily with the fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

<sup>d</sup> 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.

<sup>e</sup> Number of patients with LDL-cholesterol measured.

<sup>f</sup> Fasting.

608 **Treatment-Experienced Patients**

609 The percentages of adult treatment-experienced patients treated with combination therapy  
610 including REYATAZ/ritonavir with Grade 3-4 laboratory abnormalities are presented in  
611 Table 16.

612

**Table 16: Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Experienced Patients, Study AI424-045<sup>a</sup>**

Variable	Limit <sup>c</sup>	48 weeks <sup>b</sup>	
		REYATAZ/ritonavir 300/100 mg once daily + tenofovir + NRTI (n=119)	lopinavir/ritonavir 400/100 mg twice daily <sup>d</sup> + tenofovir + NRTI (n=118)
Chemistry	<u>High</u>		
SGOT/AST	≥5.1 x ULN	3%	3%
SGPT/ALT	≥5.1 x ULN	4%	3%
Total Bilirubin	≥2.6 x ULN	49%	<1%
Lipase	≥2.1 x ULN	5%	6%
Creatine Kinase	≥5.1 x ULN	8%	8%
Total Cholesterol	≥240 mg/dL	25%	26%
Triglycerides	≥751 mg/dL	8%	12%
Glucose	≥251 mg/dL	5%	<1%
Hematology	<u>Low</u>		
Platelets	<50,000 cells/mm <sup>3</sup>	2%	3%
Neutrophils	<750 cells/mm <sup>3</sup>	7%	8%

<sup>a</sup> Based on regimen(s) containing REYATAZ.

<sup>b</sup> Median time on therapy.

<sup>c</sup> ULN = upper limit of normal.

<sup>d</sup> As a fixed-dose combination.

613 ***Lipids, Change from Baseline***

614 For Study AI424-045, changes from baseline in fasting LDL-cholesterol, HDL-  
615 cholesterol, total cholesterol, and fasting triglycerides are shown in Table 17. The  
616 observed magnitude of dyslipidemia was less with REYATAZ/ritonavir than with  
617 lopinavir/ritonavir. However, the clinical impact of such findings has not been  
618 demonstrated.

**Table 17: Lipid Values, Mean Change from Baseline, Study AI424-045**

	REYATAZ/ritonavir <sup>a,b</sup>			lopinavir/ritonavir <sup>b,c</sup>		
	Baseline	Week 48		Baseline	Week 48	
	mg/dL	mg/dL	Change <sup>d</sup>	mg/dL	mg/dL	Change <sup>d</sup>
	(n=111 <sup>e</sup> )	(n=75 <sup>e</sup> )	(n=74 <sup>e</sup> )	(n=108 <sup>e</sup> )	(n=76 <sup>e</sup> )	(n=73 <sup>e</sup> )
LDL-Cholesterol <sup>f</sup>	108	98	-10%	104	103	+1%
HDL-Cholesterol	40	39	-7%	39	41	+2%
Total Cholesterol	188	170	-8%	181	187	+6%
Triglycerides <sup>f</sup>	215	161	-4%	196	224	+30%

- <sup>a</sup> REYATAZ 300 mg once daily + ritonavir + tenofovir + 1 NRTI.
- <sup>b</sup> Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. Use of serum lipid-reducing agents was more common in the lopinavir/ritonavir treatment arm (19%) than in the REYATAZ/ritonavir arm (8%).
- <sup>c</sup> Lopinavir/ritonavir (400/100 mg) BID + tenofovir + 1 NRTI.
- <sup>d</sup> 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.
- <sup>e</sup> Number of patients with LDL-cholesterol measured.
- <sup>f</sup> Fasting.

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

620 Liver function tests should be monitored in patients with a history of hepatitis B or C. In  
621 studies AI424-008 and AI424-034, 74 patients treated with 400 mg of REYATAZ once  
622 daily, 58 who received efavirenz, and 12 who received nelfinavir were seropositive for  
623 hepatitis B and/or C at study entry. ALT levels >5 times the upper limit of normal (ULN)  
624 developed in 15% of the REYATAZ-treated patients, 14% of the efavirenz-treated  
625 patients, and 17% of the nelfinavir-treated patients. AST levels >5 times ULN developed  
626 in 9% of the REYATAZ-treated patients, 5% of the efavirenz-treated patients, and 17%  
627 of the nelfinavir-treated patients. Within atazanavir and control regimens, no difference  
628 in frequency of bilirubin elevations was noted between seropositive and seronegative  
629 patients.

630 In study AI424-045, 20 patients treated with REYATAZ/ritonavir 300 mg/100 mg  
631 once daily and 18 patients treated with lopinavir/ritonavir 400 mg/100 mg twice daily  
632 were seropositive for hepatitis B and/or C at study entry. ALT levels >5 times ULN  
633 developed in 25% (5/20) of the REYATAZ/ritonavir-treated patients and 6% (1/18) of  
634 the lopinavir/ritonavir-treated patients. AST levels >5 times ULN developed in 10%  
635 (2/20) of the REYATAZ/ritonavir-treated patients and 6% (1/18) of the  
636 lopinavir/ritonavir-treated patients (see **PRECAUTIONS: General**).

## 637 **OVERDOSAGE**

638 Human experience of acute overdose with REYATAZ is limited. Single doses up to  
639 1200 mg have been taken by healthy volunteers without symptomatic untoward effects.  
640 A single self-administered overdose of 29.2 g of REYATAZ in an HIV-infected patient  
641 (73 times the 400-mg recommended dose) was associated with asymptomatic bifascicular  
642 block and PR interval prolongation. These events resolved spontaneously. At high doses  
643 that lead to high drug exposures, jaundice due to indirect (unconjugated)  
644 hyperbilirubinemia (without associated liver function test changes) or PR interval  
645 prolongation may be observed. (See **WARNINGS, PRECAUTIONS, and CLINICAL**  
646 **PHARMACOLOGY: Effects on Electrocardiogram.**)

647 Treatment of overdosage with REYATAZ should consist of general supportive  
648 measures, including monitoring of vital signs and ECG, and observations of the patient's  
649 clinical status. If indicated, elimination of unabsorbed atazanavir should be achieved by  
650 emesis or gastric lavage. Administration of activated charcoal may also be used to aid  
651 removal of unabsorbed drug. There is no specific antidote for overdose with REYATAZ  
652 (atazanavir sulfate). Since atazanavir is extensively metabolized by the liver and is  
653 highly protein bound, dialysis is unlikely to be beneficial in significant removal of this  
654 medicine.

## 655 **DOSAGE AND ADMINISTRATION**

### 656 **Adults**

657 REYATAZ Capsules must be taken with food.

658 The recommended oral dose of REYATAZ is as follows:

#### 659 *Therapy-Naive Patients*

- 660 • REYATAZ 400 mg (two 200-mg capsules) once daily taken with food.

661 There are no data regarding the use of REYATAZ/ritonavir in therapy-naive  
662 patients.

663 *Therapy-Experienced Patients*

- 664 • REYATAZ 300 mg (two 150-mg capsules) once daily plus ritonavir 100  
665 mg once daily taken with food.

666 REYATAZ without ritonavir is not recommended for treatment-experienced  
667 patients with prior virologic failure (see **Description of Clinical Studies**).

668 Efficacy and safety of REYATAZ with ritonavir in doses greater than 100 mg  
669 once daily have not been established. The use of higher ritonavir doses might alter the  
670 safety profile of atazanavir (cardiac effects, hyperbilirubinemia) and, therefore, is not  
671 recommended. Prescribers should consult the complete prescribing information for  
672 NORVIR<sup>®</sup> (ritonavir) when using this agent.

673 Important dosing information:

674 Efavirenz. In treatment-naïve patients who receive efavirenz and  
675 REYATAZ, the recommended dose is REYATAZ 300 mg with ritonavir  
676 100 mg and efavirenz 600 mg (all once daily). Dosing  
677 recommendations for efavirenz and REYATAZ in treatment-  
678 experienced patients have not been established.

679 Didanosine. When coadministered with didanosine buffered or enteric-  
680 coated formulations, REYATAZ should be given (with food) 2 hours  
681 before or 1 hour after didanosine.

682 Tenofovir disoproxil fumarate. When coadministered with tenofovir, it  
683 is recommended that REYATAZ 300 mg be given with ritonavir 100 mg  
684 and tenofovir 300 mg (all as a single daily dose with food). **REYATAZ**  
685 **without ritonavir should not be coadministered with tenofovir.**

686 H<sub>2</sub>-receptor antagonists.

687 *Treatment-naïve patients*: REYATAZ 400 mg once daily with food at  
688 least 2 hours before and at least 10 hours after the H<sub>2</sub>-receptor antagonist  
689 OR REYATAZ 300 mg with ritonavir 100 mg once daily with food,  
690 without the need for separation from the H<sub>2</sub>-receptor antagonist.

691 *Treatment-experienced patients:* REYATAZ 300 mg with ritonavir  
692 100 mg once daily with food at least 2 hours before and at least 10 hours  
693 after the H<sub>2</sub>-receptor antagonist.

694 For these drugs and other antiretroviral agents for which dosing modification may  
695 be appropriate, see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions** and  
696 **PRECAUTIONS**, Table 11.

## 697 **Patients with Renal Impairment**

698 There are insufficient data to recommend a dosage adjustment for patients with renal  
699 impairment (see **CLINICAL PHARMACOLOGY: Special Populations, Impaired**  
700 *Renal Function*).

## 701 **Patients with Hepatic Impairment**

702 REYATAZ should be used with caution in patients with mild to moderate hepatic  
703 impairment. For patients with moderate hepatic impairment (Child-Pugh Class B) who  
704 have not experienced prior virologic failure, a dose reduction to 300 mg once daily  
705 should be considered. REYATAZ should not be used in patients with severe hepatic  
706 impairment (Child-Pugh Class C). REYATAZ/ritonavir has not been studied in subjects  
707 with hepatic impairment and is not recommended. (See **PRECAUTIONS** and  
708 **CLINICAL PHARMACOLOGY: Special Populations, Impaired Hepatic Function**.)

## 709 **HOW SUPPLIED**

710 REYATAZ<sup>®</sup> (atazanavir sulfate) Capsules are available in the following strengths and  
711 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.

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

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

715

716 Bristol-Myers Squibb Company

717 Princeton, NJ 08543 USA

718

719 XXXXXXXXXXX

Revised \_\_\_\_\_

720 **Patient Information**

721

**REYATAZ**<sup>®</sup> (RAY-ah-taz)

Rx only

722

(generic name = **atazanavir sulfate**)

723

**Capsules**

724

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

725

Read the section "What important information should I know about taking REYATAZ

726

with other medicines?"

727

Read the Patient Information that comes with REYATAZ before you start using it and

728

each time you get a refill. There may be new information. This leaflet provides a

729

summary about REYATAZ and does not include everything there is to know about your

730

medicine. This information does not take the place of talking with your healthcare

731

provider about your medical condition or treatment.

732

### **What is REYATAZ?**

733

REYATAZ is a prescription medicine used with other anti-HIV medicines to treat people

734

who are infected with the human immunodeficiency virus (HIV). HIV is the virus that

735

causes acquired immune deficiency syndrome (AIDS). REYATAZ is a type of anti-HIV

736

medicine called a protease inhibitor. HIV infection destroys CD4+ (T) cells, which are

737

important to the immune system. The immune system helps fight infection. After a large

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number of T cells are destroyed, AIDS develops. REYATAZ helps to block HIV

739

protease, an enzyme that is needed for the HIV virus to multiply. REYATAZ may lower

740

the amount of HIV in your blood, help your body keep its supply of CD4+ (T) cells, and

741

reduce the risk of death and illness associated with HIV.

742

### **Does REYATAZ cure HIV or AIDS?**

743

**REYATAZ does not cure HIV infection or AIDS.** At present there is no cure for HIV

744

infection. People taking REYATAZ may still get opportunistic infections or other

745

conditions that happen with HIV infection. Opportunistic infections are infections that

746

develop because the immune system is weak. Some of these conditions are pneumonia,

747

herpes virus infections, and *Mycobacterium avium* complex (MAC) infections. **It is very**

748

**important that you see your healthcare provider regularly while taking REYATAZ.**

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

## 754 **Who should not take REYATAZ?**

### 755 **Do not take REYATAZ if you:**

- 756 • **are taking certain medicines.** (See “What important information should I know  
757 about taking REYATAZ with other medicines?”) Serious life-threatening side effects  
758 or death may happen. Before you take REYATAZ, tell your healthcare provider  
759 about all medicines you are taking or planning to take. These include other  
760 prescription and nonprescription medicines, vitamins, and herbal supplements.
- 761 • **are allergic to REYATAZ or to any of its ingredients.** The active ingredient is  
762 atazanavir sulfate. See the end of this leaflet for a complete list of ingredients in  
763 REYATAZ. Tell your healthcare provider if you think you have had an allergic  
764 reaction to any of these ingredients.

## 765 **What should I tell my healthcare provider before I take** 766 **REYATAZ?**

### 767 **Tell your healthcare provider:**

- 768 • **If you are pregnant or planning to become pregnant.** It is not known if  
769 REYATAZ can harm your unborn baby. Pregnant women have experienced serious  
770 side effects when taking REYATAZ with other HIV medicines called nucleoside  
771 analogues. You and your healthcare provider will need to decide if REYATAZ is  
772 right for you. If you use REYATAZ while you are pregnant, talk to your healthcare  
773 provider about the Antiretroviral Pregnancy Registry.
- 774 • **If you are breast-feeding.** You should not breast-feed if you are HIV-positive  
775 because of the chance of passing HIV to your baby. Also, it is not known if  
776 REYATAZ can pass into your breast milk and if it can harm your baby. If you are a  
777 woman who has or will have a baby, talk with your healthcare provider about the best  
778 way to feed your baby.
- 779 • **If you have liver problems or are infected with the hepatitis B or C virus.** See  
780 “What are the possible side effects of REYATAZ?”

- 781 • **If you have diabetes.** See "What are the possible side effects of REYATAZ?"  
782 • **If you have hemophilia.** See "What are the possible side effects of REYATAZ?"  
783 • **About all the medicines you take** including prescription and nonprescription  
784 medicines, vitamins, and herbal supplements. Keep a list of your medicines with you  
785 to show your healthcare provider. For more information, see "What important  
786 information should I know about taking REYATAZ with other medicines?" and  
787 "Who should not take REYATAZ?" Some medicines can cause serious side effects if  
788 taken with REYATAZ.

## 789 **How should I take REYATAZ?**

- 790 • **Take REYATAZ once every day exactly as instructed by your healthcare**  
791 **provider.** Your healthcare provider will prescribe the amount of REYATAZ that is  
792 right for you.
- 793 ▪ For adults who have never taken anti-HIV medicines before, the usual dose is 400  
794 mg (two 200-mg capsules) once daily taken with food.
  - 795 ▪ For adults who have taken anti-HIV medicines in the past, the usual dose is 300  
796 mg (two 150-mg capsules) plus 100 mg of NORVIR<sup>®</sup> (ritonavir) once daily taken  
797 with food.
- 798 Your dose will depend on your liver function and on the other anti-HIV medicines  
799 that you are taking. REYATAZ is always used with other anti-HIV medicines. If you  
800 are taking REYATAZ with SUSTIVA<sup>®</sup> (efavirenz) or with VIREAD<sup>®</sup> (tenofovir  
801 disoproxil fumarate), you should also be taking NORVIR<sup>®</sup> (ritonavir).
- 802 • **Always take REYATAZ with food** (a meal or snack) to help it work better. Swallow  
803 the capsules whole. **Do not open the capsules.** Take REYATAZ at the same time  
804 each day.
- 805 • **If you are taking antacids or VIDEX<sup>®</sup> (didanosine) Chewable/Dispersible**  
806 **Buffered Tablets or Enteric-Coated Tablets,** take REYATAZ 2 hours before or  
807 1 hour after these medicines.
- 808 • **If you are taking medicines for indigestion, heartburn, or ulcers such as AXID<sup>®</sup>**  
809 **(nizatidine), PEPCID AC<sup>®</sup> (famotidine), TAGAMET<sup>®</sup> (cimetidine), or**  
810 **ZANTAC<sup>®</sup> (ranitidine),** talk to your healthcare provider.

- 811 • **Do not change your dose or stop taking REYATAZ without first talking with**  
812 **your healthcare provider.** It is important to stay under a healthcare provider's care  
813 while taking REYATAZ.
- 814 • **When your supply of REYATAZ starts to run low,** get more from your healthcare  
815 provider or pharmacy. It is important not to run out of REYATAZ. The amount of  
816 HIV in your blood may increase if the medicine is stopped for even a short time.
- 817 • **If you miss a dose of REYATAZ,** take it as soon as possible and then take your next  
818 scheduled dose at its regular time. If, however, it is within 6 hours of your next dose,  
819 do not take the missed dose. Wait and take the next dose at the regular time. Do not  
820 double the next dose. **It is important that you do not miss any doses of REYATAZ**  
821 **or your other anti-HIV medicines.**
- 822 • **If you take more than the prescribed dose of REYATAZ,** call your healthcare  
823 provider or poison control center right away.

## 824 **Can children take REYATAZ?**

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

## 827 **What are the possible side effects of REYATAZ?**

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

### 832 **The following side effects have been reported with REYATAZ:**

- 833 • **rash** (redness and itching) sometimes occurs in patients taking REYATAZ, most  
834 often in the first few weeks after the medicine is started. Rashes usually go away  
835 within 2 weeks with no change in treatment. Tell your healthcare provider if rash  
836 occurs.
- 837 • **yellowing of the skin or eyes.** These effects may be due to increases in bilirubin  
838 levels in the blood (bilirubin is made by the liver). Call your healthcare provider if  
839 your skin or the white part of your eyes turn yellow. Although these effects may not  
840 be damaging to your liver, skin, or eyes, it is important to tell your healthcare  
841 provider promptly if they occur.

- 842 • **a change in the way your heart beats (heart rhythm change).** Call your healthcare  
843 provider right away if you get dizzy or lightheaded. These could be symptoms of a  
844 heart problem.
- 845 • **diabetes and high blood sugar (hyperglycemia)** sometimes happen in patients  
846 taking protease inhibitor medicines like REYATAZ. Some patients had diabetes  
847 before taking protease inhibitors while others did not. Some patients may need  
848 changes in their diabetes medicine.
- 849 • **if you have liver disease** including hepatitis B or C, your liver disease may get worse  
850 when you take anti-HIV medicines like REYATAZ.
- 851 • **some patients with hemophilia** have increased bleeding problems with protease  
852 inhibitors like REYATAZ.
- 853 • **changes in body fat.** These changes may include an increased amount of fat in the  
854 upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from  
855 the legs, arms, and face may also happen. The cause and long-term health effects of  
856 these conditions are not known at this time.

857 Other common side effects of REYATAZ taken with other anti-HIV medicines  
858 include nausea; headache; stomach pain; vomiting; diarrhea; depression; fever; dizziness;  
859 trouble sleeping; numbness, tingling, or burning of hands or feet; and muscle pain.

## 860 **What important information should I know about taking** 861 **REYATAZ with other medicines\*?**

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

- 866 • Ergot medicines: dihydroergotamine, ergonovine, ergotamine, and methylergonovine  
867 such as CAFERGOT<sup>®</sup>, MIGRANAL<sup>®</sup>, D.H.E. 45<sup>®</sup>, ergotrate maleate,  
868 METHERGINE<sup>®</sup>, and others (used for migraine headaches).
- 869 • HALCION<sup>®</sup> (triazolam, used for insomnia).
- 870 • VERSED<sup>®</sup> (midazolam, used for sedation).
- 871 • ORAP<sup>®</sup> (pimozide, used for Tourette's disorder).

- 872 • PROPULSID<sup>®</sup> (cisapride, used for certain stomach problems).

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

- 875 • CAMPTOSAR<sup>®</sup> (irinotecan, used for cancer),  
876 • CRIXIVAN<sup>®</sup> (indinavir, used for HIV infection). Both REYATAZ and CRIXIVAN  
877 sometimes cause increased levels of bilirubin in the blood.  
878 • Cholesterol-lowering medicines MEVACOR<sup>®</sup> (lovastatin) or ZOCOR<sup>®</sup> (simvastatin).

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

- 882 • Rifampin (also known as RIMACTANE<sup>®</sup>, RIFADIN<sup>®</sup>, RIFATER<sup>®</sup>, or  
883 RIFAMATE<sup>®</sup>, used for tuberculosis).  
884 • St. John's wort (*Hypericum perforatum*), an herbal product sold as a dietary  
885 supplement, or products containing St. John's wort.  
886 • "Proton-pump inhibitors" used for indigestion, heartburn, or ulcers such as AcipHex<sup>®</sup>  
887 (rabeprazole), NEXIUM<sup>®</sup> (esomeprazole), PREVACID<sup>®</sup> (lansoprazole),  
888 PRILOSEC<sup>®</sup> (omeprazole), or PROTONIX<sup>®</sup> (pantoprazole).

889 **Do not take the following medicine if you are taking REYATAZ and NORVIR<sup>®</sup>**  
890 **together.**

- 891 • VFEND<sup>®</sup> (voriconazole).

892 **The following medicines may require your healthcare provider to monitor your**  
893 **therapy more closely:**

- 894 • CIALIS<sup>®</sup> (tadalafil), LEVITRA<sup>®</sup> (vardenafil), or VIAGRA<sup>®</sup> (sildenafil). REYATAZ  
895 may increase the chances of serious side effects that can happen with CIALIS,  
896 LEVITRA, or VIAGRA. Do not use CIALIS, LEVITRA, or VIAGRA while you are  
897 taking REYATAZ unless your healthcare provider tells you it is okay.  
898 • LIPITOR<sup>®</sup> (atorvastatin). There is an increased chance of serious side effects if you  
899 take REYATAZ with this cholesterol-lowering medicine.

- 900 • Medicines for abnormal heart rhythm: CORDARONE<sup>®</sup> (amiodarone), lidocaine,  
901 quinidine (also known as CARDIOQUIN<sup>®</sup>, QUINIDEX<sup>®</sup>, and others).
- 902 • VASCOR<sup>®</sup> (bepridil, used for chest pain).
- 903 • COUMADIN<sup>®</sup> (warfarin).
- 904 • Tricyclic antidepressants such as ELAVIL<sup>®</sup> (amitriptyline), NORPRAMIN<sup>®</sup>  
905 (desipramine), SINEQUAN<sup>®</sup> (doxepin), SURMONTIL<sup>®</sup> (trimipramine),  
906 TOFRANIL<sup>®</sup> (imipramine), or VIVACTIL<sup>®</sup> (protriptyline).
- 907 • Medicines to prevent organ transplant rejection: SANDIMMUNE<sup>®</sup> or NEORAL<sup>®</sup>  
908 (cyclosporin), RAPAMUNE<sup>®</sup> (sirolimus), or PROGRAF<sup>®</sup> (tacrolimus).
- 909 • The antidepressant trazodone (DESYREL<sup>®</sup> and others).
- 910 • Fluticasone propionate (ADVAIR<sup>®</sup>, FLONASE<sup>®</sup>, FLOVENT<sup>®</sup>), given by nose or  
911 inhaled to treat allergic symptoms or asthma. Your doctor may choose not to keep  
912 you on fluticasone, especially if you are also taking NORVIR<sup>®</sup>.

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

- 915 • FORTOVASE<sup>®</sup>, INVIRASE<sup>®</sup> (saquinavir).
- 916 • NORVIR<sup>®</sup> (ritonavir).
- 917 • SUSTIVA<sup>®</sup> (efavirenz).
- 918 • Antacids or buffered medicines.
- 919 • VIDEX<sup>®</sup> (didanosine).
- 920 • VIREAD<sup>®</sup> (tenofovir disoproxil fumarate).
- 921 • MYCOBUTIN<sup>®</sup> (rifabutin).
- 922 • Calcium channel blockers such as CARDIZEM<sup>®</sup> or TIAZAC<sup>®</sup> (diltiazem),  
923 COVERA-HS<sup>®</sup> or ISOPTIN SR<sup>®</sup> (verapamil) and others.
- 924 • BIAXIN<sup>®</sup> (clarithromycin).
- 925 • Medicines for indigestion, heartburn, or ulcers such as AXID<sup>®</sup> (nizatidine),  
926 PEPCID AC<sup>®</sup> (famotidine), TAGAMET<sup>®</sup> (cimetidine), or ZANTAC<sup>®</sup> (ranitidine).

927 **Women who use birth control pills or “the patch” should choose a different kind of**  
928 **contraception.** REYATAZ may affect the safety and effectiveness of birth control pills  
929 or the patch. Talk to your healthcare provider about choosing an effective contraceptive.

930 **Remember:**

931 **1. Know all the medicines you take.**

932 **2. Tell your healthcare provider about all the medicines you take.**

933 **3. Do not start a new medicine without talking to your healthcare provider.**

934 **How should I store REYATAZ?**

935 • Store REYATAZ Capsules at room temperature, 59° to 86° F (15° to 30° C). Do **not**  
936 store this medicine in a damp place such as a bathroom medicine cabinet or near the  
937 kitchen sink.

938 • Keep your medicine in a tightly closed container.

939 • Throw away REYATAZ when it is outdated or no longer needed by flushing it down  
940 the toilet or pouring it down the sink.

941 **General information about REYATAZ**

942 This medicine was prescribed for your particular condition. Do not use REYATAZ for  
943 another condition. Do not give REYATAZ to other people, even if they have the same  
944 symptoms you have. It may harm them. **Keep REYATAZ and all medicines out of the**  
945 **reach of children and pets.**

946 This summary does not include everything there is to know about REYATAZ. Medicines  
947 are sometimes prescribed for conditions that are not mentioned in patient information  
948 leaflets. Remember no written summary can replace careful discussion with your  
949 healthcare provider. If you would like more information, talk with your healthcare  
950 provider or you can call 1-800-321-1335.

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

952 **Active Ingredient:** atazanavir sulfate

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

955

956 \* VIDEX<sup>®</sup> is a registered trademark of Bristol-Myers Squibb Company. COUMADIN<sup>®</sup>  
957 and SUSTIVA<sup>®</sup> are registered trademarks of Bristol-Myers Squibb Pharma Company.  
958 DESYREL<sup>®</sup> is a registered trademark of Mead Johnson and Company. Other brands  
959 listed are the trademarks of their respective owners and are not trademarks of Bristol-  
960 Myers Squibb Company.

961

962 Bristol-Myers Squibb Company  
963 Princeton, NJ 08543 USA

964

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

967 XXXXXXXXXX Revised \_\_\_\_\_

968 Based on package insert dated \_\_\_\_\_

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/s/

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Jeffrey Murray  
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