REYATAZ®

Rx only

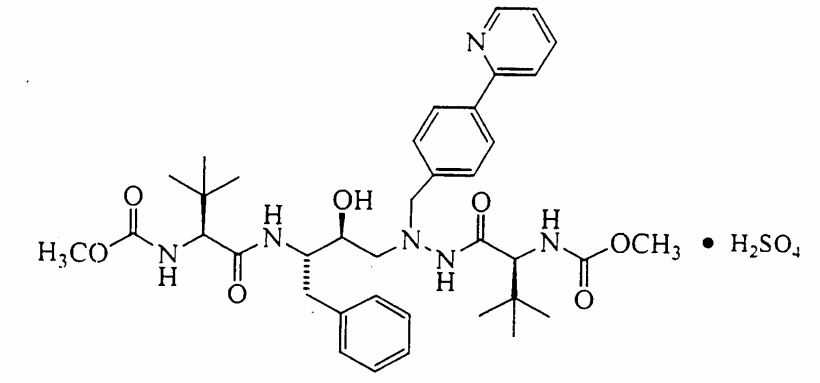
(atazanavir sulfate) Capsules

(Patient Information Leaflet Included)

DESCRIPTION

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

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



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

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

CLINICAL PHARMACOLOGY

Microbiology

Mechanism of Action

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

Antiviral Activity *In Vitro*

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

Resistance

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

Clinical Studies of Treatment-Naive Patients: ATV-resistant clinical isolates from treatment-naive patients who experienced virologic failure developed an I50L mutation (after an average of 50 weeks of ATV therapy), often in combination with an A71V mutation. In

treatment-naive patients, viral isolates that developed the I50L mutation showed phenotypic resistance to ATV but retained *in vitro* susceptibility to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir); however, there are no clinical data available to demonstrate the effect of the I50L mutation on the efficacy of subsequently administered PIs.

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

Cross-Resistance

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

Genotypic and/or phenotypic analysis of baseline virus may aid in determining ATV susceptibility before initiation of ATV/RTV therapy. An association between virologic response at 48 weeks and the number and type of primary PI-resistance-associated mutations detected in baseline HIV-1 isolates from antiretroviral-experienced patients receiving

ATV/RTV once daily or lopinavir (LPV)/RTV twice daily in Study AI424-045 is shown in Table 1.

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

	Virologic Response = HIV RNA <400 copies/mL[b]	
Number and Type of Baseline PI Mutations[a]	**ATV/RTV (n=110)**	**LPV/RTV (n=113)**
3 or more primary PI mutations including:[c]		
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)
Number of baseline primary PI mutations[a]		
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)

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

[b] Results should be interpreted with caution because the subgroups were small.

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

The response rates of antiretroviral-experienced patients in Study AI424-045 were analyzed by baseline phenotype (shift in *in vitro* susceptibility relative to reference, Table 2).

The analyses are based on a select patient population with 62% of patients receiving an NNRTI-based regimen before study entry compared to 35% receiving a PI-based regimen. Additional data are needed to determine clinically relevant break points for REYATAZ.

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

Baseline Phenotype[a]	Virologic Response = HIV RNA <400 copies/mL[b] 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)

[a] Fold change in *in vitro* susceptibility relative to the wild-type reference.

[b] Results should be interpreted with caution because the subgroups were small.

Pharmacokinetics

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

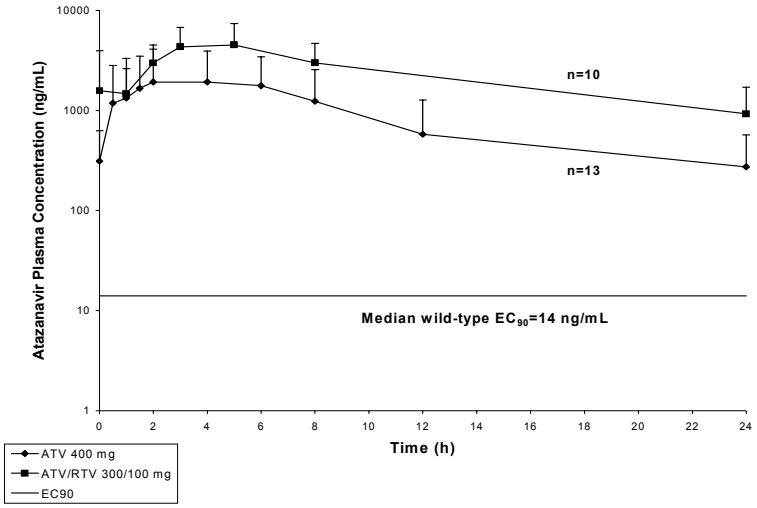
Table 3: Steady-State Pharmacokinetics of Atazanavir in Healthy Subjects or HIV-Infected Patients in the Fed State

	400 mg once daily		300 mg with ritonavir 100 mg once daily	
Parameter	**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)[a]	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)[b]	1441 (757)	862 (838)

[a] n=26.
[b] n=12.

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

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



Absorption

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

Food Effect

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

Distribution

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

Metabolism

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

Elimination

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

Effects on Electrocardiogram

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

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

Special Populations

Age/Gender

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

Race

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

Pediatrics

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

Impaired Renal Function

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

Impaired Hepatic Function

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

or severely impaired hepatic function (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). The pharmacokinetics of REYATAZ in combination with ritonavir have not been studied in subjects with hepatic impairment.

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

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

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

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

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

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

Table 4: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	n	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
				C_{max}	AUC	C_{min}
atenolol	50 mg QD, d 7-11 and d 19-23	400 mg QD, d 1-11	19	1.00 (0.89, 1.12)	0.93 (0.85, 1.01)	0.74 (0.65, 0.86)
clarithromycin	500 mg 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)[b]	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose simultaneously with ddI and d4T	32[c]	0.11 (0.06, 0.18)	0.13 (0.08, 0.21)	0.16 (0.10, 0.27)
	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose 1 hour after ddI + d4T	32[c]	1.12 (0.67, 1.18)	1.03 (0.64, 1.67)	1.03 (0.61, 1.73)
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)
ketoconazole	200 mg QD, d 7-13	400 mg QD, d 1-13	14	0.99 (0.77, 1.28)	1.10 (0.89, 1.37)	1.03 (0.53, 2.01)
rifabutin	150 mg QD, d 15-28	400 mg QD, d 1-28	7	1.34 (1.14, 1.59)	1.15 (0.98, 1.34)	1.13 (0.68, 1.87)
ritonavir[d]	100 mg QD, d 11-20	300 mg QD, d 1-20	28	1.86 (1.69, 2.05)	3.38 (3.13, 3.63)	11.89 (10.23, 13.82)
tenofovir[e]	300 mg QD, d 9-16	400 mg QD, d 2-16	34	0.79 (0.73, 0.86)	0.75 (0.70, 0.81)	0.60 (0.52, 0.68)
	300 mg QD, d 15-42	300 mg/ritonavir 100 mg QD, d 1-42	10	0.72[f] (0.50, 1.05)	0.75[f] (0.58, 0.97)	0.77[f] (0.54, 1.10)

[a] Data provided are under fed conditions unless otherwise noted.

[b] All drugs were given under fasted conditions.

[c] One subject did not receive REYATAZ.

[d] Compared with atazanavir 400 mg QD historical data, administration of atazanavir/ritonavir 300/100 mg QD increased the atazanavir geometric mean values of C_{max}, AUC, and C_{min} by 18%, 103%, and 671%, respectively.

[e] tenofovir disoproxil fumarate.

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

Table 5: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of REYATAZ[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	n	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without REYATAZ; No effect = 1.00		
				C_{max}	AUC	C_{min}
atenolol	50 mg QD, d 7-11 and d 19-23	400 mg QD, d 1-11	19	1.34 (1.26, 1.42)	1.25 (1.16, 1.34)	1.02 (0.88, 1.19)
clarithromycin	500 mg BID, d 7-10 and d 18-21	400 mg QD, d 1-10	21	1.50 (1.32, 1.71) OH-clarithromycin: 0.28 (0.24, 0.33)	1.94 (1.75, 2.16) OH-clarithromycin: 0.30 (0.26, 0.34)	2.60 (2.35, 2.88) OH-clarithromycin: 0.38 (0.34, 0.42)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)[b]	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose simultaneous with ddI and d4T	32[c]	ddI: 0.92 (0.84, 1.02) d4T: 1.08 (0.96, 1.22)	ddI: 0.98 (0.92, 1.05) d4T: 1.00 (0.97, 1.03)	NA d4T: 1.04 (0.94, 1.16)
diltiazem	180 mg QD, d 7-11 and d 19-23	400 mg QD, d 1-11	28	1.98 (1.78, 2.19) desacetyl-diltiazem: 2.72 (2.44, 3.03)	2.25 (2.09, 2.16) desacetyl-diltiazem: 2.65 (2.45, 2.87)	2.42 (2.14, 2.73) desacetyl-diltiazem: 2.21 (2.02, 2.42)
ethinyl estradiol & norethindrone	Ortho-Novum® 7/7/7 QD, d 1-29	400 mg QD, d 16-29	19	ethinyl estradiol: 1.15 (0.99, 1.32) norethindrone: 1.67 (1.42, 1.96)	ethinyl estradiol: 1.48 (1.31, 1.68) norethindrone: 2.10 (1.68, 2.62)	ethinyl estradiol: 1.91 (1.57, 2.33) norethindrone: 3.62 (2.57, 5.09)
rifabutin	300 mg QD, d 1-10 then 150 mg QD, d 11-20	600 mg QD[d], d 11-20	3	1.18 (0.94, 1.48) 25-O-desacetyl-rifabutin: 8.20 (5.90, 11.40)	2.10 (1.57, 2.79) 25-O-desacetyl-rifabutin: 22.01 (15.97, 30.34)	3.43 (1.98, 5.96) 25-O-desacetyl-rifabutin: 75.6 (30.1, 190.0)
saquinavir (soft gelatin capsules)[e]	1200 mg QD, d 1-13	400 mg QD, d 7-13	7	4.39 (3.24, 5.95)	5.49 (4.04, 7.47)	6.86 (5.29, 8.91)
tenofovir[f]	300 mg QD, d 9-16 and d 24-30	400 mg QD, d 2-16	33	1.14 (1.08, 1.20)	1.24 (1.21, 1.28)	1.22 (1.15, 1.30)
lamivudine + zidovudine	150 mg lamivudine + 300 mg zidovudine BID, d 1-12	400 mg QD, d 7-12	19	lamivudine: 1.04 (0.92, 1.16) zidovudine: 1.05 (0.88, 1.24) zidovudine glucuronide: 0.95 (0.88, 1.02)	lamivudine: 1.03 (0.98, 1.08) zidovudine: 1.05 (0.96, 1.14) zidovudine glucuronide: 1.00 (0.97, 1.03)	lamivudine: 1.12 (1.04, 1.21) zidovudine: 0.69 (0.57, 0.84) zidovudine glucuronide: 0.82 (0.62, 1.08)

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

INDICATIONS AND USAGE

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

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

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

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

Description of Clinical Studies

Patients Without Prior Antiretroviral Therapy

Study AI424-034: REYATAZ once daily compared to efavirenz once daily, each in combination with fixed-dose lamivudine + zidovudine twice daily. Study AI424-034 was a randomized, double-blind, multicenter trial comparing REYATAZ (400 mg once daily) to efavirenz (600 mg once daily), each in combination with a fixed-dose combination of lamivudine (3TC) (150 mg) and zidovudine (ZDV) (300 mg) given twice daily, in 810 antiretroviral treatment-naive patients. Patients had a mean age of 34 years (range: 18 to 73), 36% were Hispanic, 33% were Caucasian, and 65% were male. The mean baseline CD4+ cell count was 321 cells/mm^3 (range: 64 to 1424 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.8 $\log_{10}$ copies/mL (range: 2.2 to 5.9 $\log_{10}$ copies/mL). 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[d] (n=405)	efavirenz 600 mg once daily + lamivudine + zidovudine[d] (n=405)
Responder[a]	67% (32%)	62% (37%)
Virologic failure[b]	20%	21%
Rebound	17%	16%
Never suppressed through Week 48	3%	5%
Death	–	<1%
Discontinued due to adverse event	5%	7%
Discontinued for other reasons[c]	8%	10%

[a] Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48. Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.0 or 1.5 as geographically appropriate.
[b] Includes confirmed viral rebound and failure to achieve confirmed HIV RNA <400 copies/mL through Week 48.
[c] Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.
[d] As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

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

Study AI424-008: REYATAZ 400 mg once daily compared to REYATAZ 600 mg once daily, and compared to nelfinavir 1250 mg twice daily, each in combination with stavudine and lamivudine twice daily. Study AI424-008 was a 48-week, randomized, multicenter trial, blinded to dose of REYATAZ, comparing REYATAZ at two dose levels (400 mg and 600 mg once daily) to nelfinavir (1250 mg twice daily), each in combination with stavudine (40 mg) and lamivudine (150 mg) given twice daily, in 467 antiretroviral treatment-naive patients. Patients had a mean age of 35 years (range: 18 to 69), 55% were Caucasian, and 63% were male. The mean baseline CD4+ cell count was 295 cells/mm^3 (range: 4 to 1003 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.7 log_{10} copies/mL (range: 1.8 to 5.9 log_{10} copies/mL). Treatment response 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[a]	67% (33%)	59% (38%)
Virologic failure[b]	24%	27%
Rebound	14%	14%
Never suppressed through Week 48	10%	13%
Death	<1%	—
Discontinued due to adverse event	1%	3%
Discontinued for other reasons[c]	7%	10%

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

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

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

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

Patients With Prior Antiretroviral Therapy

Study AI424-045: REYATAZ once daily + ritonavir once daily compared to REYATAZ once daily + saquinavir (soft gelatin capsules) once daily, and compared to lopinavir + ritonavir twice daily, each in combination with tenofovir + one NRTI. Study AI424-045 is an ongoing, randomized, multicenter trial comparing REYATAZ (300 mg once daily) with ritonavir (100 mg once daily) to REYATAZ (400 mg once daily) with saquinavir soft gelatin

capsules (1200 mg once daily), and to lopinavir + ritonavir (400/100 mg twice daily), each in combination with tenofovir and one NRTI, in 347 (of 358 randomized) patients who experienced virologic failure on HAART regimens containing PIs, NRTIs, and NNRTIs. The mean time of prior exposure to antiretrovirals was 139 weeks for PIs, 283 weeks for NRTIs, and 85 weeks for NNRTIs. The mean age was 41 years (range: 24 to 74); 60% were Caucasian, and 78% were male. The mean baseline CD4+ cell count was 338 cells/mm^3 (range: 14 to 1543 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.4 $\log_{10}$ copies/mL (range: 2.6 to 5.88 $\log_{10}$ copies/mL).

Treatment outcomes through Week 48 for the REYATAZ/ritonavir and lopinavir/ritonavir treatment arms are presented in Table 8. **REYATAZ/ritonavir and lopinavir/ritonavir were similar for the primary efficacy outcome measure of time-averaged difference in change from baseline in HIV RNA level. Study AI424-045 was not large enough to reach a definitive conclusion that REYATAZ/ritonavir and lopinavir/ritonavir are equivalent on the secondary efficacy outcome measure of proportions below the HIV RNA lower limit of detection.** See also Tables 1 and 2 in **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[a] (REYATAZ-lopinavir/ritonavir) (CI)
HIV RNA Change from Baseline (log_{10} copies/mL)[b]	-1.58	-1.70	+0.12[c] (-0.17, 0.41)
CD4+ Change from Baseline (cells/mm^3)[d]	116	123	-7 (-67, 52)
Percent of Patients Responding[e]			
HIV RNA <400 copies/mL[b]	55%	57%	-2.2% (-14.8%, 10.5%)
HIV RNA <50 copies/mL[b]	38%	45%	-7.1% (-19.6%, 5.4%)

[a] 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.

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

[c] Protocol-defined primary efficacy outcome measure.

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

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

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

In Study AI424-045, the mean change from baseline in plasma HIV-1 RNA for REYATAZ 400 mg with saquinavir (n=115) was –1.55 log_{10} copies/mL, and the time-averaged difference in change in HIV-1 RNA levels versus lopinavir/ritonavir was 0.33. The corresponding mean increase in CD4+ cell count was 72 cells/mm^3. Through 48 weeks of treatment, the proportion of patients in this treatment arm with plasma HIV-1 RNA <400 (<50) copies/mL was 38% (26%). In this study, coadministration of REYATAZ and saquinavir did not provide adequate efficacy (see **PRECAUTIONS: Drug Interactions**, Table 11).

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

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

CONTRAINDICATIONS

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

Coadministration of REYATAZ is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are 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*

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 10 for additional drugs that should not be coadministered with REYATAZ.

WARNINGS

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

Drug Interactions

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

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

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

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

PR Interval Prolongation

Atazanavir has been shown to prolong the PR interval of the electrocardiogram in some patients. In healthy volunteers and in patients, abnormalities in atrioventricular (AV) conduction were asymptomatic and generally limited to first-degree AV block. There have been rare reports of second-degree AV block and other conduction abnormalities and no reports of third-degree AV block (see **OVERDOSAGE**). In clinical trials, asymptomatic first-degree AV block was observed in 5.9% of atazanavir-treated patients (n=920), 5.2% of

lopinavir/ritonavir-treated patients (n=252), 10.4% of nelfinavir-treated patients (n=48), and 3.0% of efavirenz-treated patients (n=329). In Study AI424-045, asymptomatic first-degree AV block was observed in 5% (6/118) of atazanavir/ritonavir-treated patients and 5% (6/116) of lopinavir/ritonavir-treated patients who had on-study electrocardiogram measurements. Because of limited clinical experience, atazanavir should be used with caution in patients with preexisting conduction system disease (eg, marked first-degree AV block or second- or third-degree AV block). (See **CLINICAL PHARMACOLOGY: Effects on Electrocardiogram**.)

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

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

Diabetes Mellitus/Hyperglycemia

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

PRECAUTIONS

General

Hyperbilirubinemia

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

Rash

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

Hepatic Impairment and Toxicity

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

Resistance/Cross-Resistance

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

Hemophilia

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

Fat Redistribution

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

Immune Reconstitution Syndrome

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

Information for Patients

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

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain

under the care of a physician while using REYATAZ. Patients should be advised to take REYATAZ with food every day and take other concomitant antiretroviral therapy as prescribed. REYATAZ must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of REYATAZ is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

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

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

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

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

REYATAZ should be taken with food to enhance absorption.

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

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

Drug Interactions

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

The potential for drug interactions with REYATAZ changes when REYATAZ is coadministered with the potent CYP3A inhibitor ritonavir. The magnitude of CYP3A-mediated drug interactions (effect on atazanavir or effect on coadministered drug) may change when REYATAZ is coadministered with ritonavir. See the complete prescribing information for Norvir® (ritonavir) for information on drug interactions with ritonavir.

Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir are expected if antacids, buffered medications, H_2-receptor antagonists, and proton-pump inhibitors are administrated with atazanavir.

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

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

Table 10: 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.
Ergot Derivatives: 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.
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 (*Hypericum perforatum*)	Patients taking REYATAZ should not use products containing St. John's wort (*Hypericum perforatum*) because coadministration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance.

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Table 11: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] 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**
HIV Antiviral Agents		
Nucleoside Reverse Transcriptase Inhibitors (NRTIs): didanosine buffered formulations	↓ atazanavir	Coadministration of REYATAZ with didanosine buffered tablets did not alter exposure to didanosine; however, exposure to atazanavir was markedly decreased (presumably due to the increase in gastric pH caused by buffers in the didanosine tablets). In addition, it is recommended that didanosine be administered on an empty stomach; therefore, REYATAZ should be given (with food) 2 h before or 1 h after didanosine buffered formulations (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**). Because didanosine EC capsules are to be given on an empty stomach and REYATAZ is to be given with food, they should be administered at different times.

Nucleotide Reverse Transcriptase Inhibitors: tenofovir disoproxil fumarate	↓ atazanavir ↑ tenofovir	Tenofovir may decrease the AUC and C_{min} of atazanavir. When coadministered with tenofovir, it is recommended that REYATAZ 300 mg be given with ritonavir 100 mg and tenofovir 300 mg (all as a single daily dose with food). **REYATAZ without ritonavir should not be coadministered with tenofovir.** REYATAZ increases tenofovir concentrations. The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving REYATAZ and tenofovir should be monitored for tenofovir-associated adverse events.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs): efavirenz	↓ atazanavir	In treatment-naive 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.
Non-nucleoside Reverse Transcriptase Inhibitors: nevirapine	↓ atazanavir	***REYATAZ/ritonavir****:* 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.
Protease Inhibitors: 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 **Description of Clinical Studies**).
Protease Inhibitors: 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® (ritonavir) for information on drug interactions with ritonavir.
Protease Inhibitors: others	↑ other protease inhibitor	***REYATAZ/ritonavir:*** 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.
Other Agents		
Antacids and buffered medications	↓ atazanavir	Reduced plasma concentrations of atazanavir are expected if antacids, including buffered medications, are administered with REYATAZ. REYATAZ should be administered 2 h before or 1 h after these medications.
Antiarrhythmics: amiodarone, 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.
Anticoagulants: warfarin	↑ warfarin	Coadministration with REYATAZ has the potential to produce serious and/or life-threatening bleeding and has not been studied. It is recommended that INR (International Normalized Ratio) be monitored.
Antidepressants: tricyclic antidepressants	↑ tricyclic antidepressants	Coadministration with REYATAZ has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with REYATAZ.
Antifungals: ketoconazole itraconazole	***REYATAZ/ ritonavir:*** ↑ ketoconazole ↑ itraconazole	Coadministration of ketoconazole has only been studied with REYATAZ without ritonavir (negligible increase in atazanavir AUC and C_{max}). Due to the effect of ritonavir on ketoconazole, high doses of ketoconazole and itraconazole (>200 mg/day) should be used cautiously with REYATAZ/ritonavir.
Antifungals: voriconazole	Effect is unknown	Coadministration of voriconazole with REYATAZ, with or without ritonavir, has not been studied. However, administration of voriconazole with ritonavir 400 mg every 12 hours decreased voriconazole steady-state AUC by an average of 82%. The effect of lower ritonavir doses on voriconazole is not known at this time. Until data are available, voriconazole should not be administered to patients receiving REYATAZ/ritonavir. Coadministration of voriconazole with REYATAZ (without ritonavir) may increase atazanavir concentrations; however, no data are available.
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. 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.
HMG-CoA reductase inhibitors: atorvastatin	↑ atorvastatin	The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including REYATAZ, are used in combination with atorvastatin. Caution should be exercised.
H_2-Receptor antagonists	↓ atazanavir	Reduced plasma concentrations of atazanavir are expected if H_2-receptor antagonists are administered with REYATAZ. This may result in loss of therapeutic effect and development of resistance. To lessen the effect of H_2-receptor antagonists on atazanavir exposure, it is recommended that an H_2-receptor antagonist and REYATAZ be administered as far apart as possible, preferably 12 hours apart.
Immunosuppressants: cyclosporin, sirolimus, tacrolimus	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with REYATAZ.
Macrolide antibiotics: clarithromycin	↑ clarithromycin ↓ 14-OH clarithromycin ↑ atazanavir	Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a dose reduction of clarithromycin by 50% should be considered when it is coadministered with REYATAZ. In addition, concentrations of the active metabolite 14-OH clarithromycin are significantly reduced; consider alternative therapy for indications other than infections due to *Mycobacterium avium* complex. Coadministration of REYATAZ/ritonavir with clarithromycin has not been studied.
Hormonal contraceptives: 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.
PDE5 inhibitors: sildenafil tadalafil vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Coadministration with REYATAZ has not been studied but may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, visual changes, and priapism. Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Use tadalafil with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.

[a] For magnitude of interactions see **CLINICAL PHARMACOLOGY**: Tables 4 and 5.

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Two-year carcinogenicity studies in mice and rats were conducted with atazanavir. At the high dose in female mice, the incidence of benign hepatocellular adenomas was increased at systemic exposures 7.2–fold higher than those in humans at the recommended 400-mg clinical dose. There were no increases in the incidence of tumors in male mice at any dose in the study. In rats, no significant positive trends in the incidence of neoplasms occurred at systemic exposures up to 5.7–fold higher than those in humans at the recommended 400–mg clinical dose. The clinical relevance of the carcinogenic findings in female mice is unknown.

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

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

Pregnancy

Pregnancy Category B

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

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

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

ADVERSE REACTIONS

Adult Patients

Treatment-Emergent Adverse Events in Treatment-Naive Patients

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

Table 12: Selected Treatment-Emergent Adverse Events[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Naive Patients[b]

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

* None reported in this treatment arm.

[a] Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

[b] Based on regimens containing REYATAZ.

[c] Median time on therapy.

[d] Includes long-term follow-up.

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

Treatment-Emergent Adverse Events in Treatment-Experienced Patients

Selected drug-related clinical adverse events of moderate-severe intensity in ≥2% of treatment-experienced patients receiving REYATAZ/ritonavir are presented in Table 13. For other information regarding observed or potentially serious adverse events, see **WARNINGS** and **PRECAUTIONS**.

Table 13: Selected Treatment-Emergent Adverse Events[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Experienced Patients,[b] Study AI424-045

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

* None reported in this treatment arm.

[a] Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

[b] Based on the regimen containing REYATAZ.

[c] Median time on therapy.

[d] As a fixed-dose combination.

Laboratory Abnormalities

Treatment-Naive Patients

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

Table 14: Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Naive Patients[a]

		Phase III Study AI424-034		Phase II Studies AI424-007, -008	
		64 weeks[b]	64 weeks[b]	120 weeks[b,c]	73 weeks[b,c]
		REYATAZ 400 mg once daily + lamivudine + zidovudine[e]	efavirenz 600 mg once daily + lamivudine + zidovudine[e]	REYATAZ 400 mg once daily + stavudine + lamivudine or + stavudine + didanosine	nelfinavir 750 mg TID or 1250 mg BID + stavudine + lamivudine or + stavudine + didanosine
Variable	**Limit[d]**	**(n=404)**	**(n=401)**	**(n=279)**	**(n=191)**
Chemistry	High				
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	Low				
Hemoglobin	<8.0 g/dL	5%	3%	<1%	4%
Neutrophils	<750 cells/mm^3	7%	9%	3%	7%

* None reported in this treatment arm.
[a] Based on regimen(s) containing REYATAZ.
[b] Median time on therapy.
[c] Includes long-term follow-up.
[d] ULN = upper limit of normal.
[e] As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

Lipids, Change from Baseline

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

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

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

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

[b] 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%).

[c] Efavirenz 600 mg once daily with the fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

[d] 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.

[e] Number of patients with LDL-cholesterol measured.

[f] Fasting.

Treatment-Experienced Patients

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

Table 16: Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Experienced Patients, Study AI424-045[a]

Variable	Limit[c]	48 weeks[b] REYATAZ/ritonavir 300/100 mg once daily + tenofovir + NRTI (n=119)	48 weeks[b] lopinavir/ritonavir 400/100 mg twice daily[d] + tenofovir + NRTI (n=118)
Chemistry	High		
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	Low		
Platelets	<50,000 /mm^3	2%	3%
Neutrophils	<750 cells/mm^3	7%	8%

[a] Based on regimen(s) containing REYATAZ.
[b] Median time on therapy.
[c] ULN = upper limit of normal.
[d] As a fixed-dose combination.

Lipids, Change from Baseline

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

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

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

[a] REYATAZ 300 mg once daily + ritonavir + tenofovir + 1 NRTI.

[b] 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%).

[c] Lopinavir/ritonavir (400/100 mg) BID + tenofovir + 1 NRTI.

[d] 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.

[e] Number of patients with LDL-cholesterol measured.

[f] Fasting.

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

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

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

OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

Adults

REYATAZ Capsules must be taken with food.

The recommended oral dose of REYATAZ is as follows:

Therapy-Naive Patients

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

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

Therapy-Experienced Patients

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

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

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

Important dosing information:

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

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

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

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

Patients with Renal Impairment

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

Patients with Hepatic Impairment

REYATAZ should be used with caution in patients with mild to moderate hepatic impairment. For patients with moderate hepatic impairment (Child-Pugh Class B) who have not experienced prior virologic failure, a dose reduction to 300 mg once daily should be considered. REYATAZ should not be used in patients with severe hepatic impairment

(Child-Pugh Class C). REYATAZ/ritonavir has not been studied in subjects with hepatic impairment and is not recommended. (See **PRECAUTIONS** and **CLINICAL PHARMACOLOGY: Special Populations,** *Impaired Hepatic Function*.)

HOW SUPPLIED

REYATAZ® (atazanavir sulfate) Capsules are available in the following strengths and 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.					

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

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

Bristol-Myers Squibb Virology

Bristol-Myers Squibb Company

Princeton, NJ 08543 USA

XXXXXXXX Revised _____

Patient Information

REYATAZ® (RAY-ah-taz)

Rx only

(generic name = **atazanavir sulfate**)

Capsules

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

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

What is REYATAZ?

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

Does REYATAZ cure HIV or AIDS?

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

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

Who should not take REYATAZ?

Do not take REYATAZ if you:

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

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

Tell your healthcare provider:

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

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

How should I take REYATAZ?

- **Take REYATAZ once every day exactly as instructed by your healthcare provider.** Your healthcare provider will prescribe the amount of REYATAZ that is right for you.
  - For adults who have never taken anti-HIV medicines before, the usual dose is 400 mg (two 200-mg capsules) once daily taken with food.
  - For adults who have taken anti-HIV medicines in the past, the usual dose is 300 mg (two 150-mg capsules) plus 100 mg of NORVIR® (ritonavir) once daily taken with food.

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

Can children take REYATAZ?

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

What are the possible side effects of REYATAZ?

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

The following side effects have been reported with REYATAZ:

- **rash** (redness and itching) sometimes occurs in patients taking REYATAZ, most often in the first few weeks after the medicine is started. Rashes usually go away within 2 weeks with no change in treatment. Tell your healthcare provider if rash occurs.
- **yellowing of the skin or eyes.** These effects may be due to increases in bilirubin levels in the blood (bilirubin is made by the liver). Call your healthcare provider if your skin or the white part of your eyes turn yellow. Although these effects may not be damaging to your liver, skin, or eyes, it is important to tell your healthcare provider promptly if they occur.
- **a change in the way your heart beats (heart rhythm change).** Call your healthcare provider right away if you get dizzy or lightheaded. These could be symptoms of a heart problem.
- **diabetes and high blood sugar (hyperglycemia)** sometimes happen in patients taking protease inhibitor medicines like REYATAZ. Some patients had diabetes before taking protease inhibitors while others did not. Some patients may need changes in their diabetes medicine.
- **if you have liver disease** including hepatitis B or C, your liver disease may get worse when you take anti-HIV medicines like REYATAZ.
- **some patients with hemophilia** have increased bleeding problems with protease inhibitors like REYATAZ.
- **changes in body fat.** These changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

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

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

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

- Ergot medicines: dihydroergotamine, ergonovine, ergotamine, and methylergonovine such as CAFERGOT®, MIGRANAL®, D.H.E. 45®, ergotrate maleate, METHERGINE®, and others (used for migraine headaches).
- HALCION® (triazolam, used for insomnia).
- VERSED® (midazolam, used for sedation).
- ORAP® (pimozide, used for Tourette's disorder).
- PROPULSID® (cisapride, used for certain stomach problems).

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

- CAMPTOSAR® (irinotecan, used for cancer),
- CRIXIVAN® (indinavir, used for HIV infection). Both REYATAZ and CRIXIVAN sometimes cause increased levels of bilirubin in the blood.
- Cholesterol-lowering medicines MEVACOR® (lovastatin) or ZOCOR® (simvastatin).

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

- Rifampin (also known as RIMACTANE®, RIFADIN®, RIFATER®, or RIFAMATE®, used for tuberculosis).
- St. John's wort (*Hypericum perforatum*), an herbal product sold as a dietary supplement, or products containing St. John's wort.

- "Proton-pump inhibitors" used for indigestion, heartburn, or ulcers such as AcipHex® (rabeprazole), NEXIUM® (esomeprazole), PREVACID® (lansoprazole), PRILOSEC® (omeprazole), or PROTONIX® (pantoprazole).

Do not take the following medicine if you are taking REYATAZ and NORVIR® together.

- VFEND® (voriconazole).

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

- CIALIS® (tadalafil), LEVITRA® (vardenafil), or VIAGRA® (sildenafil). REYATAZ may increase the chances of serious side effects that can happen with CIALIS, LEVITRA, or VIAGRA. Do not use CIALIS, LEVITRA, or VIAGRA while you are taking REYATAZ unless your healthcare provider tells you it is okay.
- LIPITOR® (atorvastatin). There is an increased chance of serious side effects if you take REYATAZ with this cholesterol-lowering medicine.
- Medicines for abnormal heart rhythm: CORDARONE® (amiodarone), lidocaine, quinidine (also known as CARDIOQUIN®, QUINIDEX®, and others).
- VASCOR® (bepridil, used for chest pain).
- COUMADIN® (warfarin).
- Tricyclic antidepressants such as ELAVIL® (amitriptyline), NORPRAMIN® (desipramine), SINEQUAN® (doxepin), SURMONTIL® (trimipramine), TOFRANIL® (imipramine), or VIVACTIL® (protriptyline).
- Medicines to prevent organ transplant rejection: SANDIMMUNE® or NEORAL® (cyclosporin), RAPAMUNE® (sirolimus), or PROGRAF® (tacrolimus).

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

- FORTOVASE®, INVIRASE® (saquinavir).
- NORVIR® (ritonavir).
- SUSTIVA® (efavirenz).
- VIDEX® (didanosine) or antacids.
- VIREAD® (tenofovir disoproxil fumarate).

- MYCOBUTIN® (rifabutin).
- Calcium channel blockers such as CARDIZEM® or TIAZAC® (diltiazem), COVERA-HS® or ISOPTIN SR® (verapamil) and others.
- BIAXIN® (clarithromycin).
- Medicines for indigestion, heartburn, or ulcers such as AXID® (nizatidine), PEPCID AC® (famotidine), TAGAMET® (cimetidine), or ZANTAC® (ranitidine).

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

Remember:

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

How should I store REYATAZ?

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

General information about REYATAZ

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

This summary does not include everything there is to know about REYATAZ. Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets.

Remember no written summary can replace careful discussion with your healthcare provider. If you would like more information, talk with your healthcare provider or you can call 1-800-426-7644.

What are the ingredients in REYATAZ?

Active Ingredient: atazanavir sulfate

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

* VIDEX® is a registered trademark of Bristol-Myers Squibb Company. COUMADIN® and SUSTIVA® are registered trademarks of Bristol-Myers Squibb Pharma Company. Other brands listed are the trademarks of their respective owners and are not trademarks of Bristol-Myers Squibb Company.

Bristol-Myers Squibb Virology
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

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

XXXXXXX Revised _____

Based on package insert dated _____