

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-567**

**APPROVED LABELING**

# 1 REYATAZ™

Rx only

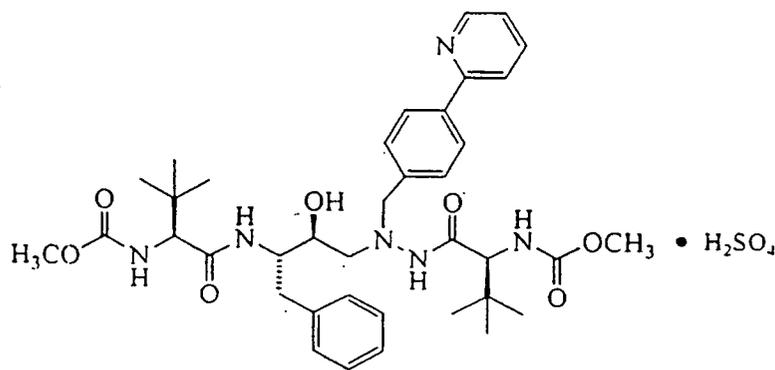
2 (atazanavir sulfate) Capsules

3 (Patient Information Leaflet Included)

## 4 DESCRIPTION

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

6 The chemical name for atazanavir sulfate is (3S,8S,9S,12S)-3,12-Bis(1,1-  
7 dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-  
8 2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate (1:1). Its molecular formula  
9 is  $C_{38}H_{52}N_6O_7 \cdot H_2SO_4$ , which corresponds to a molecular weight of 802.9 (sulfuric acid  
10 salt). The free base molecular weight is 704.9. Atazanavir sulfate has the following  
11 structural formula:



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

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

## 24 CLINICAL PHARMACOLOGY

### 25 Microbiology

#### 26 Mechanism of Action

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

#### 30 Antiviral Activity *In Vitro*

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

#### 39 Resistance *In Vitro*

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

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

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

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

### 69 **Resistance *In Vivo***

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

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

## 92 Pharmacokinetics

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

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

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

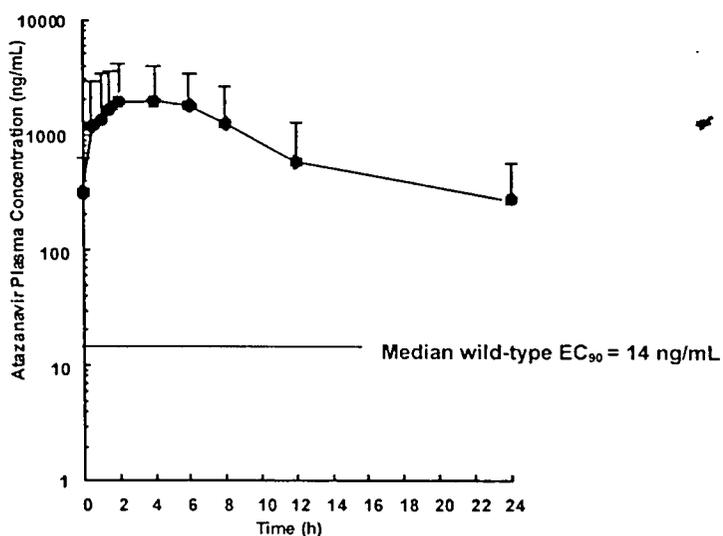
<sup>a</sup> n=12.

95

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

99  
100

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



101

102

### 103 Absorption

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

### 108 Food Effect

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

117 **Distribution**

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

125 **Metabolism**

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

133 **Elimination**

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

140 **Effects on Electrocardiogram**

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

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

## 155 **Special Populations**

### 156 **Age/Gender**

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

### 160 **Race**

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

### 163 **Pediatrics**

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

### 166 **Impaired Renal Function**

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

### 170 **Impaired Hepatic Function**

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

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

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

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

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

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

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

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

202

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

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 QD, d 7-10 and d 18-21	400 mg QD, d 1-10	29	1.06 (0.93, 1.20)	1.28 (1.16, 1.43)	1.91 (1.66, 2.21)
didanosine (ddl) (buffered tablets) plus stavudine (d4T)	ddl: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose simultaneously with ddl and d4T	32 <sup>a</sup>	0.11 (0.06, 0.18)	0.13 (0.08, 0.21)	0.16 (0.10, 0.27)
	ddl: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose 1 hour after ddl + d4T	32 <sup>a</sup>	1.12 (0.67, 1.18)	1.03 (0.64, 1.67)	1.03 (0.61, 1.73)
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)
efavirenz and ritonavir	efavirenz 600 mg QD 2 h after REYATAZ and ritonavir 100 mg QD simultaneously with REYATAZ, d 7-20	400 mg QD, d 1-6 then 300 mg QD d 7-20	13	1.14 (0.83, 1.58)	1.39 (1.02, 1.88)	1.48 (1.24, 1.76)
ketoconazole	200 mg QD, d 7-13	400 mg QD, d 1-13	14	0.99 (0.77, 1.28)	1.10 (0.89, 1.37)	1.03 (0.53, 2.01)
rifabutin	150 mg QD, d 15-28	400 mg QD, d 1-28	7	1.34 (1.14, 1.59)	1.15 (0.98, 1.34)	1.13 (0.68, 1.87)
ritonavir <sup>b</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)

<sup>a</sup> One subject did not receive REYATAZ.

<sup>b</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<sub>max</sub>, AUC, and C<sub>min</sub> by 18%, 103%, and 671%, respectively. The geometric mean values of atazanavir pharmacokinetic parameters when coadministered with ritonavir were: C<sub>max</sub> = 6129 ng/mL, AUC = 57039 ng·h/mL, and C<sub>min</sub> = 1227 ng/mL.

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

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 QD, 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)	0.38 (0.35, 0.43)
				OH-clarithromycin: 0.28 (0.24, 0.33)	OH-clarithromycin: 0.30 (0.26, 0.34)	OH-clarithromycin: 2.64 (2.36, 2.94)
didanosine (ddl) (buffered tablets) plus stavudine (d4T)	ddl: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose simultaneous with ddl and d4T	32 <sup>a</sup>	ddl: 0.92 (0.84, 1.02)	ddl: 0.98 (0.92, 1.05)	d4T: 1.04 (0.94, 1.16)
diltiazem	180 mg QD, d 7-11 and d 19-23	400 mg QD, d 1-11	28	1.98 (1.78, 2.19)	2.25 (2.09, 2.16)	0.41 (0.37, 0.47)
				desacetyl-diltiazem: 2.72 (2.44, 3.03)	desacetyl-diltiazem: 2.65 (2.45, 2.87)	desacetyl-diltiazem: 0.45 (0.41, 0.49)
ethinyl estradiol & norethindrone	Ortho-Novum® 7/7/7 QD, d 1-29	400 mg QD, d 16-29	19	ethinyl estradiol: 1.15 (0.99, 1.32)	ethinyl estradiol: 1.48 (1.31, 1.68)	ethinyl estradiol: 1.91 (1.57, 2.33)
				norethindrone: 1.67 (1.42, 1.96)	norethindrone: 2.10 (1.68, 2.62)	norethindrone: 3.62 (2.57, 5.09)
rifabutin	300 mg QD, d 1-10 then 150 mg QD, d 11-20	600 mg QD <sup>b</sup> , d 11-20	3	1.18 (0.94, 1.48)	2.10 (1.57, 2.79)	3.43 (1.98, 5.96)
				25-O-desacetyl-rifabutin: 8.20 (5.90, 11.40)	25-O-desacetyl-rifabutin: 22.01 (15.97, 30.34)	25-O-desacetyl-rifabutin: 75.6 (30.1, 190.0)
saquinavir (soft gelatin capsules) <sup>c</sup>	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)
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)	lamivudine: 1.03 (0.98, 1.08)	lamivudine: 1.12 (1.04, 1.21)
				zidovudine: 1.05 (0.88, 1.24)	zidovudine: 1.05 (0.96, 1.14)	zidovudine: 0.69 (0.57, 0.84)
				zidovudine glucuronide: 0.95 (0.88, 1.02)	zidovudine glucuronide: 1.00 (0.97, 1.03)	zidovudine glucuronide: 0.82 (0.62, 1.08)

<sup>a</sup> One subject did not receive REYATAZ.

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

<sup>c</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.

NA = not available.

204

## 205 **INDICATIONS AND USAGE**

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

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

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

### 215 **Description of Clinical Studies**

#### 216 **Patients Without Prior Antiretroviral Therapy**

217 *Study AI424-034: REYATAZ once daily compared to efavirenz once daily, each in*  
218 *combination with fixed-dose lamivudine + zidovudine twice daily.* Study AI424-034 was a  
219 randomized, double-blind, multicenter trial comparing REYATAZ (400 mg once daily) to  
220 efavirenz (600 mg once daily), each in combination with a fixed-dose combination of  
221 lamivudine (3TC) (150 mg) and zidovudine (ZDV) (300 mg) given twice daily, in 810  
222 antiretroviral treatment-naive patients. Patients had a mean age of 34 years (range: 18 to 73),  
223 36% were Hispanic, 33% were Caucasian, and 65% were male. The mean baseline CD4 cell  
224 count was 321 cells/mm<sup>3</sup> (range: 64 to 1424 cells/mm<sup>3</sup>) and the mean baseline plasma HIV-1  
225 RNA level was 4.8 log<sub>10</sub> copies/mL (range: 2.2 to 5.9 log<sub>10</sub> copies/mL). Treatment response  
226 and outcomes through Week 48 are presented in Table 4.

227

**Table 4: 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.

228

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

233 *Study AI424-008: REYATAZ 400 mg once daily compared to REYATAZ 600 mg once daily,*  
234 *and compared to nelfinavir 1250 mg twice daily, each in combination with stavudine and*  
235 *lamivudine twice daily.* Study AI424-008 was a 48-week, randomized, multicenter trial,  
236 blinded to dose of REYATAZ, comparing REYATAZ at two dose levels (400 mg and 600  
237 mg once daily) to nelfinavir (1250 mg twice daily), each in combination with stavudine (40  
238 mg) and lamivudine (150 mg) given twice daily, in 467 antiretroviral treatment-naive  
239 patients. Patients had a mean age of 35 years (range: 18 to 69), 55% were Caucasian, and  
240 63% were male. The mean baseline CD4 cell count was 295 cells/mm<sup>3</sup> (range: 4 to 1003  
241 cells/mm<sup>3</sup>) and the mean baseline plasma HIV-1 RNA level was 4.7 log<sub>10</sub> copies/mL (range:  
242 1.8 to 5.9 log<sub>10</sub> copies/mL). Treatment response and outcomes through Week 48 are  
243 presented in Table 5.

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

Outcome	REYATAZ 400 mg once daily + lamivudine + stavudine (n=181)	nelfinavir 1250 mg twice daily + lamivudine + stavudine (n=91)
Responder <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.

244

245 Through 48 weeks of therapy, the mean increase from baseline in CD4 cell count was  
246 234 cells/mm<sup>3</sup> for the REYATAZ 400-mg arm and 211 cells/mm<sup>3</sup> for the nelfinavir arm.

#### 247 **Patients With Prior Antiretroviral Therapy**

248 *Study AI424-043: REYATAZ once daily compared to lopinavir + ritonavir twice daily, each*  
249 *in combination with two nucleosides.* Study AI424-043 is an ongoing, randomized, open-  
250 label, multicenter trial comparing REYATAZ (400 mg once daily) to lopinavir + ritonavir  
251 (400/100 mg twice daily), each in combination with two NRTIs, in 300 patients who  
252 experienced virologic failure to only one prior PI-containing regimen. For the 229 patients  
253 who have been assessed for efficacy, the mean time of prior exposure to antiretrovirals was  
254 140 weeks for PIs, 180 weeks for NRTIs, and 85 weeks for NNRTIs (13% of patients). The  
255 mean age was 38 years (range: 23 to 64); 53% were Hispanic, 41% were Caucasian, and 81%  
256 were male. The mean baseline CD4 cell count was 318 cells/mm<sup>3</sup> (range: 18 to 1118  
257 cells/mm<sup>3</sup>) and the mean baseline plasma HIV-1 RNA level was 4.17 log<sub>10</sub> copies/mL  
258 (range: 2.60 to 5.87 log<sub>10</sub> copies/mL). Treatment response and outcomes through Week 24  
259 are presented in Table 6.

260

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

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

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

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

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

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

261

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

264 **CONTRAINDICATIONS**

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

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

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

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

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

270

271 **WARNINGS**

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

275 **Drug Interactions**

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

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

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

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

## 300 PR Interval Prolongation

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

311 In a pharmacokinetic study between atazanavir 400 mg once daily and diltiazem 180  
312 mg once daily, a CYP3A4 substrate, there was a 2-fold increase in the diltiazem plasma  
313 concentration and an additive effect on the PR interval. When used in combination with  
314 atazanavir, a dose reduction of diltiazem by one half should be considered and ECG  
315 monitoring is recommended. In a pharmacokinetic study between atazanavir 400 mg once  
316 daily and atenolol 50 mg once daily, there was no substantial additive effect of atazanavir  
317 and atenolol on the PR interval. When used in combination with atazanavir, there is no need  
318 to adjust the dose of atenolol. (See **PRECAUTIONS: Drug Interactions**.)

319 Pharmacokinetic studies between atazanavir and other drugs that prolong the PR  
320 interval including beta blockers (other than atenolol), verapamil, and digoxin have not been  
321 performed. An additive effect of atazanavir and these drugs cannot be excluded; therefore,  
322 caution should be exercised when atazanavir is given concurrently with these drugs,  
323 especially those that are metabolized by CYP3A4 (eg, verapamil). (See **PRECAUTIONS:**  
324 **Drug Interactions**.)

## 325 Diabetes Mellitus/Hyperglycemia

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

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

## 335 **PRECAUTIONS**

### 336 **General**

#### 337 **Hyperbilirubinemia**

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

#### 348 **Hepatic Impairment and Toxicity**

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

#### 355 **Resistance/Cross-Resistance**

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

#### 359 **Hemophilia**

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

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

### 365 **Lactic Acidosis Syndrome**

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

### 371 **Fat Redistribution**

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

### 377 **Information for Patients**

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

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

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

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

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

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

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

404 REYATAZ should be taken with food to enhance absorption.

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

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

## 414 **Drug Interactions**

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

424 Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of  
 425 atazanavir are expected if antacids, buffered medications, H<sub>2</sub>-receptor antagonists, and  
 426 proton-pump inhibitors are administered with atazanavir.

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

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

**Table 8: Drugs That Should Not Be Administered with REYATAZ**

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

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

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir or Concomitant Drug	Clinical Comment
<b>HIV Antiviral Agents</b>		
Nucleoside Reverse Transcriptase Inhibitors (NRTIs): didanosine buffered formulations	↓ atazanavir	Coadministration with REYATAZ did not alter exposure to didanosine; however, exposure to atazanavir was markedly decreased by coadministration of REYATAZ with didanosine buffered tablets (presumably due to the increase in gastric pH caused by buffers in the didanosine tablets). In addition, it is recommended that didanosine be administered on an empty stomach; therefore, REYATAZ should be given (with food) 2 h before or 1 h after didanosine buffered formulations (see <b>CLINICAL PHARMACOLOGY: Drug-Drug Interactions</b> ). (Although no interaction is expected with didanosine EC capsules, because didanosine EC capsules are to be given on an empty stomach and REYATAZ is to be given with food, they should be administered at different times.)
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs): efavirenz	↓ atazanavir	If REYATAZ is to be coadministered with efavirenz, which decreases atazanavir exposure, it is recommended that REYATAZ 300 mg with ritonavir 100 mg be coadministered with efavirenz 600 mg (all as a single daily dose with food), as this combination results in atazanavir exposure that approximates the mean exposure to atazanavir produced by 400 mg of REYATAZ alone. REYATAZ without ritonavir should not be coadministered with efavirenz.
Protease Inhibitors: saquinavir (soft gelatin capsules)	↑ saquinavir	Appropriate dosing recommendations for this combination, with respect to efficacy and safety, have not been established.
Protease Inhibitors: ritonavir	↑ atazanavir	Coadministration of REYATAZ and ritonavir is currently under clinical investigation. If REYATAZ is coadministered with ritonavir, it is recommended that REYATAZ 300 mg once daily be given with ritonavir 100 mg once daily with food.
<b>Other Agents</b>		
Antacids and buffered medications	↓ atazanavir	Reduced plasma concentrations of atazanavir are expected if antacids, including buffered medications, are administered with REYATAZ. REYATAZ should be administered 2 hours before or 1 hour after these medications.
Antiarrhythmics: amiodarone, lidocaine (systemic), quinidine	↑ amiodarone, lidocaine (systemic), quinidine	Coadministration with REYATAZ has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with REYATAZ.
Anticoagulants: warfarin	↑ warfarin	Coadministration with REYATAZ has the potential to produce serious and/or life-threatening bleeding and has not been studied. It is recommended that INR (International Normalization Ratio) be monitored.
Antidepressants: tricyclic antidepressants	↑ tricyclic antidepressants	Coadministration with REYATAZ has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with REYATAZ.
Antimycobacterials: rifabutin	↑ rifabutin	A rifabutin dose reduction of up to 75% (eg, 150 mg every other day or 3 times per week) is recommended.
Calcium channel blockers: diltiazem	↑ diltiazem and desacetyl-diltiazem	Caution is warranted. A dose reduction of diltiazem by 50% should be considered. ECG monitoring is recommended.
eg, felodipine, nifedipine, nicardipine, and verapamil	↑ calcium channel blocker	Caution is warranted. Dose titration of the calcium channel blocker should be considered. ECG monitoring is recommended.
Erectile dysfunction agents: sildenafil	↑ sildenafil	Coadministration may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism. Use sildenafil with caution at a reduced dose of 25 mg every 48 hours and monitor for adverse events.
HMG-CoA reductase inhibitors: atorvastatin	↑ atorvastatin	The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including REYATAZ, are used in combination with atorvastatin. Caution should be exercised.

H <sub>2</sub> -Receptor antagonists	↓ atazanavir	Reduced plasma concentrations of atazanavir are expected if H <sub>2</sub> -receptor antagonists are administered with REYATAZ. This may result in loss of therapeutic effect and development of resistance. To lessen the effect of H <sub>2</sub> -receptor antagonists on atazanavir exposure, it is recommended that an H <sub>2</sub> -receptor antagonist and REYATAZ be administered as far apart as possible, preferably 12 hours apart.
Immunosuppressants: cyclosporin, sirolimus, tacrolimus	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with REYATAZ.
Macrolide antibiotics: clarithromycin	↑ clarithromycin ↓ 14-OH clarithromycin ↑ atazanavir	Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a dose reduction of clarithromycin by 50% should be considered when it is coadministered with REYATAZ. In addition, concentrations of the active metabolite 14-OH clarithromycin are significantly reduced; consider alternative therapy for indications other than infections due to <i>Mycobacterium avium</i> complex.
Oral contraceptives: ethinyl estradiol and norethindrone	↑ ethinyl estradiol ↑ norethindrone	Mean concentrations of ethinyl estradiol, when coadministered as a 35-μg dose with REYATAZ, are increased to a level between mean concentrations produced by a 35-μg and a 50-μg ethinyl estradiol dose. Decreased HDL or increased insulin resistance may be associated with increased mean concentrations of norethindrone, when coadministered with REYATAZ, particularly in diabetic women. Caution should be exercised. It is recommended that the lowest effective dose of each oral contraceptive component be used.

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\* For magnitude of interactions see **CLINICAL PHARMACOLOGY**: Tables 2 and 3.

435

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

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

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

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

449 **Pregnancy**

450 **Pregnancy Category B**

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

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

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

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

472 **Nursing Mothers**

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

479 **Pediatric Use**

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

483 **Geriatric Use**

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

491 **ADVERSE REACTIONS**

492 **Adult Patients**

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

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

**Table 10: Selected Treatment-Emergent Adverse Events of Moderate or Severe Intensity Reported in  $\geq 3\%$  of Adult Treatment-Naive Patients<sup>a</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>d</sup>  (n=404)	64 weeks <sup>b</sup> efavirenz 600 mg once daily + lamivudine + zidovudine <sup>d</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)
<b>Body as a Whole</b>				
Headache	14	13	10	8
Fever	4	6	5	5
Pain	3	2	1	2
Fatigue	2	2	3	2
Back pain	2	5	6	3
<b>Digestive System</b>				
Nausea	16	13	10	6
Jaundice/scleral icterus	7	<1	8	*
Abdominal pain	6	5	10	8
Vomiting	6	8	8	7
Diarrhea	6	7	8	25
<b>Metabolic and Nutritional System</b>				
Lipodystrophy	1	1	8	3
<b>Musculoskeletal System</b>				
Arthralgia	<1	2	4	4
<b>Nervous System</b>				
Depression	4	5	8	3
Insomnia	3	5	1	<1
Dizziness	3	8	1	*
Peripheral neurologic symptoms	1	2	8	7
<b>Respiratory System</b>				
Increased cough	3	4	5	1
<b>Skin and Appendages</b>				
Rash	9	13	10	3

\* 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> As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

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

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

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

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

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

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

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

519 *Endocrine system:* decreased male fertility.

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

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

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

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

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

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

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

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

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

### 536 Laboratory Abnormalities

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

539

**Table 11: Selected Grade 3-4 Laboratory Abnormalities Reported in  $\geq 2\%$  of Adult Treatment-Naïve 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)
<b>Chemistry</b>					
	<u>High</u>				
SGOT/AST	$\geq 5.1 \times \text{ULN}$	2%	2%	7%	5%
SGPT/ALT	$\geq 5.1 \times \text{ULN}$	4%	3%	9%	7%
Total Bilirubin	$\geq 2.6 \times \text{ULN}$	35%	<1%	47%	3%
Amylase	$\geq 2.1 \times \text{ULN}$	*	*	14%	10%
Lipase	$\geq 2.1 \times \text{ULN}$	<1%	1%	4%	5%
<b>Hematology</b>					
	<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.

540

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

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

552 **Lipids**

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

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

	REYATAZ <sup>a</sup>			efavirenz <sup>b</sup>		
	Baseline mg/dL (n=383 <sup>d</sup> )	Week 48 mg/dL (n=283 <sup>d</sup> )	Change <sup>c</sup> (n=272 <sup>d</sup> )	Baseline mg/dL (n=378 <sup>d</sup> )	Week 48 mg/dL (n=264 <sup>d</sup> )	Change <sup>c</sup> (n=253 <sup>d</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>e</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> Efavirenz 600 mg once daily with the fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

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

<sup>e</sup> Fasting.

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

**Table 13: Selected Grade 3-4 Laboratory Abnormalities Reported in  $\geq 2\%$  of Adult Treatment-Experienced Patients<sup>a</sup>**

Variable	Limit <sup>c</sup>	Phase III Study AI424-043		Phase III Study AI424-045		
		24 weeks <sup>b</sup> REYATAZ 400 mg once daily + 2 NRTIs (n=144)	24 weeks <sup>b</sup> lopinavir + ritonavir (400/100 mg) BID <sup>d</sup> + 2 NRTIs (n=146)	15 weeks <sup>b</sup> REYATAZ 300 mg once daily + ritonavir 100 mg once daily + tenofovir + NRTI (n=119)	12 weeks <sup>b</sup> REYATAZ 400 mg once daily + saquinavir <sup>e</sup> 1200 mg once daily + tenofovir + NRTI (n=110)	13 weeks <sup>b</sup> lopinavir + ritonavir (400/100 mg) BID <sup>d</sup> + tenofovir + NRTI (n=118)
Chemistry	High					
SGOT/AST	$\geq 5.1 \times \text{ULN}$	3%	1%	<1%	2%	<1%
SGPT/ALT	$\geq 5.1 \times \text{ULN}$	6%	1%	3%	3%	3%
Total Bilirubin	$\geq 2.6 \times \text{ULN}$	22%	*	40%	13%	*
Lipase	$\geq 2.1 \times \text{ULN}$	4%	3%	4%	<1%	6%
Hematology	Low					
Platelets	$< 50,000 / \text{mm}^3$	*	*	<1%	4%	<1%
Neutrophils	$< 750 \text{ cells}/\text{mm}^3$	5%	3%	4%	5%	4%

\* 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> ULN=upper limit of normal.

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

<sup>e</sup> Soft gelatin capsules.

558

## 559 Lipids

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

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

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

<sup>a</sup> REYATAZ 400 mg once daily + 2 NRTIs.

<sup>b</sup> Lopinavir + ritonavir (400/100 mg) BID + 2 NRTIs.

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

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

<sup>e</sup> Protocol-defined co-primary safety outcome measure.

<sup>f</sup> Fasting.

562

563 **OVERDOSAGE**

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

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

579 **DOSAGE AND ADMINISTRATION**

580 **Adults**

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

583 Important dosing information:

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

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

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

#### 594 **Patients with Renal Impairment**

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

#### 598 **Patients with Hepatic Impairment**

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

#### 604 **HOW SUPPLIED**

605 REYATAZ™ (atazanavir sulfate) Capsules are available in the following strengths and  
606 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.

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

609

610 US Patent Nos: 5849911 and 6087383.

611

612

613 Bristol-Myers Squibb Virology

614 Bristol-Myers Squibb Company

615 Princeton, NJ 08543 USA

616

Issued \_\_\_\_\_

1 **Patient Information**

2 **REYATAZ™** (RAY-ah-taz)

**Rx only**

3 (generic name = **atazanavir sulfate**)

4 **Capsules**

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

6 Read the section "What important information should I know about taking REYATAZ  
7 with other medicines?"

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

13 **What is REYATAZ?**

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

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

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

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

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

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

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

## 46 **What should I tell my healthcare provider before I take** 47 **REYATAZ?**

48 **Tell your healthcare provider:**

- 49 • **If you are pregnant or planning to become pregnant.** It is not known if  
50 REYATAZ can harm your unborn baby. Pregnant women have experienced serious  
51 side effects when taking REYATAZ with other HIV medicines called nucleoside  
52 analogues. You and your healthcare provider will need to decide if REYATAZ is  
53 right for you. If you use REYATAZ while you are pregnant, talk to your healthcare  
54 provider about the Antiretroviral Pregnancy Registry.
- 55 • **If you are breast-feeding.** You should not breast feed if you are HIV-positive  
56 because of the chance of passing HIV to your baby. Also, it is not known if  
57 REYATAZ can pass into your breast milk and if it can harm your baby. If you are a  
58 woman who has or will have a baby, talk with your healthcare provider about the best  
59 way to feed your baby.
- 60 • **If you have liver problems or are infected with the hepatitis B or C virus.** See  
61 "What are the possible side effects of REYATAZ?"
- 62 • **If you have diabetes.** See "What are the possible side effects of REYATAZ?"

- 63 • **If you have hemophilia.** See "What are the possible side effects of REYATAZ?"  
64 • **About all the medicines you take** including prescription and nonprescription  
65 medicines, vitamins, and herbal supplements. Keep a list of your medicines with you  
66 to show your healthcare provider. For more information, see "What important  
67 information I should know about taking REYATAZ with other medicines?" and  
68 "Who should not take REYATAZ?" Some medicines can cause serious side effects if  
69 you also take REYATAZ.

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

- 71 • **Take REYATAZ once every day exactly as instructed by your healthcare**  
72 **provider.** Your healthcare provider will prescribe the amount of REYATAZ that is  
73 right for you. Your dose will depend on your liver function and on the other anti-HIV  
74 medicines that you are taking. REYATAZ is always used with other anti-HIV  
75 medicines. If you are taking REYATAZ and Sustiva<sup>®</sup> (efavirenz), you should also be  
76 taking Norvir<sup>®</sup> (ritonavir).
- 77 • **Always take REYATAZ with food** (a meal or snack) to help it work better. Swallow  
78 the capsules whole. **Do not open the capsules.** Try to take REYATAZ at the same  
79 time each day.
- 80 • **If you are taking antacids or Videx<sup>®</sup> (didanosine) Chewable/Dispersible**  
81 **Buffered Tablets,** take REYATAZ 2 hours before or 1 hour after these medicines.
- 82 • **Do not change your dose or stop taking REYATAZ without first talking with your**  
83 **healthcare provider.** It is important to stay under a healthcare provider's care while taking  
84 REYATAZ.
- 85 • **When your supply of REYATAZ starts to run low,** get more from your healthcare  
86 provider or pharmacy. It is important not to run out of REYATAZ. The amount of  
87 HIV in your blood may increase if the medicine is stopped for even a short time.
- 88 • **If you miss a dose of REYATAZ,** take it as soon as possible and then take your next  
89 scheduled dose at its regular time. If, however, it is within 6 hours of your next dose,  
90 do not take the missed dose. Wait and take the next dose at the regular time. Do not  
91 double the next dose. **It is important that you do not miss any doses of REYATAZ**  
92 **or your other anti-HIV medicines.**
- 93 • **If you take more than the prescribed dose of REYATAZ,** call your healthcare  
94 provider or poison control center right away.

95 **Can children take REYATAZ?**

96 REYATAZ has not been fully studied in children under 16 years of age. REYATAZ is  
97 not recommended for use in babies under the age of 3 months.

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

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

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

- 104 • **yellowing of the skin or eyes.** These effects may be due to increases in bilirubin  
105 levels in the blood (bilirubin is made by the liver). Call your healthcare provider if  
106 your skin or the white part of your eyes turn yellow. Although these effects may not  
107 be damaging to your liver, skin, or eyes, it is important to tell your healthcare  
108 provider promptly if they occur.
- 109 • **a change in the way your heart beats (heart rhythm change).** Call your healthcare  
110 provider right away if you get dizzy or lightheaded. These could be symptoms of a  
111 heart problem.
- 112 • **diabetes and high blood sugar (hyperglycemia)** sometimes happen in patients  
113 taking protease inhibitor medicines like REYATAZ. Some patients had diabetes  
114 before taking protease inhibitors while others did not. Some patients may need  
115 changes in their diabetes medicine.
- 116 • **if you have liver disease** including hepatitis B or C, your liver disease may get worse  
117 when you take anti-HIV medicines like REYATAZ.
- 118 • **some patients with hemophilia** have increased bleeding problems with protease  
119 inhibitors like REYATAZ.
- 120 • **a serious condition called lactic acidosis syndrome** (a severe buildup of an acid in  
121 the blood that sometimes causes death). Some people who have taken REYATAZ  
122 with anti-HIV medicines called nucleoside analogues have developed lactic acidosis  
123 syndrome. Lactic acidosis syndrome has happened more in people who are female or  
124 obese (very overweight). Lactic acidosis syndrome is a medical emergency and must  
125 be treated in the hospital. **Call your healthcare provider right away and do not**

126 **continue to take REYATAZ and your other anti-HIV medicines unless**  
127 **instructed to by your healthcare provider if you get any of the following signs of**  
128 **lactic acidosis syndrome:**

- 129 • You have persistent nausea, vomiting, or unusual or unexpected stomach  
130 discomfort,
- 131 • You feel very weak and tired,
- 132 • You have trouble breathing,
- 133 • You have weakness, especially in your arm and legs.
- 134 • **changes in body fat.** These changes may include an increased amount of fat in the  
135 upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from  
136 the legs, arms, and face may also happen. The cause and long-term health effects of  
137 these conditions are not known at this time.

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

#### 142 **What important information should I know about taking** 143 **REYATAZ with other medicines\*?**

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

- 148 • Ergot medicines: dihydroergotamine, ergonovine, ergotamine, and methylergonovine  
149 such as Cafergot<sup>®</sup>, Migranal<sup>®</sup>, D.H.E. 45<sup>®</sup>, ergotrate maleate, Methergine<sup>®</sup>, and  
150 others (used for migraine headaches),
- 151 • Halcion<sup>®</sup> (triazolam, used for insomnia),
- 152 • Versed<sup>®</sup> (midazolam, used for sedation),
- 153 • Orap<sup>®</sup> (pimozide, used for Tourette's disorder),
- 154 • Propulsid<sup>®</sup> (cisapride, used for certain stomach problems).

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

- 157 • Camptosar<sup>®</sup> (irinotecan, used for cancer),

- 158 • Vascor<sup>®</sup> (bepridil, used for high blood pressure),
- 159 • Crixivan<sup>®</sup> (indinavir, used for HIV infection). Both REYATAZ and Crixivan
- 160 sometimes cause increased levels of bilirubin in the blood.
- 161 • Cholesterol-lowering medicines Mevacor<sup>®</sup> (lovastatin) or Zocor<sup>®</sup> (simvastatin).

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

- 165 • Rifampin (also known as Rimactane<sup>®</sup>, Rifadin<sup>®</sup>, Rifater<sup>®</sup>, or Rifamate<sup>®</sup>, used for
- 166 tuberculosis).
- 167 • St. John's wort (*Hypericum perforatum*), an herbal product sold as a dietary
- 168 supplement, or products containing St. John's wort.
- 169 • "Proton-pump inhibitors" used for indigestion, heartburn, or ulcers such as AcipHex<sup>®</sup>
- 170 (rabeprazole), Nexium<sup>®</sup> (esomeprazole), Prevacid<sup>®</sup> (lansoprazole), Prilosec<sup>®</sup>
- 171 (omeprazole), or Protonix<sup>®</sup> (pantoprazole).

172 **The following medicines may require your healthcare provider to monitor your**  
173 **therapy more closely:**

- 174 • Viagra<sup>®</sup> (sildenafil). REYATAZ may increase the chances of serious side effects that
- 175 can happen with Viagra. Do not use Viagra while you are taking REYATAZ, unless
- 176 your healthcare provider tells you it is okay.
- 177 • Lipitor<sup>®</sup> (atorvastatin). There is an increased chance of serious side effects if you take
- 178 REYATAZ with this cholesterol-lowering medicine.
- 179 • Medicines for abnormal heart rhythm: Cordarone<sup>®</sup> (amiodarone), lidocaine, quinidine
- 180 (also known as Cardioquin<sup>®</sup>, Quinidex<sup>®</sup>, and others).
- 181 • Coumadin<sup>®</sup> (warfarin).
- 182 • Tricyclic antidepressants such as Elavil<sup>®</sup> (amitriptyline), Norpramin<sup>®</sup> (desipramine),
- 183 Sinequan<sup>®</sup> (doxepin), Surmontil<sup>®</sup> (trimipramine), Tofranil<sup>®</sup> (imipramine), or
- 184 Vivactil<sup>®</sup> (protriptyline).
- 185 • Medicines to prevent organ transplant rejection: Sandimmune<sup>®</sup> or Neoral<sup>®</sup>
- 186 (cyclosporin), Rapamune<sup>®</sup> (sirolimus), or Prograf<sup>®</sup> (tacrolimus).

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

- 189 • Sustiva<sup>®</sup> (efavirenz).
- 190 • Fortovase<sup>®</sup>, Invirase<sup>®</sup> (saquinavir).
- 191 • Norvir<sup>®</sup> (ritonavir).
- 192 • Mycobutin<sup>®</sup> (rifabutin).
- 193 • Calcium channel blockers such as Cardizem<sup>®</sup> or Tiazac<sup>®</sup> (diltiazem), Covera-HS<sup>®</sup> or  
194 Isoptin SR<sup>®</sup> (verapamil) and others.
- 195 • Biaxin<sup>®</sup> (clarithromycin).
- 196 • oral contraceptives ("the pill").
- 197 • Videx<sup>®</sup> (didanosine) or antacids.
- 198 • Medicines for indigestion, heartburn, or ulcers such as Axid<sup>®</sup> (nizatidine), Pepcid  
199 AC<sup>®</sup> (famotidine), Tagamet<sup>®</sup> (cimetidine), or Zantac<sup>®</sup> (ranitidine).

200 **Remember:**

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

204 **How should I store REYATAZ?**

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

211 **General information about REYATAZ**

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

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

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

222 **Active Ingredient:** atazanavir sulfate

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

225

226 \* Videx<sup>®</sup> is a registered trademark of Bristol-Myers Squibb Company. Coumadin<sup>®</sup> and  
227 Sustiva<sup>®</sup> are registered trademarks of Bristol-Myers Squibb Pharma Company. Other  
228 brands listed are the trademarks of their respective owners and are not trademarks of  
229 Bristol-Myers Squibb Company.

230

231 Bristol-Myers Squibb Virology  
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233 Princeton, NJ 08543 USA

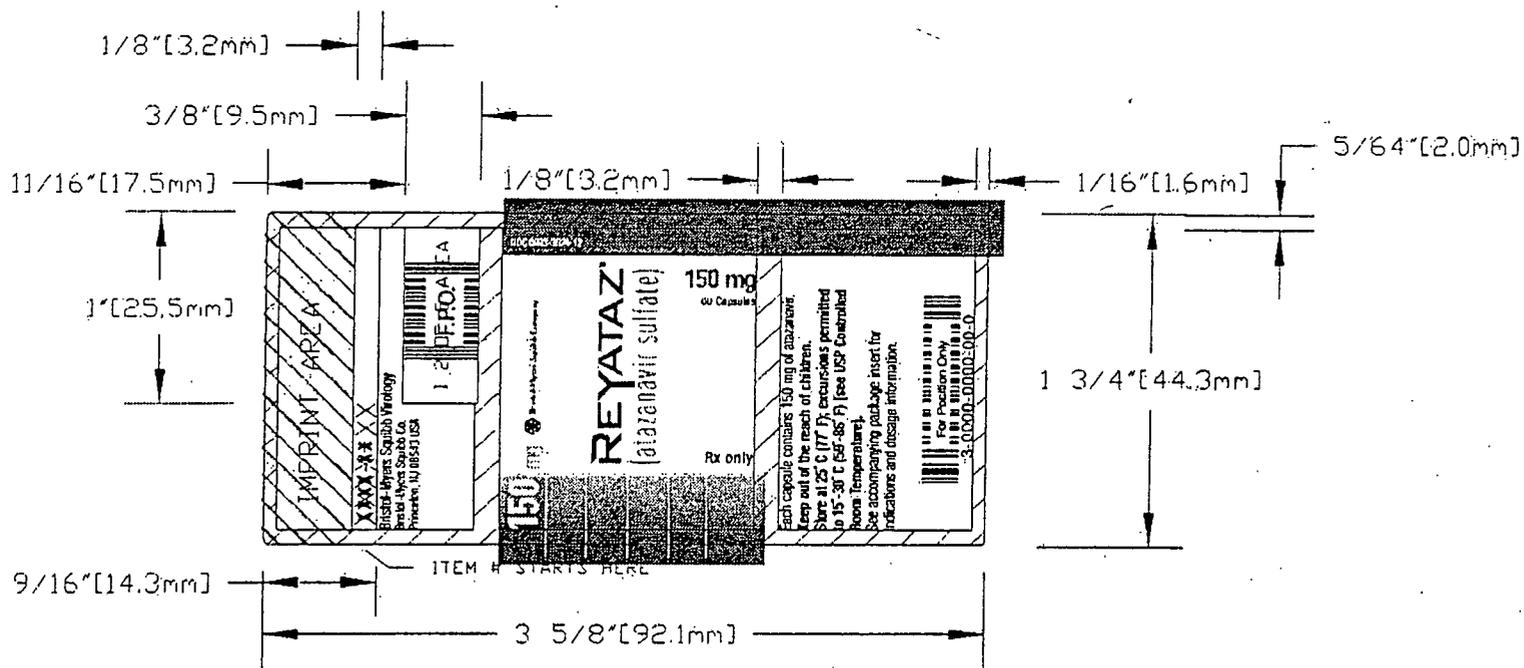
234

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

237 xxxxxxxx Issued xxxxx xxxx Based on xxxxxx (xx/xx)

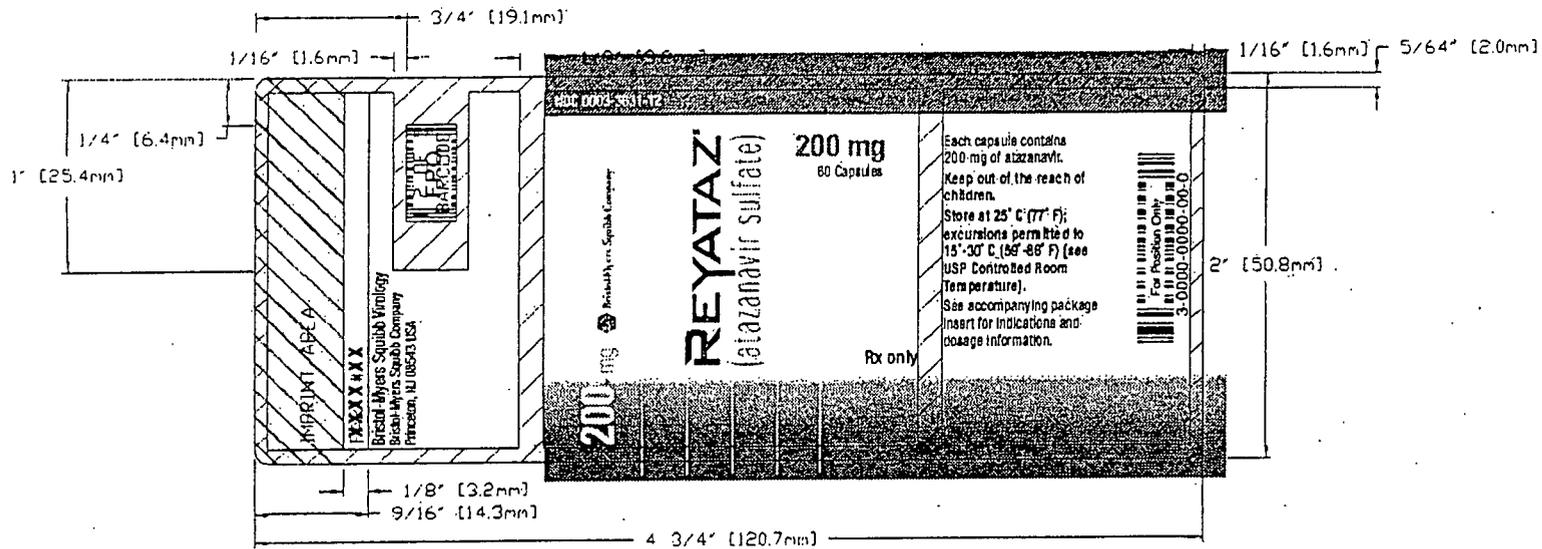
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NOTE:  
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NOTE

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FOR USE WITH 200CC BOTTLE

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