Bristol Myers Squibb

REYATAZ®

(atazanavir) Capsules

Full Prescribing Information

1 INDICATIONS AND USAGE

REYATAZ [atazanavir (as sulfate)] 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 96 weeks duration in antiretroviral-naive and 48 weeks duration in antiretroviral-treatment-experienced adult patients, and limited data from children aged 6 to less than 18 years.

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

- 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 *Clinical Studies (13.2)*].
- The number of baseline primary protease inhibitor mutations affects the virologic response to REYATAZ/ritonavir [see *Clinical Pharmacology (11.4)*].

2 DOSAGE AND ADMINISTRATION

General Dosing Recommendations:

- REYATAZ Capsules must be taken with food.
- Do not open the capsules.
- The recommended oral dosage of REYATAZ depends on the treatment history of the patient and the use of other coadministered drugs [see *Drug Interactions (7.3)*]. When coadministered with H_2-receptor antagonists or proton-pump inhibitors, dose separation may be required [see *Dosage and Administration (2.1)*].
- When coadministered with didanosine buffered or enteric-coated formulations, REYATAZ should be given (with food) 2 hours before or 1 hour after didanosine.
- REYATAZ without ritonavir is not recommended for treatment-experienced adults or pediatric patients with prior virologic failure [see *Clinical Studies (13)*].

- 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 ritonavir when using this agent.

2.1 Recommended Adult Dosage

Table 1 summarizes the recommended REYATAZ dosing regimen in adults. All REYATAZ dosing regimens are to be administered as a single dose with food.

Table 1: REYATAZ Dosing Regimens

Treatment-Naive Patients	**REYATAZ 300 mg with ritonavir 100 mg once daily**
If unable to tolerate ritonavir	**REYATAZ 400 mg once daily**
When combined with any of the following: Tenofovir H_2-receptor antagonist Proton-pump inhibitor • The H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 40 mg twice daily. Administer REYATAZ and ritonavir simultaneously with, and/or at least 10 hours after the H_2-receptor antagonist. • If unable to tolerate ritonavir, administer REYATAZ 400 mg once daily at least 2 hours before and at least 10 hours after the H_2-receptor antagonist. No single dose of the H_2-receptor antagonist should exceed a dose comparable to famotidine 20 mg and the total daily dose should not exceed a dose comparable to famotidine 40 mg. • The proton-pump inhibitor dose should not exceed a dose comparable to omeprazole 20 mg daily and must be taken approximately 12 hours prior to REYATAZ and ritonavir.	**REYATAZ 300 mg with ritonavir 100 mg once daily**
Coadministration of REYATAZ with efavirenz is generally not recommended. If REYATAZ combined with efavirenz is judged unavoidable, close monitoring is recommended.	
When combined with efavirenz Efavirenz should be administered on an empty stomach, preferably at bedtime.	**REYATAZ 400 mg with ritonavir 100 mg once daily**
Treatment-Experienced Patients	**REYATAZ 300 mg with ritonavir 100 mg once daily**
Do not coadminister with proton-pump inhibitors or efavirenz in treatment-experienced patients.	
When given with an H_2-receptor antagonist The H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily. Administer REYATAZ and ritonavir simultaneously with, and/or at least 10 hours after the H_2-receptor antagonist.	**REYATAZ 300 mg with ritonavir 100 mg once daily**
When given with both tenofovir *and* an H_2-receptor antagonist The H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily. Administer REYATAZ and ritonavir simultaneously with, and/or at least 10 hours after the H_2-receptor antagonist.	**REYATAZ 400 mg with ritonavir 100 mg once daily**

[For these drugs and other antiretroviral agents for which dosing modification may be appropriate, see *Drug Interactions (7)*.]

2.2 Recommended Pediatric Dosage

The recommended daily dosage of REYATAZ capsules for pediatric patients (6 to less than 18 years of age) is based on body weight and should not exceed the recommended adult dosage. REYATAZ capsules must be taken with food. The data are insufficient to recommend dosing of REYATAZ capsules for any of the following: (1) patients less than 6 years of age, (2) without ritonavir in any pediatric patient less than 13 years of age, and (3) patients less than 40 kg receiving concomitant tenofovir, H_2-receptor antagonists, or proton-pump inhibitors.

The recommended dosage of REYATAZ with ritonavir in pediatric patients at least 6 years of age is shown in Table 2.

Table 2: Recommended Dosage of REYATAZ Capsules and ritonavir in Pediatric Patients (6 to less than 18 years of age)[a, b]

Body Weight	REYATAZ Daily Dosage	Ritonavir Daily Dosage
Treatment-Naive and Treatment-Experienced [c]		
Less than 15 kg	Capsules not recommended	N/A
At least 15 kg to less than 35 kg	200 mg	100 mg
At least 35 kg	300 mg	100 mg
Treatment-Naive, at least 13 years old and cannot tolerate ritonavir [c]		
At least 40 kg	400 mg	N/A

[a] The REYATAZ and ritonavir dose should be taken together once daily with food.

[b] The same recommendations regarding the timing and maximum doses of concomitant PPIs and H2RAs in adults also apply to pediatric patients. See *Drug Interactions (7)* for instructions concerning coadministration of acid-reducing medications (eg, H2RA or PPIs), and other antiretroviral drugs (eg, efavirenz, tenofovir DF, and didanosine).

[c] In treatment-experienced patients, REYATAZ capsules must be administered with ritonavir.

For treatment-naive patients at least 13 years of age and at least 40 kg, who are unable to tolerate ritonavir, the recommended dose is REYATAZ 400 mg (without ritonavir) once daily with food. For patients at least 13 years of age and at least 40 kg receiving concomitant tenofovir, H_2-receptor antagonists, or proton-pump inhibitors, REYATAZ should not be administered without ritonavir.

2.3 Pregnancy

Dosing During Pregnancy and the Postpartum Period:

- REYATAZ should not be administered without ritonavir.
- REYATAZ should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir.
- For pregnant patients, no dose adjustment is required for REYATAZ with the following exceptions:
    - For treatment-experienced pregnant women during the second or third trimester, when REYATAZ is coadministered with either an H_2-receptor antagonist **or** tenofovir DF, REYATAZ 400 mg with ritonavir 100 mg once daily is recommended. There are insufficient data to recommend a REYATAZ dose for use with both an H_2-receptor antagonist *and* tenofovir DF in treatment-experienced pregnant women.
- During the second and third trimesters of pregnancy, REYATAZ 300 mg with ritonavir 100 mg may not provide sufficient exposure to atazanavir, especially when the activity of atazanavir or the whole regimen may be compromised due to drug resistance. Since there are limited data available and due to inter-patient variability during pregnancy, Therapeutic Drug Monitoring (TDM) may be considered to ensure adequate exposure.
- No dose adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir exposures could be higher during the first 2 months after delivery. [See *Use in Specific Populations (8.1)* and *Clinical Pharmacology (11.3)*.]

2.4 Renal Impairment

For patients with renal impairment, including those with severe renal impairment who are not managed with hemodialysis, no dose adjustment is required for REYATAZ. Treatment-naive patients with end stage renal disease managed with hemodialysis should receive REYATAZ 300 mg with ritonavir 100 mg. REYATAZ without ritonavir should not be administered to treatment-naive patients managed with hemodialysis.

REYATAZ should not be administered to HIV-treatment-experienced patients with end stage renal disease managed with hemodialysis. [See *Use in Specific Populations (8.6)*.]

2.5 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 *Warnings and Precautions (5.5)* and *Use in Specific Populations (8.7).*]

3 DOSAGE FORMS AND STRENGTHS

- 150 mg capsule with blue cap and powder blue body, printed with white ink “BMS 150 mg” on the cap and with blue ink “3624” on the body.
- 200 mg capsule with blue cap and blue body, printed with white ink “BMS 200 mg” on the cap and with white ink “3631” on the body.
- 300 mg capsule with red cap and blue body, printed with white ink “BMS 300 mg” on the cap and with white ink “3622” on the body.

4 CONTRAINDICATIONS

REYATAZ is contraindicated:

- in patients with previously demonstrated clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product.

- when coadministered with drugs that are highly dependent on CYP3A or UGT1A1 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events.

- when coadministered with drugs that strongly induce CYP3A and may lead to lower exposure and loss of efficacy of REYATAZ.

These and other contraindicated drugs are listed in Table 3.

Table 3: Drugs That Are Contraindicated with REYATAZ

Drug class	Drugs within class that are contraindicated with REYATAZ	Clinical Comment
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Potential for increased alfuzosin concentrations, which can result in hypotension.
Antiarrhythmics	Quinidine	REYATAZ/ritonavir: Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Calcium Channel Blockers	Bepridil	REYATAZ/ritonavir: Potential for serious and/or life-threatening adverse events.
Antimycobacterials	Rifampin	Rifampin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect and development of resistance.
Antineoplastics	Irinotecan	Atazanavir inhibits UGT1A1 and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.
	Apalutamide	Apalutamide is expected to substantially decrease plasma concentrations of atazanavir and ritonavir, which may result in loss of virologic response and possible resistance to atazanavir and/or ritonavir or other protease inhibitors.
Benzodiazepines	Triazolam, orally administered midazolam[a]	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with REYATAZ may cause large increases in the concentration of these benzodiazepines. Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
Ergot Derivatives	Dihydroergotamine, ergotamine, ergonovine, methylergonovine	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	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products	St. John's wort (*Hypericum perforatum*)	Patients taking REYATAZ should not use products containing St. John's wort because coadministration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance.
Hepatitis C Direct-Acting Antivirals	Elbasvir/grazoprevir	REYATAZ: Contraindicated because of the potential increase in the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations.
	Glecaprevir/pibrentasvir	REYATAZ: Contraindicated because of the increased risk of ALT elevations due to an increase in glecaprevir and pibrentasvir plasma concentrations.

Lipid-modifying agents: HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for serious reactions such as myopathy including rhabdomyolysis.
Other lipid-modifying agents	Lomitapide	REYATAZ: Contraindicated because of the potential for risk of markedly increased transaminase levels and hepatoxicity associated with increased plasma concentrations of lomitapide. The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.
Antipsychotics	Lurasidone	Potential for serious and/or life-threatening reactions if REYATAZ is coadministered with ritonavir.
	Pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
PDE5 inhibitor	Sildenafil[b] when dosed as REVATIO® for the treatment of pulmonary arterial hypertension	A safe and effective dose in combination with REYATAZ has not been established for sildenafil (REVATIO®) when used for the treatment of pulmonary hypertension. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, priapism and syncope).
Protease Inhibitors	Indinavir	Both REYATAZ and indinavir are associated with indirect (unconjugated) hyperbilirubinemia.
Non-nucleoside Reverse Transcriptase Inhibitors	Nevirapine	Nevirapine substantially decreases atazanavir exposure which may result in loss of therapeutic effect and development of resistance. Potential risk for nevirapine-associated adverse reactions due to increased nevirapine exposures.

[a] See *Drug Interactions, Table 14 (7)* for parenterally administered midazolam.

[b] See *Drug Interactions, Table 14 (7)* for sildenafil when dosed as VIAGRA® for erectile dysfunction.

5 WARNINGS AND PRECAUTIONS

5.1 Drug Interactions

See Table 3 for a listing of drugs that are contraindicated for use with REYATAZ due to potentially life-threatening adverse events, significant drug interactions, or loss of virologic activity [see *Contraindications (4)*]. Please refer to Table 14 for established and other potentially significant drug interactions [see *Drug Interactions (7.3)*].

5.2 Cardiac Conduction Abnormalities

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 reports of second-degree AV block and other conduction abnormalities [see *Adverse Reactions (6.4)* and *Overdosage (9)*]. In clinical trials that included electrocardiograms, 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 in patients with preexisting conduction system disease (eg, marked first-degree AV block or second- or third-degree AV block), atazanavir should be used with caution in these patients. [See *Clinical Pharmacology (11.2)*.]

Atazanavir in combination with diltiazem increased diltiazem plasma concentration by 2-fold with 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, no clinically significant additive effect of atazanavir and atenolol on the PR interval was observed. Dose adjustment of atenolol is not required when used in combination with atazanavir. [See *Drug Interactions (7)* and *Clinical Pharmacology (11.2)*.] Pharmacokinetic studies between atazanavir and other drugs that prolong the PR interval including beta blockers [other than atenolol, see *Drug Interactions (7)*], 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).

Asymptomatic PR interval prolongation was more frequent in pediatric patients than adults. Asymptomatic first- and second-degree AV block was reported in pediatric patients. Caution should be used with medicinal products known to induce PR prolongations. In pediatric patients with preexisting conduction problems (second-degree or higher atrioventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk. Cardiac monitoring is recommended based on the presence of clinical findings (eg, bradycardia).

5.3 Rash

In controlled clinical trials, rash (all grades, regardless of causality) occurred in approximately 20% of patients treated with REYATAZ. The median time to onset of rash in clinical studies was 7.3 weeks and the median duration of rash was 1.4 weeks. Rashes were generally mild-to-moderate maculopapular skin eruptions. Treatment-emergent adverse reactions of moderate or severe rash (occurring at a rate of ≥2%) are presented for the individual clinical studies [see *Adverse Reactions (6.1)*]. Dosing with REYATAZ was often continued without interruption in patients who developed rash. The discontinuation rate for rash in clinical trials was <1%. REYATAZ should be discontinued if severe rash develops. Cases of Stevens-Johnson syndrome, erythema multiforme,

and toxic skin eruptions including drug rash, eosinophilia, and systemic symptoms (DRESS) syndrome have been reported in patients receiving REYATAZ. [See *Contraindications (4).*]

5.4 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 (6.1, 6.2)*.]

5.5 Hepatotoxicity

Caution should be exercised when administering REYATAZ to patients with hepatic impairment because atazanavir concentrations may be increased [see *Dosage and Administration (2.5)*]. Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases before treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. In these patients, hepatic laboratory testing should be conducted prior to initiating therapy with REYATAZ and during treatment. [See *Adverse Reactions (6.3)* and *Use in Specific Populations (8.7).*]

5.6 Nephrolithiasis and Cholelithiasis

Cases of nephrolithiasis and/or cholelithiasis have been reported during postmarketing surveillance in HIV-infected patients receiving REYATAZ therapy. Some patients required hospitalization for additional management and some had complications. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made. If signs or symptoms of nephrolithiasis and/or cholelithiasis occur, temporary interruption or discontinuation of therapy may be considered. [See *Adverse Reactions (6.4).*]

5.7 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. [See *Adverse Reactions (6.4)*.]

5.8 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 jiroveci* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.9 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.

5.10 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.

5.11 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 (11.4)*.]

5.12 Chronic Kidney Disease

Chronic kidney disease in HIV-infected patients treated with atazanavir, with or without ritonavir, has been reported during postmarketing surveillance. REYATAZ should be used with caution, particularly in those patients with other risk factors for chronic kidney disease.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- cardiac conduction abnormalities [see *Warnings and Precautions (5.2)*]
- rash [see *Warnings and Precautions (5.3)*]
- hyperbilirubinemia [see *Warnings and Precautions (5.4)*]
- nephrolithiasis and cholelithiasis [see *Warnings and Precautions (5.6)*]
- chronic kidney disease [*see Warnings and Precautions (5.12)*]

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

6.1 Clinical Trial Experience in Adults

Treatment-Emergent Adverse Reactions in Treatment-Naive Patients

The safety profile of REYATAZ in treatment-naive adults is based on 1625 HIV-1 infected patients in clinical trials. 536 patients received REYATAZ 300 mg with ritonavir 100 mg and 1089 patients received REYATAZ 400 mg or higher (without ritonavir).

The most common adverse reactions are nausea, jaundice/scleral icterus, and rash.

Selected clinical adverse reactions of moderate or severe intensity reported in ≥2% of treatment-naive patients receiving combination therapy including REYATAZ 300 mg with ritonavir 100 mg and REYATAZ 400 mg (without ritonavir) are presented in Tables 4 and 5, respectively.

Table 4: Selected Treatment-Emergent Adverse Reactions[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Naive Patients,[b] Study AI424-138

	96 weeks[c] REYATAZ 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine[d] (n=441)	96 weeks[c] lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir with emtricitabine[d] (n=437)
Digestive System		
Nausea	4%	8%
Jaundice/scleral icterus	5%	*
Diarrhea	2%	12%
Skin and Appendages		
Rash	3%	2%
Hepatobiliary Disorders		
Hyperbilirubinemia[e]	10%	<1%

* 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: 300 mg tenofovir, 200 mg emtricitabine once daily.

[e] Hyperbilirubinemia also includes blood bilirubin increased, abnormal blood bilirubin and blood bilirubin unconjugated increased from the Investigations System Organ Class of MedDRA.

Table 5: Selected Treatment-Emergent Adverse Reactions[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Naive Patients,[b] Studies AI424-034, AI424-007, and AI424-008

	Study AI424-034		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%
Abdominal pain	4%	4%	4%	2%
Diarrhea	1%	2%	3%	16%
Nervous System				
Insomnia	3%	3%	<1%	*
Dizziness	2%	7%	<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 Reactions in Treatment-Experienced Patients

The safety profile of REYATAZ in treatment-experienced adults is based on 119 HIV-1 infected patients in clinical trials.

The most common adverse reactions are jaundice/scleral icterus and myalgia.

Selected clinical adverse reactions of moderate or severe intensity reported in ≥2% of treatment-experienced patients receiving REYATAZ/ritonavir are presented in Table 6.

Table 6: Selected Treatment-Emergent Adverse Reactions[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 in Treatment-Naive Patients

The percentages of adult treatment-naive patients treated with combination therapy including REYATAZ [atazanavir (as sulfate)] 300 mg with ritonavir 100 mg and REYATAZ 400 mg (without ritonavir) with Grade 3–4 laboratory abnormalities are presented in Tables 7 and 8, respectively.

Table 7: Grade 3–4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Naive Patients,[a] Study AI424-138

Variable	Limit[c]	96 weeks[b] REYATAZ 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine[d] (n=441)	96 weeks[b] lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir with emtricitabine[d] (n=437)
Chemistry	High		
SGOT/AST	≥5.1 × ULN	3%	1%
SGPT/ALT	≥5.1 × ULN	3%	2%
Total Bilirubin	≥2.6 × ULN	44%	<1%
Lipase	≥2.1 × ULN	2%	2%
Creatine Kinase	≥5.1 × ULN	8%	7%
Total Cholesterol	≥240 mg/dL	11%	25%
Hematology	Low		
Neutrophils	<750 cells/mm^3	5%	2%

[a] Based on the regimen containing REYATAZ.

[b] Median time on therapy.

[c] ULN = upper limit of normal.

[d] As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

Table 8: Grade 3–4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Naive Patients,[a] Studies AI424-034, AI424-007, and AI424-008

		Study AI424-034		Studies AI424-007, -008	
		64 weeks[b] REYATAZ 400 mg once daily + lamivudine + zidovudine[e]	64 weeks[b] efavirenz 600 mg once daily + lamivudine + zidovudine[e]	120 weeks[b,c] REYATAZ 400 mg once daily + stavudine + lamivudine or + stavudine + didanosine	73 weeks[b,c] nelfinavir 750 mg TID or 1250 mg BID + stavudine + lamivudine or + stavudine + didanosine
Variable	**Limit[d]**	**(n=404)**	**(n=401)**	**(n=279)**	**(n=191)**
Chemistry	High				
SGOT/AST	≥5.1 × ULN	2%	2%	7%	5%
SGPT/ALT	≥5.1 × ULN	4%	3%	9%	7%
Total Bilirubin	≥2.6 × ULN	35%	<1%	47%	3%
Amylase	≥2.1 × ULN	*	*	14%	10%
Lipase	≥2.1 × ULN	<1%	1%	4%	5%
Creatine Kinase	≥5.1 × 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.

Laboratory Abnormalities in 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 9.

Table 9: 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 × ULN	3%	3%
SGPT/ALT	≥5.1 × ULN	4%	3%
Total Bilirubin	≥2.6 × ULN	49%	<1%
Lipase	≥2.1 × ULN	5%	6%
Creatine Kinase	≥5.1 × 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 cells/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 in Treatment-Naive Patients

For Study AI424-138, AI424-089, and Study AI424-034, changes from baseline in LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides are shown in Tables 10, 11, and 12, respectively.

Table 10: Lipid Values, Mean Change from Baseline, Study AI424-138

	REYATAZ/ritonavir[a,b]					lopinavir/ritonavir[b,c]				
	Baseline	Week 48		Week 96		Baseline	Week 48		Week 96	
	mg/dL (n=428[e])	mg/dL (n=372[e])	Change[d] (n=372[e])	mg/dL (n=342[e])	Change[d] (n=342[e])	mg/dL (n=424[e])	mg/dL (n=335[e])	Change[d] (n=335[e])	mg/dL (n=291[e])	Change[d] (n=291[e])
LDL-Cholesterol[f]	92	105	+14%	105	+14%	93	111	+19%	110	+17%
HDL-Cholesterol[f]	37	46	+29%	44	+21%	36	48	+37%	46	+29%
Total Cholesterol[f]	149	169	+13%	169	+13%	150	187	+25%	186	+25%
Triglycerides[f]	126	145	+15%	140	+13%	129	194	+52%	184	+50%

a REYATAZ 300 mg with ritonavir 100 mg once daily with the fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

b Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 1% in the lopinavir/ritonavir treatment arm and 1% in the REYATAZ/ritonavir arm. Through Week 48, serum lipid-reducing agents were used in 8% in the lopinavir/ritonavir treatment arm and 2% in the REYATAZ/ritonavir arm. Through Week 96, serum lipid-reducing agents were used in 10% in the lopinavir/ritonavir treatment arm and 3% in the REYATAZ/ritonavir arm.

c Lopinavir 400 mg with ritonavir 100 mg twice daily with the fixed-dose combination 300 mg tenofovir, 200 mg emtricitabine once daily.

d The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 or Week 96 values and is not a simple difference of the baseline and Week 48 or Week 96 mean values, respectively.

e Number of patients with LDL-cholesterol measured.

f Fasting.

Table 11: Lipid Values, Mean Change from Baseline, Study AI424-089

	REYATAZ/ritonavir[a] 300/100 mg once daily			REYATAZ[a] 400 mg once daily		
	Baseline mg/dL (n=93[c])	Week 96 mg/dL (n=68[c])	Week 96 Change[b] (n=68[c])	Baseline mg/dL (n=103[c])	Week 96 mg/dL (n=75[c])	Week 96 Change[b] (n=75[c])
LDL-Cholesterol[d]	96	123	+28%	97	112	+14%
HDL-Cholesterol	38	52	+34%	38	49	+29%
Total Cholesterol	158	185	+18%	163	178	+9%
Triglycerides[d]	139	172	+35%	151	194	+19%

a Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 0% in the REYATAZ 400 mg treatment arm and 1% in the REYATAZ/ritonavir (300/100) arm. Through Week 96, serum lipid-reducing agents were used in 5% in the REYATAZ 400 mg treatment arm and 7% in the REYATAZ/ritonavir (300/100) arm.

b The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 96 values and is not a simple difference of the baseline and Week 96 mean values.

c Number of patients with LDL-cholesterol measured.

d Fasting.

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

	REYATAZ[a,b]			efavirenz[b,c]		
	Baseline mg/dL (n=383[e])	**Week 48 mg/dL (n=283[e])**	**Week 48 Change[d] (n=272[e])**	**Baseline mg/dL (n=378[e])**	**Week 48 mg/dL (n=264[e])**	**Week 48 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. At baseline, serum lipid-reducing agents were used in 0% in the efavirenz treatment arm and <1% in the REYATAZ arm. Through Week 48 serum lipid-reducing agents were used in 3% in the efavirenz treatment arm and 1% in the REYATAZ arm.

[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.

Lipids, Change from Baseline in Treatment-Experienced Patients

For Study AI424-045, changes from baseline in LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides are shown in Table 13. 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 13: Lipid Values, Mean Change from Baseline, Study AI424-045

	REYATAZ/ritonavir[a,b]			lopinavir/ritonavir[b,c]		
	Baseline mg/dL (n=111[e])	Week 48 mg/dL (n=75[e])	Week 48 Change[d] (n=74[e])	Baseline mg/dL (n=108[e])	Week 48 mg/dL (n=76[e])	Week 48 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. At baseline, serum lipid-reducing agents were used in 4% in the lopinavir/ritonavir treatment arm and 4% in the REYATAZ/ritonavir arm. Through Week 48, serum lipid-reducing agents were used in 19% in the lopinavir/ritonavir treatment arm and 8% in the REYATAZ/ritonavir arm.

[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.

6.2 Clinical Trial Experience in Pediatric Patients

The safety and tolerability of REYATAZ Capsules with and without ritonavir have been established in pediatric patients at least 6 years of age from the open-label, multicenter clinical trial PACTG 1020A.

The safety profile of REYATAZ in pediatric patients (6 to less than 18 years of age) was generally similar to that observed in clinical studies of REYATAZ in adults. The most common Grade 2–4 adverse events (≥5%, regardless of causality) reported in pediatric patients were cough (21%), fever (18%), jaundice/scleral icterus (15%), rash (14%), vomiting (12%), diarrhea (9%), headache (8%), peripheral edema (7%), extremity pain (6%), nasal congestion (6%), oropharyngeal pain (6%), wheezing (6%), and rhinorrhea (6%). Both asymptomatic first-degree (30%) and second-degree (<2%) of atrioventricular block were reported in pediatric patients. The most common Grade 3–4 laboratory abnormalities occurring in pediatric patients were elevation of total bilirubin (≥3.2 mg/dL, 58%), neutropenia (9%), and hypoglycemia (4%). All other Grade 3–4 laboratory abnormalities occurred with a frequency of less than 3%.

6.3 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 Study AI424-138, 60 patients treated with REYATAZ/ritonavir 300 mg/100 mg once daily, and 51 patients treated with lopinavir/ritonavir 400 mg/100 mg twice daily, each with fixed dose tenofovir-emtricitabine, were seropositive for hepatitis B and/or C at study entry. ALT levels >5

times ULN developed in 10% (6/60) of the REYATAZ/ritonavir-treated patients and 8% (4/50) of the lopinavir/ritonavir-treated patients. AST levels >5 times ULN developed in 10% (6/60) of the REYATAZ/ritonavir-treated patients and none (0/50) of the lopinavir/ritonavir-treated 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.

In Studies AI424-008 and AI424-034, 74 patients treated with 400 mg of REYATAZ [atazanavir (as sulfate)] 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. [See *Warnings and Precautions (5.5)*.]

6.4 Postmarketing Experience

The following events have been identified during postmarketing use of REYATAZ. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: edema

Cardiovascular System: second-degree AV block, third-degree AV block, left bundle branch block, QTc prolongation [see *Warnings and Precautions (5.2)*]

Gastrointestinal System: pancreatitis

Hepatic System: hepatic function abnormalities

Hepatobiliary Disorders: cholelithiasis [see *Warnings and Precautions (5.6)*], cholecystitis, cholestasis

Metabolic System and Nutrition Disorders: diabetes mellitus, hyperglycemia [see *Warnings and Precautions (5.7)*]

Musculoskeletal System: arthralgia

Renal System: nephrolithiasis [see *Warnings and Precautions (5.6)*], interstitial nephritis, granulomatous interstitial nephritis, chronic kidney disease

Skin and subcutaneous tissue disorders: angioedema

Skin and Appendages: alopecia, maculopapular rash [see *Contraindications (4)* and *Warnings and Precautions (5.3)*], pruritus

7 DRUG INTERACTIONS

See also *Contraindications (4)* and *Clinical Pharmacology (11.3)*.

7.1 Potential for REYATAZ to Affect Other Drugs

Atazanavir is an inhibitor of CYP3A and UGT1A1. Coadministration of REYATAZ and drugs primarily metabolized by CYP3A or UGT1A1 may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects.

Atazanavir is a weak inhibitor of CYP2C8. Caution should be used when REYATAZ without ritonavir is coadministered with drugs highly dependent on CYP2C8 with narrow therapeutic indices (eg, paclitaxel, repaglinide). When REYATAZ with ritonavir is coadministered with substrates of CYP2C8, clinically significant interactions are not expected. [See *Clinical Pharmacology, Table 15 (11.3)*.]

The magnitude of CYP3A-mediated drug interactions on coadministered drug may change when REYATAZ is coadministered with ritonavir. See the complete prescribing information for ritonavir for information on drug interactions with ritonavir.

7.2 Potential for Other Drugs to Affect Atazanavir

Atazanavir is a CYP3A4 substrate; therefore, drugs that induce CYP3A4 may decrease atazanavir plasma concentrations and reduce REYATAZ's therapeutic effect.

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

7.3 Established and Other Potentially Significant Drug Interactions

Table 14 provides dosing recommendations as a result of drug interactions with REYATAZ. 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 14: 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 enteric-coated (EC) capsules	↓ atazanavir ↓ didanosine	Coadministration of REYATAZ with didanosine buffered tablets resulted in a marked decrease in atazanavir exposure. It is recommended that REYATAZ be given (with food) 2 h before or 1 h after didanosine buffered formulations. Simultaneous administration of didanosine EC and REYATAZ with food results in a decrease in didanosine exposure. Thus, REYATAZ and didanosine EC should be administered at different times.
Nucleotide Reverse Transcriptase Inhibitors: tenofovir disoproxil fumarate (DF)	↓ atazanavir ↑ tenofovir	Tenofovir DF may decrease the AUC and C_{min} of atazanavir. When coadministered with tenofovir DF, 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 DF should be monitored for tenofovir-associated adverse events. For pregnant women taking REYATAZ with ritonavir and tenofovir, see *Dosage and Administration (2.3).*
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs):		
efavirenz	↓ atazanavir	Efavirenz decreases atazanavir exposure. ***In treatment-naive patients:*** If REYATAZ is combined with efavirenz, REYATAZ 400 mg (two 200-mg capsules) with ritonavir 100 mg should be administered once daily all as a single dose with food, and efavirenz 600 mg should be administered once daily on an empty stomach, preferably at bedtime. ***In treatment-experienced patients:*** Do not coadminister REYATAZ with efavirenz in treatment-experienced patients due to decreased atazanavir exposure.
nevirapine	↓ atazanavir ↑ nevirapine	Do not coadminister REYATAZ with nevirapine because: • Nevirapine substantially decreases atazanavir exposure. • Potential risk for nevirapine associated toxicity due to increased nevirapine exposures.
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 *Clinical Studies (13.2)*].
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 ritonavir for information on drug interactions with ritonavir.
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.
HCV Antiviral Agents		

Table 14: 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**
Protease Inhibitors: boceprevir	↓ atazanavir	Exposure to atazanavir was decreased when boceprevir at 800 mg three times daily was coadministered with REYATAZ 300 mg and ritonavir 100 mg once daily while exposure to boceprevir was not significantly altered. It is not recommended to coadminister atazanavir/ritonavir and boceprevir.
telaprevir	↓telaprevir ↑atazanavir	Concomitant administration of telaprevir and atazanavir/ritonavir resulted in reduced steady-state telaprevir exposure, while steady-state atazanavir exposure was increased.
Sofosbuvir/velpatasvir/ voxilaprevir	↑ voxilaprevir	Coadministration with REYATAZ 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 hours before or 1 hour 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. Bepridil and quinidine are contraindicated if REYATAZ is coadministered with ritonavir.
Anticoagulants:		
Vitamin K antagonists: 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.
Antiplatelets:		
Ticagrelor	↑ ticagrelor	Co-administration with ticagrelor is not recommended due to potential increase in the antiplatelet activity of ticagrelor. The mechanism of the interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.
Clopidogrel	↓ clopidogrel active metabolite	Co-administration with clopidogrel is not recommended due to potential reduction of the antiplatelet activity of clopidogrel. The mechanism of the interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.
Antineoplastics:		
Apalutamide	↓ atazanavir	Co-administration with REYATAZ with or without ritonavir is contraindicated due to the potential for decreased atazanavir and ritonavir plasma concentration with subsequent loss of virologic response and possible resistance to the class of protease inhibitors [*see Contraindications (4)*]. Mechanism of interaction is CYP3A4 induction by apalutamide.
Encorafenib	↑ encorafenib	Avoid co-administration of encorafenib with REYATAZ with or without ritonavir due to potential for increase in encorafenib plasma concentration and subsequent risk of serious adverse events such as QT interval prolongation. If co-administration of encorafenib with REYATAZ with or without ritonavir cannot be avoided, modify encorafenib dose as recommended for co-administration with strong and moderate CYP3A4 inhibitors in the local prescribing information. Mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.

Table 14: 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**
Ivosidenib	↑ ivosidenib	Avoid co-administration of ivosidenib with REYATAZ with or without ritonavir due to potential for increase in ivosidenib plasma concentration and subsequent risk of serious adverse events such as QT interval prolongation. If co-administration of ivosidenib with REYATAZ with or without ritonavir cannot be avoided, modify ivosidenib dose as recommended for co-administration with strong and moderate CYP3A4 inhibitors in the local prescribing information. Mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.
Direct-acting oral anticoagulants (DOACs):		
Betrixaban, dabigatran, edoxaban	↑ betrixaban, dabigatran, edoxaban	Concomitant use of REYATAZ and ritonavir, a strong CYP3A4/P-gp inhibitor, with either betrixaban, dabigatran, or edoxaban may result in an increased exposure of the respective DOAC, which could lead to an increased risk of bleeding. Refer to the respective DOAC prescribing information regarding dosing instructions for coadministration with P-gp inhibitors.
Rivaroxaban	↑ rivaroxaban	Concomitant use of REYATAZ and ritonavir, a strong CYP3A4/P-gp inhibitor, and rivaroxaban may result in increased exposure of rivaroxaban, which could lead to an increased risk of bleeding. Avoid concomitant use of REYATAZ and ritonavir with rivaroxaban. Concomitant use of REYATAZ, a CYP3A4 inhibitor, and rivaroxaban, may result in increased exposure of rivaroxaban, which could lead to an increased risk of bleeding. Close monitoring is recommended when rivaroxaban is coadministered with REYATAZ.
Apixaban	↑ apixaban	Concomitant use of REYATAZ and ritonavir, a strong CYP3A4/P-gp inhibitor, with apixaban may result in increased exposure of apixaban, which could lead to an increased risk of bleeding. Refer to apixaban dosing instructions for coadministration with strong CYP3A4 and P-gp inhibitors in apixaban prescribing information. Concomitant use of REYATAZ, a CYP3A4 inhibitor, and apixaban may result in increased exposure of apixaban, which could lead to an increased risk of bleeding. Close monitoring is recommended when apixaban is coadministered with REYATAZ.
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.
trazodone	↑ trazodone	Concomitant use of trazodone and REYATAZ with or without ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as REYATAZ, the combination should be used with caution and a lower dose of trazodone should be considered.
Antiepileptics:		
carbamazepine	↓ atazanavir ↑ carbamazepine	Plasma concentrations of atazanavir may be decreased when carbamazepine is administered with REYATAZ without ritonavir. Coadministration of carbamazepine and REYATAZ without ritonavir is not recommended. Ritonavir may increase plasma levels of carbamazepine. If patients beginning treatment with REYATAZ/ritonavir have been titrated to a stable dose of carbamazepine, a dose reduction for carbamazepine may be necessary.

Table 14: 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**
phenytoin, phenobarbital	↓ atazanavir ↓ phenytoin ↓ phenobarbital	Plasma concentrations of atazanavir may be decreased when phenytoin or phenobarbital is administered with REYATAZ without ritonavir. Coadministration of phenytoin or phenobarbital and REYATAZ without ritonavir is not recommended. Ritonavir may decrease plasma levels of phenytoin and phenobarbital. When REYATAZ with ritonavir is coadministered with either phenytoin or phenobarbital, a dose adjustment of phenytoin or phenobarbital may be required.
lamotrigine	↓ lamotrigine	Coadministration of lamotrigine and REYATAZ ***with*** ritonavir may decrease lamotrigine plasma concentrations. Dose adjustment of lamotrigine may be required when coadministered with REYATAZ and ritonavir. Coadministration of lamotrigine and REYATAZ ***without*** ritonavir is not expected to decrease lamotrigine plasma concentrations. No dose adjustment of lamotrigine is required when coadministered with REYATAZ without ritonavir.
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.
voriconazole	***REYATAZ/ritonavir in subjects with a functional CYP2C19 allele:*** ↓voriconazole ↓atazanavir ***REYATAZ/ritonavir in subjects without a functional CYP2C19 allele:*** ↑voriconazole ↓atazanavir	Voriconazole should not be administered to patients receiving REYATAZ/ritonavir, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Patients should be carefully monitored for voriconazole-associated adverse events and loss of either voriconazole or atazanavir efficacy during the coadministration of voriconazole and REYATAZ/ritonavir. Coadministration of voriconazole with REYATAZ (without ritonavir) may affect atazanavir concentrations; however, no data are available.
Antigout: colchicine	↑ colchicine	REYATAZ should not be coadministered with colchicine to patients with renal or hepatic impairment. ***Recommended dosage of colchicine when administered with REYATAZ:*** ***Treatment of gout flares****:* 0.6 mg (1 tablet) for 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Not to repeat before 3 days. ***Prophylaxis of gout flares:*** If the original regimen was 0.6 mg *twice* a day, the regimen should be adjusted to 0.3 mg *once* a day. If the original regimen was 0.6 mg *once* a day, the regimen should be adjusted to 0.3 mg *once every other day*. ***Treatment of familial Mediterranean fever (FMF):*** Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterials: rifabutin	↑ rifabutin	A rifabutin dose reduction of up to 75% (eg, 150 mg every other day or 3 times per week) is recommended. Increased monitoring for rifabutin-associated adverse reactions including neutropenia is warranted.

Table 14: 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**
Antipsychotics: lurasidone	***REYATAZ***	***REYATAZ without ritonavir***
	↑ lurasidone	If coadministration is necessary, reduce the lurasidone dose. Refer to the lurasidone prescribing information for concomitant use with moderate CYP3A4 inhibitors.
	REYATAZ/ritonavir	***REYATAZ/ritonavir***
	↑ lurasidone	Use of lurasidone is contraindicated.
Benzodiazepines: parenterally administered midazolam[b]	↑ midazolam	Concomitant use of parenteral midazolam with REYATAZ may increase plasma concentrations of midazolam. Coadministration should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Coadministration of oral midazolam with REYATAZ is CONTRAINDICATED.
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.
Endothelin receptor antagonists: bosentan	↓ atazanavir ↑ bosentan	Plasma concentrations of atazanavir may be decreased when bosentan is administered with REYATAZ without ritonavir. Coadministration of bosentan and REYATAZ without ritonavir is not recommended.
		Coadministration of bosentan in patients on REYATAZ/ritonavir:
		For patients who have been receiving REYATAZ/ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based on individual tolerability.
		Coadministration of REYATAZ/ritonavir in patients on bosentan:
		Discontinue bosentan at least 36 hours before starting REYATAZ/ritonavir. At least 10 days after starting REYATAZ/ritonavir, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.
Kinase Inhibitors: Fostamatinib	↑ R406 (active metabolite of fostamatinib)	Concomitant use of fostamatinib with REYATAZ with or without ritonavir may increase the plasma concentration of R406, the active metabolite of fostamatinib. Monitor for toxicities of R406 exposure resulting in dose-related adverse events such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required. Mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.
HMG-CoA reductase inhibitors: atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Titrate atorvastatin and rosuvastatin doses carefully and use the lowest possible dose with careful monitoring. Rosuvastatin dose should not exceed 10 mg/day. The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including REYATAZ, are used in combination with these drugs.

Table 14: 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**
H_2-Receptor antagonists	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when REYATAZ 400 mg once daily was administered simultaneously with famotidine 40 mg twice daily, which may result in loss of therapeutic effect and development of resistance. ***In treatment-naive patients:*** REYATAZ 300 mg with ritonavir 100 mg once daily with food should be administered simultaneously with, and/or at least 10 hours after, a dose of the H_2-receptor antagonist. An H_2-receptor antagonist dose comparable to famotidine 20 mg once daily up to a dose comparable to famotidine 40 mg twice daily can be used with REYATAZ 300 mg with ritonavir 100 mg in treatment-naive patients. OR For patients unable to tolerate ritonavir, REYATAZ 400 mg once daily with food should be administered at least 2 hours before and at least 10 hours after a dose of the H_2-receptor antagonist. No single dose of the H_2-receptor antagonist should exceed a dose comparable to famotidine 20 mg, and the total daily dose should not exceed a dose comparable to famotidine 40 mg. However, REYATAZ should not be used without ritonavir in pregnant women. ***In treatment-experienced patients:*** Whenever an H_2-receptor antagonist is given to a patient receiving REYATAZ with ritonavir, the H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily, and the REYATAZ and ritonavir doses should be administered simultaneously with, and/or at least 10 hours after, the dose of the H_2-receptor antagonist. • REYATAZ 300 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with an H_2-receptor antagonist. For pregnant women taking REYATAZ with ritonavir and an H_2-receptor antagonist, see *Dosage and Administration (2.3)*. • REYATAZ 400 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with both tenofovir and an H_2-receptor antagonist. For pregnant women taking REYATAZ with ritonavir and both tenofovir and an H_2-receptor antagonist, see *Dosage and Administration (2.3)*.
Hormonal contraceptives: ethinyl estradiol and norgestimate or norethindrone	↓ ethinyl estradiol ↑ norgestimate[c]	Use with caution if coadministration of REYATAZ or REYATAZ/ritonavir with oral contraceptives is considered. If an oral contraceptive is administered with REYATAZ plus ritonavir, it is recommended that the oral contraceptive contain at least 35 mcg of ethinyl estradiol. If REYATAZ is administered without ritonavir, the oral contraceptive should contain no more than 30 mcg of ethinyl estradiol.
	↑ ethinyl estradiol ↑ norethindrone[d]	Potential safety risks include substantial increases in progesterone exposure. The long-term effects of increases in concentration of the progesteronal agent are unknown and could increase the risk of insulin resistance, dyslipidemia and acne. Coadministration of REYATAZ or REYATAZ/ritonavir with other hormonal contraceptives (eg, contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestogens other than norethindrone or norgestimate, or less than 25 mcg of ethinyl estradiol, has not been studied; therefore, alternative methods of contraception are recommended.
Immunosuppressants: cyclosporin, sirolimus, tacrolimus	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with REYATAZ.

Table 14: 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**
Inhaled beta agonist: salmeterol	↑ salmeterol	Coadministration of salmeterol with REYATAZ is not recommended. Concomitant use of salmeterol and REYATAZ may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Dexamethasone and other corticosteroids (all routes of administration)	↓ atazanavir	Coadministration with dexamethasone or other corticosteroids that induce CYP3A may result in loss of therapeutic effect of REYATAZ and development of resistance to atazanavir and/or ritonavir. Alternative corticosteroids should be considered. Coadministration with corticosteroids (all routes of administration) that are metabolized by CYP3A, particularly for long-term use, may increase the risk for development of systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Consider the potential benefit of treatment versus the risk of systemic corticosteroid effects. For coadministration of cutaneously-administered corticosteroids sensitive to CYP3A inhibition, refer to the prescribing information of the corticosteroid for conditions or uses which augment its systemic absorption. The mechanism of interaction is CYP3A4 induction by dexamethasone and CYP3A4 inhibition by atazanavir and/or ritonavir.
Inhaled/nasal steroid: fluticasone	***REYATAZ*** ↑ fluticasone	Concomitant use of fluticasone propionate and REYATAZ (without ritonavir) may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.
	REYATAZ/ritonavir ↑ fluticasone	Concomitant use of fluticasone propionate and REYATAZ/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression, have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Coadministration of fluticasone propionate or other inhaled or intranasal glucocorticoids metabolized by CYP3A4 and REYATAZ/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects [see *Warnings and Precautions (5.1)*].
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.
Opioids: buprenorphine	↑ buprenorphine ↑ norbuprenorphine	Coadministration of buprenorphine and REYATAZ with or without ritonavir increases the plasma concentration of buprenorphine and norbuprenorphine. Coadministration of REYATAZ plus ritonavir with buprenorphine warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered. Coadministration of buprenorphine and REYATAZ with ritonavir is not expected to decrease atazanavir plasma concentrations. Coadministration of buprenorphine and REYATAZ without ritonavir may decrease atazanavir plasma concentrations. REYATAZ without ritonavir should not be coadministered with buprenorphine.

Table 14: 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**
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, syncope, visual disturbances and priapism. ***Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH):*** Use of REVATIO® (sildenafil) for the treatment of pulmonary hypertension (PAH) is contraindicated with REYATAZ [see *Contraindications (4)*]. The following dose adjustments are recommended for the use of ADCIRCA® (tadalafil) with REYATAZ: Coadministration of ADCIRCA® in patients on REYATAZ (with or without ritonavir): • For patients receiving REYATAZ (with or without ritonavir) for at least one week, start ADCIRCA® at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability. Coadministration of REYATAZ (with or without ritonavir) in patients on ADCIRCA®: • Avoid the use of ADCIRCA® when starting REYATAZ (with or without ritonavir). Stop ADCIRCA® at least 24 hours before starting REYATAZ (with or without ritonavir). At least one week after starting REYATAZ (with or without ritonavir) resume ADCIRCA® at 20 mg once daily, increase to 40 mg once daily based on individual tolerability. ***Use of PDE5 inhibitors for erectile dysfunction:*** Use VIAGRA® (sildenafil) with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Use CIALIS® (tadalafil) with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. ***REYATAZ/ritonavir:*** Use LEVITRA® (vardenafil) with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events. ***REYATAZ:*** Use LEVITRA® (vardenafil) with caution at reduced doses of no more than 2.5 mg every 24 hours with increased monitoring for adverse events.
Proton-pump inhibitors: omeprazole	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when REYATAZ 400 mg or REYATAZ 300 mg/ritonavir 100 mg once daily was administered with omeprazole 40 mg once daily, which may result in loss of therapeutic effect and development of resistance. ***In treatment-naive patients****:* The proton-pump inhibitor dose should not exceed a dose comparable to omeprazole 20 mg and must be taken approximately 12 hours prior to the REYATAZ 300 mg with ritonavir 100 mg dose. ***In treatment-experienced patients****:* Proton-pump inhibitors should not be used in treatment-experienced patients receiving REYATAZ.

[a] For magnitude of interactions see *Clinical Pharmacology, Tables 18* and *19 (11.3)*.

[b] See *Contraindications (4), Table 3* for orally administered midazolam.

[c] In combination with atazanavir 300 mg and ritonavir 100 mg once daily.

[d] In combination with atazanavir 400 mg once daily.

7.4 Drugs with No Observed or Predicted Interactions with REYATAZ

Clinically significant interactions are not expected between atazanavir and substrates of CYP2C19, CYP2C9, CYP2D6, CYP2B6, CYP2A6, CYP1A2, or CYP2E1. Clinically significant interactions are not expected between atazanavir when administered with ritonavir and substrates of CYP2C8. See the complete prescribing information for NORVIR® for information on other potential drug interactions with ritonavir.

Based on known metabolic profiles, clinically significant drug interactions are not expected between REYATAZ [atazanavir (as sulfate)] and dapsone, trimethoprim/sulfamethoxazole, azithromycin, or erythromycin. REYATAZ does not interact with substrates of CYP2D6 (eg, nortriptyline, desipramine, metoprolol). Additionally, no clinically significant drug interactions were observed when REYATAZ was coadministered with methadone, fluconazole, acetaminophen, or atenolol. [See *Clinical Pharmacology, Tables 18* and *19 (11.3)*.]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

Atazanavir has been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate. However, because the studies in humans cannot rule out the possibility of harm, REYATAZ should be used during pregnancy only if clearly needed.

Cases of lactic acidosis syndrome, sometimes fatal, and symptomatic hyperlactatemia have occurred in pregnant women using REYATAZ in combination with nucleoside analogues. Nucleoside analogues are associated with an increased risk of lactic acidosis syndrome.

Hyperbilirubinemia occurs frequently in patients who take REYATAZ, including pregnant women. All infants, including neonates exposed to REYATAZ *in utero,* should be monitored for the development of severe hyperbilirubinemia during the first few days of life.

Clinical Considerations

Dosing During Pregnancy and the Postpartum Period:

- REYATAZ should not be administered without ritonavir.

- REYATAZ should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir.
- For pregnant patients, no dose adjustment is required for REYATAZ with the following exceptions:
    - For treatment-experienced pregnant women during the second or third trimester, when REYATAZ is coadministered with either an H_2-receptor antagonist **or** tenofovir, REYATAZ 400 mg with ritonavir 100 mg once daily is recommended. There are insufficient data to recommend a REYATAZ dose for use with both an H_2-receptor antagonist *and* tenofovir in treatment-experienced women.
- During the second and third trimesters of pregnancy, REYATAZ 300 mg with ritonavir 100 mg may not provide sufficient exposure to atazanavir, especially when the activity of atazanavir or the whole regimen may be compromised due to drug resistance. Since there are limited data available and due to inter-patient variability during pregnancy, Therapeutic Drug Monitoring (TDM) may be considered to ensure adequate exposure.
- No dose adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir exposures could be higher during the first 2 months after delivery. [See *Dosage and Administration (2.3)* and *Clinical Pharmacology (11.3)*.]

Human Data

Clinical Trials: In clinical trial AI424-182, REYATAZ/ritonavir (300/100 mg or 400/100 mg) in combination with zidovudine/lamivudine was administered to 41 HIV-infected pregnant women during the second or third trimester. Among the 39 women who completed the study, 38 women achieved an HIV RNA <50 copies/mL at time of delivery. Six of 20 (30%) women on REYATAZ/ritonavir 300/100 mg and 13 of 21 (62%) women on REYATAZ/ritonavir 400/100 mg experienced hyperbilirubinemia (total bilirubin greater than or equal to 2.6 times the upper limit of normal). There were no cases of lactic acidosis observed in clinical trial AI424-182.

Atazanavir drug concentrations in fetal umbilical cord blood were approximately 12-19% of maternal concentrations. Among the 40 infants born to 40 HIV-infected pregnant women, all had test results that were negative for HIV-1 DNA at the time of delivery and/or during the first 6 months postpartum. All 40 infants received antiretroviral prophylactic treatment containing zidovudine. No evidence of severe hyperbilirubinemia (total bilirubin levels greater than 20 mg/dL) or acute or chronic bilirubin encephalopathy was observed among neonates in this study. However, 10/36 (28%) infants (6 greater than or equal to 38 weeks gestational and 4 less than 38 weeks gestation) had bilirubin levels of 4 mg/dL or greater within the first day of life.

Lack of ethnic diversity was a study limitation. In the study population, 33/40 (83%) infants were Black/African American, who have a lower incidence of neonatal hyperbilirubinemia than Caucasians and Asians. In addition, women with Rh incompatibility were excluded, as well as women who had a previous infant who developed hemolytic disease and/or had neonatal pathologic jaundice (requiring phototherapy).

Additionally, of the 38 infants who had glucose samples collected in the first day of life, 3 had adequately collected serum glucose samples with values of <40 mg/dL that could not be attributed to maternal glucose intolerance, difficult delivery, or sepsis.

US Antiretroviral Pregnancy Registry (APR) Data: As of January 2010, APR has received prospective reports of 635 exposures to atazanavir-containing regimens (425 exposed in the first trimester and 160 and 50 exposed in second and third trimester respectively). Birth defects occurred in 9 of 393 (2.3%) live births (first trimester exposure) and 5 of 212 (2.4%) live births (second/third trimester exposure). There is no association between atazanavir and specific birth defects observed in the APR.

Pharmacokinetics of Atazanavir in Pregnancy

[See *Clinical Pharmacology (11.3)*.]

Animal Data

In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals at systemic drug exposure levels (AUC) 0.7 (in rabbits) to 1.2 (in rats) times those observed at the human clinical dose (300 mg/day atazanavir boosted with 100 mg/day ritonavir). In pre- and post-natal development studies in the rat, atazanavir caused body weight loss or weight gain suppression in the animal offspring with maternal drug exposure (AUC) 1.3 times the human exposure at this clinical dose. However, maternal toxicity also occurred at this exposure level.

8.2 Nursing Mothers

The United States Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Atazanavir has been detected in human milk. No data are available regarding atazanavir effects on milk production. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are taking REYATAZ**.

8.3 Pediatric Use

There are no dosing recommendations for REYATAZ in pediatric patients less than 6 years of age. REYATAZ should not be administered to pediatric patients below the age of 3 months due to the risk of kernicterus.

The safety, activity, and pharmacokinetic profiles of REYATAZ in pediatric patients ages 3 months to less than 6 years have not been established.

The safety, pharmacokinetic profile, and virologic response of REYATAZ were evaluated in pediatric patients in an open-label, multicenter clinical trial PACTG 1020A [see *Clinical Pharmacology (11.3)* and *Clinical Studies (13.3)*]. The safety profile in pediatric patients was generally similar to that observed in adults [see *Adverse Reactions (6.2)*]. Please see *Dosage and Administration (2.2)* for dosing recommendations for pediatric patients 6 years of age and older.

8.4 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.

8.5 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.

8.6 Impaired Renal Function

In healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. REYATAZ has been studied in adult subjects with severe renal impairment (n=20), including those on hemodialysis, at multiple doses of 400 mg once daily. The mean atazanavir C_{max} was 9% lower, AUC was 19% higher, and C_{min} was 96% higher in subjects with severe renal impairment not undergoing hemodialysis (n=10), than in age, weight, and gender matched subjects with normal renal function. Atazanavir was not appreciably cleared during hemodialysis. In a 4-hour dialysis session, 2.1% of the administered dose was removed. When atazanavir was administered either prior to, or following hemodialysis (n=10), the geometric means for C_{max}, AUC, and C_{min} were approximately 25 to 43% lower compared to subjects with normal renal function. The mechanism of this decrease is unknown. REYATAZ should not be administered to HIV-treatment experienced patients with end stage renal disease managed with hemodialysis. [See *Dosage and Administration (2.4)*.]

8.7 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. The pharmacokinetics of REYATAZ in combination with ritonavir have not been studied in subjects with hepatic impairment. REYATAZ should not be administered to patients with severe hepatic impairment. REYATAZ/ritonavir is not recommended for use in patients with hepatic impairment. [See *Dosage and Administration (2.5)* and *Warnings and Precautions (5.5)*.]

9 OVERDOSAGE

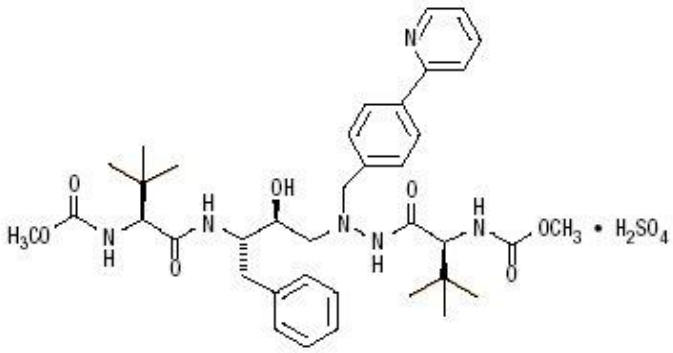
Human experience of acute overdose with REYATAZ is limited. Single doses up to 1200 mg have been taken by healthy volunteers without symptomatic untoward effects. A single self-administered overdose of 29.2 g of REYATAZ in an HIV-infected patient (73 times the 400-mg recommended dose) was associated 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 and Precautions (5.2, 5.4)* and *Clinical Pharmacology (11.2)*.]

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.

10 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 150 mg, 200 mg, or 300 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, titanium dioxide, black iron oxide, red iron oxide, and yellow iron oxide. 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.

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Atazanavir is an antiviral drug [see *Clinical Pharmacology (11.4)*].

11.2 Pharmacodynamics

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 and Precautions (5.2)*.]

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 in clinical trials had a QTc interval >500 msec. [See *Warnings and Precautions (5.2)*.]

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. 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. [See *Warnings and Precautions (5.2)*.]

11.3 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 daily (see Table 15).

Table 15: 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)

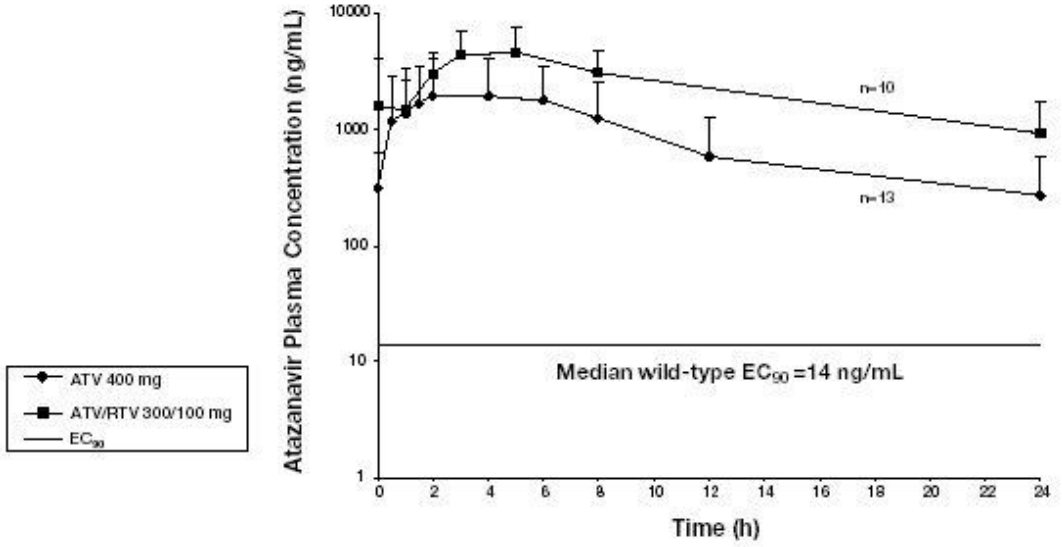
[a] n=26.

[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.

Coadministration of a single 300-mg dose of REYATAZ and a 100-mg dose of ritonavir with a light meal (336 kcal, 5.1 g fat, 9.3 g protein) resulted in a 33% increase in the AUC and a 40% increase in both the C_{max} and the 24-hour concentration of atazanavir relative to the fasting state. Coadministration with a high-fat meal (951 kcal, 54.7 g fat, 35.9 g protein) did not affect the AUC

of atazanavir relative to fasting conditions and the C_{max} was within 11% of fasting values. The 24-hour concentration following a high-fat meal was increased by approximately 33% due to delayed absorption; the median T_{max} increased from 2.0 to 5.0 hours. Coadministration of REYATAZ with ritonavir with either a light or a high-fat meal decreased the coefficient of variation of AUC and C_{max} by approximately 25% 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.

Special Populations

Pediatrics

The pharmacokinetic parameters for atazanavir at steady state in pediatric patients were predicted by a population pharmacokinetic model and are summarized in Table 16 by weight ranges that correspond to the recommended doses. [See *Dosage and Administration (2.2)*.]

Table 16: Predicted Steady-State Pharmacokinetics of Atazanavir (capsule formulation) with ritonavir in HIV-Infected Pediatric Patients

Body Weight (range in kg)	atazanavir/ritonavir Dose (mg)	C_{max} ng/mL Geometric Mean (CV%)	AUC ng•h/mL Geometric Mean (CV%)	C_{min} ng/mL Geometric Mean (CV%)
15 – <20	150/100	5213 (78.7%)	42902 (77.0%)	504 (99.5%)
20 – <40	200/100	4954 (81.7%)	42999 (78.5%)	562 (98.9%)
≥40	300/100	5040 (84.6%)	46777 (80.6%)	691 (98.5%)

Pregnancy

The pharmacokinetic data from HIV-infected pregnant women receiving REYATAZ Capsules with ritonavir are presented in Table 17.

Table 17: Steady-State Pharmacokinetics of Atazanavir with Ritonavir in HIV-Infected Pregnant Women in the Fed State

Pharmacokinetic Parameter	Atazanavir 300 mg with ritonavir 100 mg		
	2nd Trimester (n=5[a])	3rd Trimester (n=20)	Postpartum[b] (n=34)
C_{max} ng/mL	3078.85	3291.46	5721.21
Geometric mean (CV%)	(50)	(48)	(31)
AUC ng•h/mL	27657.1	34251.5	61990.4
Geometric mean (CV%)	(43)	(43)	(32)
C_{min} ng/mL[c]	538.70	668.48	1462.59
Geometric mean (CV%)	(46)	(50)	(45)

[a] Available data during the 2nd trimester are limited.

[b] Atazanavir peak concentrations and AUCs were found to be approximately 28–43% higher during the postpartum period (4–12 weeks) than those observed historically in HIV-infected, non-pregnant patients. Atazanavir plasma trough concentrations were approximately 2.2-fold higher during the postpartum period when compared to those observed historically in HIV-infected, non-pregnant patients.

[c] C_{min} is concentration 24 hours post-dose.

Drug Interaction Data

Atazanavir is a metabolism-dependent CYP3A inhibitor, with a K_{inact} value of 0.05 to 0.06 min^{-1} and K_i value of 0.84 to 1.0 µM. Atazanavir is also a direct inhibitor for UGT1A1 (K_i=1.9 µM) and CYP2C8 (K_i=2.1 µM).

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.

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 18 and 19. For information regarding clinical recommendations, see *Drug Interactions (7)*.

Table 18: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	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 (n=19) and d 19–23	400 mg QD, d 1–11 (n=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 (n=29) and d 18–21	400 mg QD, d 1–10 (n=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 × 1 dose, d4T: 40 mg × 1 dose (n=31)	400 mg × 1 dose simultaneously with ddI and d4T (n=31)	0.11 (0.06, 0.18)	0.13 (0.08, 0.21)	0.16 (0.10, 0.27)
	ddI: 200 mg × 1 dose, d4T: 40 mg × 1 dose (n=32)	400 mg × 1 dose 1 h after ddI + d4T (n=32)	1.12 (0.67, 1.18)	1.03 (0.64, 1.67)	1.03 (0.61, 1.73)
ddI (enteric-coated [EC] capsules)[c]	400 mg d 8 (fed) (n=34) 400 mg d 19 (fed) (n=31)	400 mg QD, d 2–8 (n=34) 300 mg/ritonavir 100 mg QD, d 9–19 (n=31)	1.03 (0.93, 1.14) 1.04 (1.01, 1.07)	0.99 (0.91, 1.08) 1.00 (0.96, 1.03)	0.98 (0.89, 1.08) 0.87 (0.82, 0.92)
diltiazem	180 mg QD, d 7–11 (n=30) and d 19–23	400 mg QD, d 1–11 (n=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 (n=27)	400 mg QD, d 1–20 (n=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 (n=13)	400 mg QD, d 1–6 (n=23) then 300 mg/ritonavir 100 mg QD, 2 h before efavirenz, d 7–20 (n=13)	1.14 (0.83, 1.58)	1.39 (1.02, 1.88)	1.48 (1.24, 1.76)
	600 mg QD, d 11–24 (pm) (n=14)	300 mg QD/ritonavir 100 mg QD, d 1–10 (pm) (n=22), then 400 mg QD/ritonavir 100 mg QD, d 11–24 (pm), (simultaneous with efavirenz) (n=14)	1.17 (1.08, 1.27)	1.00 (0.91, 1.10)	0.58 (0.49, 0.69)
famotidine	40 mg BID, d 7–12 (n=15)	400 mg QD, d 1–6 (n=45), d 7–12 (simultaneous administration) (n=15)	0.53 (0.34, 0.82)	0.59 (0.40, 0.87)	0.58 (0.37, 0.89)
	40 mg BID, d 7–12 (n=14)	400 mg QD (pm), d 1–6 (n=14), d 7–12 (10 h after, 2 h before famotidine) (n=14)	1.08 (0.82, 1.41)	0.95 (0.74, 1.21)	0.79 (0.60, 1.04)
	40 mg BID, d 11–20 (n=14)[d]	300 mg QD/ritonavir 100 mg QD, d 1–10 (n=46), d 11–20[d] (simultaneous administration) (n=14)	0.86 (0.79, 0.94)	0.82 (0.75, 0.89)	0.72 (0.64, 0.81)
	20 mg BID, d 11–17 (n=18)	300 mg QD/ritonavir 100 mg QD/tenofovir 300 mg QD, d 1–10 (am) (n=39), d 11–17 (am) (simultaneous administration with am famotidine) (n=18)[e,f]	0.91 (0.84, 0.99)	0.90 (0.82, 0.98)	0.81 (0.69, 0.94)

Table 18: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}
	40 mg QD (pm), d 18–24 (n=20)	300 mg QD/ritonavir 100 mg QD/tenofovir 300 mg QD, d 1–10 (am) (n=39), d 18–24 (am) (12 h after pm famotidine) (n=20)[f]	0.89 (0.81, 0.97)	0.88 (0.80, 0.96)	0.77 (0.63, 0.93)
	40 mg BID, d 18–24 (n=18)	300 mg QD/ritonavir 100 mg QD/tenofovir 300 mg QD, d 1–10 (am) (n=39), d 18–24 (am) (10 h after pm famotidine and 2 h before am famotidine) (n=18)[f]	0.74 (0.66, 0.84)	0.79 (0.70, 0.88)	0.72 (0.63, 0.83)
	40 mg BID, d 11–20 (n=15)	300 mg QD/ritonavir 100 mg QD, d 1–10 (am) (n=46), then 400 mg QD/ritonavir 100 mg QD, d 11–20 (am) (n=15)	1.02 (0.87, 1.18)	1.03 (0.86, 1.22)	0.86 (0.68, 1.08)
fluconazole	200 mg QD, d 11–20 (n=29)	300 mg QD/ritonavir 100 mg QD, d 1–10 (n=19), d 11–20 (n=29)	1.03 (0.95, 1.11)	1.04 (0.95, 1.13)	0.98 (0.85, 1.13)
grazoprevir/elbasvir	grazoprevir 200 mg QD d 1–35 (n=11)	300 mg QD/ritonavir 100 mg QD	1.12 (1.01, 1.24)	1.43 (1.30, 1.57)	1.23 (1.13, 1.34)
	elbasvir 50 mg QD d 1–35 (n=8)	300 mg QD/ritonavir 100 mg QD	1.02 (0.96, 1.08)	1.07 (0.98, 1.17)	1.15 (1.02, 1.29)
ketoconazole	200 mg QD, d 7–13 (n=14)	400 mg QD, d 1–13 (n=14)	0.99 (0.77, 1.28)	1.10 (0.89, 1.37)	1.03 (0.53, 2.01)
nevirapine[g,h]	200 mg BID, d 1–23 (n=23)	300 mg QD/ritonavir 100 mg QD, d 4–13, then 400 mg QD/ritonavir 100 mg QD, d 14–23 (n=23)[i]	0.72 (0.60, 0.86) 1.02 (0.85, 1.24)	0.58 (0.48, 0.71) 0.81 (0.65, 1.02)	0.28 (0.20, 0.40) 0.41 (0.27, 0.60)
omeprazole	40 mg QD, d 7–12 (n=16)[j]	400 mg QD, d 1–6 (n=48), d 7–12 (n=16)	0.04 (0.04, 0.05)	0.06 (0.05, 0.07)	0.05 (0.03, 0.07)
	40 mg QD, d 11–20 (n=15)[j]	300 mg QD/ritonavir 100 mg QD, d 1–20 (n=15)	0.28 (0.24, 0.32)	0.24 (0.21, 0.27)	0.22 (0.19, 0.26)
	20 mg QD, d 17–23 (am) (n=13)	300 mg QD/ritonavir 100 mg QD, d 7–16 (pm) (n=27), d 17–23 (pm) (n=13)[k,l]	0.61 (0.46, 0.81)	0.58 (0.44, 0.75)	0.54 (0.41, 0.71)
	20 mg QD, d 17–23 (am) (n=14)	300 mg QD/ritonavir 100 mg QD, d 7–16 (am) (n=27), then 400 mg QD/ritonavir 100 mg QD, d 17–23 (am) (n=14)[m,n]	0.69 (0.58, 0.83)	0.70 (0.57, 0.86)	0.69 (0.54, 0.88)
pitavastatin	4 mg QD for 5 days	300 mg QD for 5 days	1.13 (0.96, 1.32)	1.06 (0.90, 1.26)	NA
rifabutin	150 mg QD, d 15–28 (n=7)	400 mg QD, d 1–28 (n=7)	1.34 (1.14, 1.59)	1.15 (0.98, 1.34)	1.13 (0.68, 1.87)

Table 18: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}
rifampin	600 mg QD, d 17–26 (n=16)	300 mg QD/ritonavir 100 mg QD, d 7–16 (n=48), d 17–26 (n=16)	0.47 (0.41, 0.53)	0.28 (0.25, 0.32)	0.02 (0.02, 0.03)
ritonavir[o]	100 mg QD, d 11–20 (n=28)	300 mg QD, d 1–20 (n=28)	1.86 (1.69, 2.05)	3.38 (3.13, 3.63)	11.89 (10.23, 13.82)
telaprevir	750 mg q8h for 10 days (n=7)	300 mg QD/ritonavir 100 mg QD for 20 days (n=7)	0.85 (0.73, 0.98)	1.17 (0.97, 1.43)	1.85 (1.40, 2.44)
tenofovir[p]	300 mg QD, d 9–16 (n=34)	400 mg QD, d 2–16 (n=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 (n=10)	300 mg/ritonavir 100 mg QD, d 1–42 (n=10)	0.72[q] (0.50, 1.05)	0.75[q] (0.58, 0.97)	0.77[q] (0.54, 1.10)
voriconazole (Subjects with at least one functional CYP2C19 allele)	200 mg BID, d 2–3, 22–30; 400 mg BID d 1, 21 (n=20)	300 mg/ritonavir 100 mg QD, d 11–30 (n=20)	0.87 (0.80, 0.96)	0.88 (0.82, 0.95)	0.80 (0.72, 0.90)
voriconazole (Subjects without a functional CYP2C19 allele)	50 mg BID, d 2–3, 22–30; 100 mg BID d 1, 21 (n=8)	300 mg/ritonavir 100 mg QD, d 11–30 (n=8)	0.81 (0.66, 1.00)	0.80 (0.65, 0.97)	0.69 (0.54, 0.87)

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

[b] All drugs were given under fasted conditions.

[c] 400 mg ddI EC and REYATAZ were administered together with food on Days 8 and 19.

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

[e] Similar results were noted when famotidine 20 mg BID was administered 2 hours after and 10 hours before atazanavir 300 mg and ritonavir 100 mg plus tenofovir 300 mg.

[f] Atazanavir/ritonavir/tenofovir was administered after a light meal.

[g] Study was conducted in HIV-infected individuals.

[h] Compared with atazanavir 400 mg historical data without nevirapine (n=13), the ratio of geometric means (90% confidence intervals) for $C_{max,}$ AUC, and C_{min} were 1.42 (0.98, 2.05), 1.64 (1.11, 2.42), and 1.25 (0.66, 2.36), respectively, for atazanavir/ritonavir 300/100 mg; and 2.02 (1.42, 2.87), 2.28 (1.54, 3.38), and 1.80 (0.94, 3.45), respectively, for atazanavir/ritonavir 400/100 mg.

[i] Parallel group design; n=23 for atazanavir/ritonavir plus nevirapine, n=22 for atazanavir 300 mg/ritonavir 100 mg without nevirapine. Subjects were treated with nevirapine prior to study entry.

[j] Omeprazole 40 mg was administered on an empty stomach 2 hours before REYATAZ.

[k] Omeprazole 20 mg was administered 30 minutes prior to a light meal in the morning and REYATAZ 300 mg plus ritonavir 100 mg in the evening after a light meal, separated by 12 hours from omeprazole.

Table 18: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}

[l] REYATAZ 300 mg plus ritonavir 100 mg once daily separated by 12 hours from omeprazole 20 mg daily resulted in increases in atazanavir geometric mean AUC (10%) and C_{min} (2.4-fold), with a decrease in C_{max} (29%) relative to REYATAZ 400 mg once daily in the absence of omeprazole (study days 1–6).

[m] Omeprazole 20 mg was given 30 minutes prior to a light meal in the morning and REYATAZ 400 mg plus ritonavir 100 mg once daily after a light meal, 1 hour after omeprazole. Effects on atazanavir concentrations were similar when REYATAZ 400 mg plus ritonavir 100 mg was separated from omeprazole 20 mg by 12 hours.

[n] REYATAZ 400 mg plus ritonavir 100 mg once daily administered with omeprazole 20 mg once daily resulted in increases in atazanavir geometric mean AUC (32%) and C_{min} (3.3-fold), with a decrease in C_{max} (26%) relative to REYATAZ 400 mg once daily in the absence of omeprazole (study days 1–6).

[o] 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.

[p] Note that similar results were observed in studies where administration of tenofovir and REYATAZ was separated by 12 hours.

[q] 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[o]). The geometric mean values of atazanavir pharmacokinetic parameters when coadministered with ritonavir and tenofovir were: C_{max} = 3190 ng/mL, AUC = 34459 ng•h/mL, and C_{min} = 491 ng/mL. Study was conducted in HIV-infected individuals.

NA = not available.

Table 19: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of REYATAZ[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without REYATAZ; No effect = 1.00		
			C_{max}	AUC	C_{min}
acetaminophen	1 gm BID, d 1–20 (n=10)	300 mg QD/ritonavir 100 mg QD, d 11–20 (n=10)	0.87 (0.77, 0.99)	0.97 (0.91, 1.03)	1.26 (1.08, 1.46)
atenolol	50 mg QD, d 7–11 (n=19) and d 19–23	400 mg QD, d 1–11 (n=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 (n=21) and d 18–21	400 mg QD, d 1–10 (n=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 × 1 dose, d4T: 40 mg × 1 dose (n=31)	400 mg × 1 dose simultaneous with ddI and d4T (n=31)	ddI: 0.92 (0.84, 1.02) d4T: 1.08 (0.96, 1.22)	ddI: 0.98 (0.92, 1.05) d4T: 1.00 (0.97, 1.03)	NA d4T: 1.04 (0.94, 1.16)
ddI (enteric-coated [EC] capsules)[c]	400 mg d 1 (fasted), d 8 (fed) (n=34)	400 mg QD, d 2–8 (n=34)	0.64 (0.55, 0.74)	0.66 (0.60, 0.74)	1.13 (0.91, 1.41)
	400 mg d 1 (fasted), d 19 (fed) (n=31)	300 mg QD/ritonavir 100 mg QD, d 9–19 (n=31)	0.62 (0.52, 0.74)	0.66 (0.59, 0.73)	1.25 (0.92, 1.69)
diltiazem	180 mg QD, d 7–11 (n=28) and d 19–23	400 mg QD, d 1–11 (n=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[d]	Ortho-Novum® 7/7/7 QD, d 1–29 (n=19)	400 mg QD, d 16–29 (n=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)
ethinyl estradiol & norgestimate[e]	Ortho Tri-Cyclen® QD, d 1–28 (n=18), then Ortho Tri-Cyclen® LO QD, d 29–42[f] (n=14)	300 mg QD/ritonavir 100 mg QD, d 29–42 (n=14)	ethinyl estradiol: 0.84 (0.74, 0.95) 17-deacetyl norgestimate:[g] 1.68 (1.51, 1.88)	ethinyl estradiol: 0.81 (0.75, 0.87) 17-deacetyl norgestimate:[g] 1.85 (1.67, 2.05)	ethinyl estradiol: 0.63 (0.55, 0.71) 17-deacetyl norgestimate:[g] 2.02 (1.77, 2.31)
fluconazole	200 mg QD, d 1–10 (n=11) and 200 mg QD, d 11–20 (n=29)	300 mg QD/ritonavir 100 mg QD, d 11–20 (n=29)	1.05 (0.99, 1.10)	1.08 (1.02, 1.15)	1.07 (1.00, 1.15)
Grazoprevir /elbasvir	grazoprevir 200 mg QD d 1–35 (n=12)	300 mg QD/ritonavir 100 mg QD	6.24 (4.42, 8.81)	10.58 (7.78, 14.39)	11.64 (7.96, 17.02)
	elbasvir 50 mg QD d 1–35 (n=10)	300 mg QD/ritonavir 100 mg QD	4.15 (3.46, 4.97)	4.76 (4.07, 5.56)	6.45 (5.51, 7.54)

Table 19: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of REYATAZ[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without REYATAZ; No effect = 1.00		
			C_{max}	AUC	C_{min}
methadone	Stable maintenance dose, d 1–15 (n=16)	400 mg QD, d 2–15 (n=16)	(R)-methadone[h] 0.91 (0.84, 1.0) total: 0.85 (0.78, 0.93)	(R)-methadone[h] 1.03 (0.95, 1.10) total: 0.94 (0.87, 1.02)	(R)-methadone[h] 1.11 (1.02, 1.20) total: 1.02 (0.93, 1.12)
Nevirapine[i,j]	200 mg BID, d 1–23 (n=23)	300 mg QD/ ritonavir 100 mg QD, d 4–13, then	1.17 (1.09, 1.25)	1.25 (1.17, 1.34)	1.32 (1.22, 1.43)
		400 mg QD/ ritonavir 100 mg QD, d 14–23 (n=23)	1.21 (1.11, 1.32)	1.26 (1.17, 1.36)	1.35 (1.25, 1.47)
omeprazole[k]	40 mg single dose, d 7 and d 20 (n=16)	400 mg QD, d 1–12 (n=16)	1.24 (1.04, 1.47)	1.45 (1.20, 1.76)	NA
rifabutin	300 mg QD, d 1–10 then 150 mg QD, d 11–20 (n=3)	600 mg QD,[l] d 11–20 (n=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)
	150 mg twice weekly, d 1–15 (n=7)	300 mg QD/ritonavir 100 mg QD, d 1–17 (n=7)	2.49[m] (2.03, 3.06) 25-O-desacetyl-rifabutin: 7.77 (6.13, 9.83)	1.48[m] (1.19, 1.84) 25-O-desacetyl-rifabutin: 10.90 (8.14, 14.61)	1.40[m] (1.05, 1.87) 25-O-desacetyl-rifabutin: 11.45 (8.15, 16.10)
pitavastatin	4 mg QD for 5 days	300 mg QD for 5 days	1.60 (1.39, 1.85)	1.31 (1.23, 1.39)	NA
Rosiglitazone[n]	4 mg single dose, d 1, 7, 17 (n=14)	400 mg QD, d 2–7, then	1.08 (1.03, 1.13)	1.35 (1.26, 1.44)	NA
		300 mg QD/ ritonavir 100 mg QD, d 8–17 (n=14)	0.97 (0.91, 1.04)	0.83 (0.77, 0.89)	NA
rosuvastatin	10 mg single dose	300 mg QD/ ritonavir 100 mg QD for 7 days	↑ 7-fold[o]	↑ 3-fold[o]	NA
Saquinavir[p] (soft gelatin capsules)	1200 mg QD, d 1–13 (n=7)	400 mg QD, d 7–13 (n=7)	4.39 (3.24, 5.95)	5.49 (4.04, 7.47)	6.86 (5.29, 8.91)
telaprevir	750 mg q8h for 10 days (n=14)	300 mg QD/ ritonavir 100 mg QD for 20 days (n=14)	0.79 (0.74, 0.84)	0.80 (0.76, 0.85)	0.85 (0.75, 0.98)
Tenofovir[q]	300 mg QD, d 9–16 (n=33) and d 24–30 (n=33)	400 mg QD, d 2–16 (n=33)	1.14 (1.08, 1.20)	1.24 (1.21, 1.28)	1.22 (1.15, 1.30)
	300 mg QD, d 1–7 (pm) (n=14) d 25–34 (pm) (n=12)[i]	300 mg QD/ritonavir 100 mg QD, d 25–34 (am) (n=12)[r]	1.34 (1.20, 1.51)	1.37 (1.30, 1.45)	1.29 (1.21, 1.36)

Table 19: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of REYATAZ[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without REYATAZ; No effect = 1.00		
			C_{max}	AUC	C_{min}
voriconazole (Subjects with at least one functional CYP2C19 allele)	200 mg BID, d 2–3, 22–30; 400 mg BID d 1, 21 (n=20)	300 mg/ritonavir 100 mg QD, d 11–30 (n=20)	0.90 (0.78, 1.04)	0.67 (0.58, 0.78)	0.61 (0.51, 0.72)
voriconazole (Subjects without a functional CPY2C19 allele)	50 mg BID, d 2–3, 22–30; 100 mg BID d 1, 21 (n=8)	300 mg/ritonavir 100 mg QD, d 11–30 (n=8)	4.38 (3.55, 5.39)	5.61 (4.51, 6.99)	7.65 (5.71, 10.2)
lamivudine + zidovudine	150 mg lamivudine + 300 mg zidovudine BID, d 1–12 (n=19)	400 mg QD, d 7–12 (n=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] 400 mg ddI EC and REYATAZ were administered together with food on Days 8 and 19.

[d] Upon further dose normalization of ethinyl estradiol 25 mcg with atazanavir relative to ethinyl estradiol 35 mcg without atazanavir, the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 0.82 (0.73, 0.92), 1.06 (0.95, 1.17), and 1.35 (1.11, 1.63), respectively.

[e] Upon further dose normalization of ethinyl estradiol 35 mcg with atazanavir/ritonavir relative to ethinyl estradiol 25 mcg without atazanavir/ritonavir, the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 1.17 (1.03, 1.34), 1.13 (1.05, 1.22), and 0.88 (0.77, 1.00), respectively.

[f] All subjects were on a 28 day lead-in period; one full cycle of Ortho Tri-Cyclen®. Ortho Tri-Cyclen® contains 35 mcg of ethinyl estradiol. Ortho Tri-Cyclen® LO contains 25 mcg of ethinyl estradiol. Results were dose normalized to an ethinyl estradiol dose of 35 mcg.

[g] 17-deacetyl norgestimate is the active component of norgestimate.

[h] (R)-methadone is the active isomer of methadone.

[i] Study was conducted in HIV-infected individuals.

[j] Subjects were treated with nevirapine prior to study entry.

[k] Omeprazole was used as a metabolic probe for CYP2C19. Omeprazole was given 2 hours after REYATAZ on Day 7; and was given alone 2 hours after a light meal on Day 20.

[l] Not the recommended therapeutic dose of atazanavir.

[m] When compared to rifabutin 150 mg QD alone d 1-10 (n=14). Total of Rifabutin + 25-O-desacetyl-rifabutin: AUC 2.19 (1.78, 2.69).

[n] Rosiglitazone used as a probe substrate for CYP2C8.

[o] Mean ratio (with/without coadministered drug), ↑ indicates an increase in rosuvastatin exposure.

[p] 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.

[q] Note that similar results were observed in a study where administration of tenofovir and REYATAZ was separated by 12 hours.

[r] Administration of tenofovir and REYATAZ was temporally separated by 12 hours.

NA = not available.

11.4 Microbiology

Mechanism of Action

Atazanavir 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 Cell Culture

Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC_{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. ATV has activity against HIV-1 Group M subtype viruses A, B, C, D, AE, AG, F, G, and J isolates in cell culture. ATV has variable activity against HIV-2 isolates (1.9 to 32 nM), with EC_{50} values above the EC_{50} values of failure isolates. Two-drug combination antiviral activity studies with ATV showed no antagonism in cell culture with NNRTIs (delavirdine, efavirenz, and nevirapine), PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), NRTIs (abacavir, 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 Cell Culture: HIV-1 isolates with a decreased susceptibility to atazanavir have been selected in cell culture and obtained from patients treated with atazanavir or atazanavir/ritonavir. HIV-1 isolates with 93- to 183-fold reduced susceptibility to atazanavir from three different viral strains were selected in cell culture by 5 months. The substitutions in these HIV-1 viruses that contributed to atazanavir resistance include I50L, N88S, I84V, A71V, and M46I. Changes were also observed at the protease cleavage sites following drug selection. Recombinant viruses containing the I50L substitution without other major PI substitutions were growth impaired and displayed increased susceptibility in cell culture to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). The I50L and I50V substitutions yielded selective resistance to atazanavir and amprenavir, respectively, and did not appear to be cross-resistant.

Clinical Studies of Treatment-Naive Patients: Comparison of Ritonavir-Boosted REYATAZ vs. Unboosted REYATAZ: Study AI424-089 compared REYATAZ 300 mg once daily with ritonavir 100 mg vs. REYATAZ 400 mg once daily when administered with lamivudine and extended-release stavudine in HIV-infected treatment-naive patients. A summary of the number of virologic failures and virologic failure isolates with ATV resistance in each arm is shown in Table 20.

Table 20: Summary of Virologic Failures[a] at Week 96 in Study AI424-089: Comparison of Ritonavir Boosted REYATAZ vs. Unboosted REYATAZ: Randomized Patients

	REYATAZ 300 mg + ritonavir 100 mg (n=95)	REYATAZ 400 mg (n=105)
Virologic Failure (≥50 copies/mL) at Week 96	15 (16%)	34 (32%)
Virologic Failure with Genotypes and Phenotypes Data	5	17
Virologic Failure Isolates with ATV-resistance at Week 96	0/5 (0%)[b]	4/17 (24%)[b]
Virologic Failure Isolates with I50L Emergence at Week 96[c]	0/5 (0%)[b]	2/17 (12%)[b]
Virologic Failure Isolates with Lamivudine Resistance at Week 96	2/5 (40%)[b]	11/17 (65%)[b]

[a] Virologic failure includes patients who were never suppressed through Week 96 and on study at Week 96, had virologic rebound or discontinued due to insufficient viral load response.

[b] Percentage of Virologic Failure Isolates with genotypic and phenotypic data.

[c] Mixture of I50I/L emerged in 2 other ATV 400 mg-treated patients. Neither isolate was phenotypically resistant to ATV.

Clinical Studies of Treatment-Naive Patients Receiving REYATAZ 300 mg With Ritonavir 100 mg: In Phase III study AI424-138, an as-treated genotypic and phenotypic analysis was conducted on samples from patients who experienced virologic failure (HIV-1 RNA ≥400 copies/mL) or discontinued before achieving suppression on ATV/RTV (n=39; 9%) and LPV/RTV (n=39; 9%) through 96 weeks of treatment. In the ATV/RTV arm, one of the virologic failure isolates had 56-fold decreases in ATV susceptibility emerge on therapy with the development of PI resistance-associated substitutions L10F, V32I, K43T, M46I, A71I, G73S, I85I/V, and L90M. The NRTI resistance-associated substitution M184V also emerged on treatment in this isolate conferring emtricitabine resistance. Two ATV/RTV-virologic failure isolates had baseline phenotypic ATV resistance and IAS-defined major PI resistance-associated substitutions at baseline. The I50L substitution emerged on study in one of these failure isolates and was associated with a 17-fold decrease in ATV susceptibility from baseline and the other failure isolate with baseline ATV resistance and PI substitutions (M46M/I and I84I/V) had additional IAS-defined major PI substitutions (V32I, M46I, and I84V) emerge on ATV treatment associated with a 3-fold decrease in ATV susceptibility from baseline. Five of the treatment failure isolates in the ATV/RTV arm developed phenotypic emtricitabine resistance with the emergence of either the M184I (n=1) or the M184V (n=4) substitution on therapy and none developed phenotypic tenofovir disoproxil resistance. In the LPV/RTV arm, one of the virologic failure patient isolates had a 69-fold decrease in LPV susceptibility emerge on therapy with the development of PI substitutions L10V, V11I, I54V, G73S and V82A in addition to baseline PI substitutions L10L/I, V32I, I54I/V, A71I, G73G/S, V82V/A, L89V and L90M. Six LPV/RTV virologic failure isolates developed the

M184V substitution and phenotypic emtricitabine resistance and two developed phenotypic tenofovir disoproxil resistance.

Clinical Studies of Treatment-Naive Patients Receiving REYATAZ 400 mg Without Ritonavir: Atazanavir-resistant clinical isolates from treatment-naive patients who experienced virologic failure on REYATAZ 400 mg treatment without ritonavir often developed an I50L substitution (after an average of 50 weeks of atazanavir therapy), often in combination with an A71V substitution, but also developed one or more other PI substitutions (eg, V32I, L33F, G73S, V82A, I85V, or N88S) with or without the I50L substitution. In treatment-naive patients, viral isolates that developed the I50L substitution, without other major PI substitutions, showed phenotypic resistance to atazanavir but retained in cell culture 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 substitution on the efficacy of subsequently administered PIs.

Clinical Studies of Treatment-Experienced Patients: In studies of treatment-experienced patients treated with atazanavir or atazanavir/ritonavir, most atazanavir-resistant isolates from patients who experienced virologic failure developed substitutions that were associated with resistance to multiple PIs and displayed decreased susceptibility to multiple PIs. The most common protease substitutions to develop in the viral isolates of patients who failed treatment with atazanavir 300 mg once daily and ritonavir 100 mg once daily (together with tenofovir DF 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 substitutions that developed on atazanavir/ritonavir 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 substitutions were present in the HIV-1 virus of the patient at baseline, ATV resistance developed through substitutions associated with resistance to other PIs and could include the development of the I50L substitution. The I50L substitution has been detected in treatment-experienced patients experiencing virologic failure after long-term treatment. Protease cleavage site changes also emerged on atazanavir treatment but their presence did not correlate with the level of atazanavir resistance.

Cross-Resistance

Cross-resistance among PIs has been observed. Baseline phenotypic and genotypic analyses of clinical isolates from atazanavir clinical trials of PI-experienced patients showed that isolates cross-resistant to multiple PIs were cross-resistant to atazanavir. Greater than 90% of the isolates with substitutions that included I84V or G48V were resistant to atazanavir. Greater than 60% of isolates containing L90M, G73S/T/C, A71V/T, I54V, M46I/L, or a change at V82 were resistant to atazanavir, and 38% of isolates containing a D30N substitution in addition to other changes were resistant to atazanavir. Isolates resistant to atazanavir 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 substitution in addition to other PI resistance-associated substitution were also cross-resistant to other PIs.

Baseline Genotype/Phenotype and Virologic Outcome Analyses

Genotypic and/or phenotypic analysis of baseline virus may aid in determining atazanavir susceptibility before initiation of atazanavir/ritonavir therapy. An association between virologic response at 48 weeks and the number and type of primary PI resistance-associated substitutions detected in baseline HIV-1 isolates from antiretroviral-experienced patients receiving atazanavir/ritonavir once daily or lopinavir/ritonavir twice daily in Study AI424-045 is shown in Table 21.

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

Table 21: HIV RNA Response by Number and Type of Baseline PI Substitution, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

	Virologic Response = HIV RNA <400 copies/mL[b]	
Number and Type of Baseline PI Substitutions[a]	**atazanavir/ritonavir (n=110)**	**lopinavir/ritonavir (n=113)**
3 or more primary PI substitutions 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 substitutions[a]		
All patients, as-treated	58% (64/110)	59% (67/113)
0–2 PI substitutions	75% (50/67)	75% (50/67)
3–4 PI substitutions	41% (14/34)	43% (12/28)
5 or more PI substitutions	0% (0/9)	28% (5/18)

Table 21: HIV RNA Response by Number and Type of Baseline PI Substitution, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

[a] Primary substitutions 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 substitutions V32I, I47V, G48V, I50V, and F53L.

The response rates of antiretroviral-experienced patients in Study AI424-045 were analyzed by baseline phenotype (shift in susceptibility in cell culture relative to reference, Table 22). 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 22: 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] atazanavir/ritonavir (n=111)	Virologic Response = HIV RNA <400 copies/mL[b] lopinavir/ritonavir (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 susceptibility in cell culture relative to the wild-type reference.

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

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term carcinogenicity studies in mice and rats were carried out with atazanavir for two years. In the mouse study, drug-related increases in hepatocellular adenomas were found in females at 360 mg/kg/day. The systemic drug exposure (AUC) at the NOAEL (No Observable Adverse Effect Level) in females (120 mg/kg/day) was 2.8 times and in males (80 mg/kg/day) was 2.9 times higher than those in humans at the clinical dose (300 mg/day atazanavir boosted with 100 mg/day ritonavir, non-pregnant patients). In the rat study, no drug-related increases in tumor incidence

were observed at doses up to 1200 mg/kg/day, for which AUCs were 1.1 (males) or 3.9 (females) times those measured in humans at the clinical dose.

Mutagenesis

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).

Impairment of Fertility

At the systemic drug exposure levels (AUC) 0.9 (in male rats) or 2.3 (in female rats) times that of the human clinical dose (300 mg/day atazanavir boosted with 100 mg/day ritonavir), significant effects on mating, fertility, or early embryonic development were not observed.

13 CLINICAL STUDIES

13.1 Adult Patients Without Prior Antiretroviral Therapy

Study AI424-138: a 96-week study comparing the antiviral efficacy and safety of atazanavir/ritonavir with lopinavir/ritonavir, each in combination with fixed-dose tenofovir-emtricitabine in HIV-1 infected treatment-naive subjects. Study AI424-138 is a 96-week open-label, randomized, multicenter study, comparing REYATAZ (300 mg once daily) with ritonavir (100 mg once daily) to lopinavir with ritonavir (400/100 mg twice daily), each in combination with fixed-dose tenofovir with emtricitabine (300/200 mg once daily), in 878 antiretroviral treatment-naive treated patients. Patients had a mean age of 36 years (range: 19–72), 49% were Caucasian, 18% Black, 9% Asian, 23% Hispanic/Mestizo/mixed race, and 68% were male. The median baseline plasma CD4+ cell count was 204 cells/mm^3 (range: 2 to 810 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.94 $\log_{10}$ copies/mL (range: 2.60 to 5.88 $\log_{10}$ copies/mL). Treatment response and outcomes through Week 96 are presented in Table 23.

Table 23: Outcomes of Treatment Through Week 96 (Study AI424-138)

Outcome	REYATAZ 300 mg + ritonavir 100 mg (once daily) with tenofovir/emtricitabine (once daily)[a] (n=441)	lopinavir 400 mg + ritonavir 100 mg (twice daily) with tenofovir/emtricitabine (once daily)[a] (n=437)
Responder[b,c,d]	75%	68%
Virologic failure[e]	17%	19%
Rebound	8%	10%
Never suppressed through Week 96	9%	9%
Death	1%	1%
Discontinued due to adverse event	3%	5%
Discontinued for other reasons[f]	4%	7%

[a] As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

[b] Patients achieved HIV RNA <50 copies/mL at Week 96. Roche Amplicor®, v1.5 ultra-sensitive assay.

[c] Pre-specified ITT analysis at Week 48 using as-randomized cohort: ATV/RTV 78% and LPV/RTV 76% [difference estimate: 1.7% (95% confidence interval: −3.8%, 7.1%)].

[d] Pre-specific ITT analysis at Week 96 using as-randomized cohort: ATV/RTV 74% and LPV/RTV 68% [difference estimate: 6.1% (95% confidence interval: 0.3%, 12.0%)].

[e] Includes viral rebound and failure to achieve confirmed HIV RNA <50 copies/mL through Week 96.

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

Through 96 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/ritonavir (165 of 223 patients, 74%) and lopinavir/ritonavir (148 of 222 patients, 67%) arms. At 96 weeks, the median increase from baseline in CD4+ cell count was 261 cells/mm^3 for the REYATAZ/ritonavir arm and 273 cells/mm^3 for the lopinavir/ritonavir arm.

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 24.

Table 24: 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. Amplicor HIV-1 Monitor Assay†, test version 1.0 or 1.5 as geographically appropriate.

[b] Includes 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 25.

Table 25: 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. Amplicor HIV-1 Monitor Assay†, test version 1.0 or 1.5 as geographically appropriate.

[b] Includes 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.

13.2 Adult 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 26. 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 *Clinical Pharmacology, Tables 21* and *22 (11.4)*.]

Table 26: 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] 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 *Drug Interactions (7)*].

Study AI424-045 also compared changes from baseline in lipid values. [See *Adverse Reactions (6.1)*.]

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.

13.3 Pediatric Patients

Assessment of the pharmacokinetics, safety, tolerability, and efficacy of REYATAZ is based on data from the open-label, multicenter clinical trial PACTG 1020A conducted in patients from 3 months to 21 years of age. In this study, 193 patients (86 antiretroviral-naive and 107 antiretroviral-experienced) received once daily REYATAZ, with or without ritonavir, in combination with two NRTIs. The clinical data derived from this study are inadequate to support the use of atazanavir (with or without ritonavir) in children below 6 years of age.

One-hundred and five patients (6 to less than 18 years of age) treated with the REYATAZ capsule formulation, with or without ritonavir, were evaluated. Using an ITT analysis, the overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <400 copies/mL at Week 96 were 51% (22/43) and 34% (21/62), respectively. The overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <50 copies/mL at Week 96 were 47% (20/43) and 24% (15/62), respectively. The median increase from baseline in absolute CD4 count at 96 weeks of therapy was 335 cells/mm^3 in antiretroviral-naive patients and 220 cells/mm^3 in antiretroviral-experienced patients.

14 HOW SUPPLIED/STORAGE AND HANDLING

REYATAZ [atazanavir (as 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**
		cap	**body**	
150 mg	blue/powder blue	BMS 150 mg (white)	3624 (blue)	60
200 mg	blue/blue	BMS 200 mg (white)	3631 (white)	60
300 mg	red/blue	BMS 300 mg (white)	3622 (white)	30

*atazanavir equivalent as atazanavir sulfate.

Certain dosage strengths may not be available in all countries.

Store below 30°C.

† Amplicor HIV-1 Monitor is a registered trademark of Roche Molecular Systems, Inc.

15 PATIENT COUNSELING INFORMATION

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**.

REYATAZ is not a cure for HIV-1 infection and patients may continue to experience illness associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using REYATAZ.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** It is not known if REYATAZ can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in breast milk.

15.1 Dosing Instructions

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.

15.2 Drug Interactions

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 PDE5 inhibitor-associated adverse events including hypotension, syncope, visual disturbances, and priapism, and should promptly report any symptoms to their doctor.

Patients should be informed that REVATIO® (used to treat pulmonary arterial hypertension) is contraindicated with REYATAZ and that dose adjustments are necessary when REYATAZ is used with CIALIS®, LEVITRA®, or VIAGRA® (used to treat erectile dysfunction), or ADCIRCA® (used to treat pulmonary arterial hypertension).

15.3 Cardiac Conduction Abnormalities

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

15.4 Rash

Patients should be informed that mild rashes without other symptoms have been reported with REYATAZ use. These rashes go away within two weeks with no change in treatment. However, there have been a few reports of severe skin reactions (eg, Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions) with REYATAZ use. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by one or more of the following: fever, general malaise, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must discontinue REYATAZ and seek medical evaluation immediately.

15.5 Hyperbilirubinemia

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.

15.6 Fat Redistribution

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.

15.7 Chronic Kidney Disease

Inform patients that treatment with REYATAZ may lead to the development of chronic kidney disease, and to maintain adequate hydration while taking REYATAZ.

15.8 Nephrolithiasis and Cholelithiasis

Patients should be informed that kidney stones and/or gallstones have been reported with REYATAZ use. Some patients with kidney stones and/or gallstones required hospitalization for additional management and some had complications. Discontinuation of REYATAZ may be necessary as part of the medical management of these adverse events.

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Revision date: May 2023