

PRODUCT MONOGRAPH

Pr **REYATAZ** *

(atazanavir sulfate)

Capsules

150, 200 and 300 mg atazanavir

Azapeptide Inhibitor of HIV-1 Protease

Bristol-Myers Squibb Canada
2365 Côte-de-Liesse
Montreal, Canada

Date of Preparation :
December 3, 2003

* TM of Bristol-Myers Squibb Company used
under licence by Bristol-Myers Squibb Canada

Date of Revision :
06 November 2009

Control Number: 128844; 131741

Table of Contents

| | |
|---|----|
| PART I : HEALTH PROFESSIONAL INFORMATION | 3 |
| SUMMARY PRODUCT INFORMATION..... | 3 |
| INDICATIONS AND CLINICAL USE | 3 |
| CONTRAINDICATIONS..... | 4 |
| WARNINGS AND PRECAUTIONS | 4 |
| ADVERSE REACTIONS | 10 |
| DRUG INTERACTIONS..... | 23 |
| DOSAGE AND ADMINISTRATION | 34 |
| OVERDOSAGE..... | 36 |
| ACTION AND CLINICAL PHARMACOLOGY | 37 |
| STORAGE AND STABILITY | 41 |
| DOSAGE FORMS, COMPOSITION AND PACKAGING..... | 42 |
| | |
| PART II : SCIENTIFIC INFORMATION | 43 |
| PHARMACEUTICAL INFORMATION | 43 |
| CLINICAL TRIALS | 44 |
| DETAILED PHARMACOLOGY | 50 |
| MICROBIOLOGY | 58 |
| TOXICOLOGY..... | 61 |
| REFERENCES..... | 64 |
| | |
| PART III : CONSUMER INFORMATION | 66 |
| ABOUT THIS MEDICATION | 66 |
| WARNINGS AND PRECAUTIONS | 67 |
| INTERACTIONS WITH THIS MEDICATION | 67 |
| PROPER USE OF THIS MEDICATION | 68 |
| SIDE EFFECTS AND WHAT TO DO ABOUT THEM..... | 69 |
| HOW TO STORE IT..... | 70 |

Pr **REYATAZ** *

(atazanavir sulfate)

PART I : HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Non medicinal Ingredients |
|--------------------------------|--|---|
| Oral | Capsules, 150, 200 and 300 mg atazanavir | lactose monohydrate <i>For a complete listing, see Dosage Forms, Composition and Packaging section</i> |

INDICATIONS AND CLINICAL USE

REYATAZ (atazanavir 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-naïve patients and 48 weeks duration in antiretroviral-treatment-experienced patients.

In antiretroviral-treatment experienced patients with prior virologic failure, coadministration of REYATAZ/ritonavir is recommended (see CLINICAL TRIALS).

The number of baseline primary protease inhibitor mutations affects the virologic response to REYATAZ/ritonavir (see MICROBIOLOGY - Resistance *in vivo*).

(See WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION, MICROBIOLOGY - Resistance *in vivo*.)

Geriatrics (> 65 years of age)

Clinical studies of REYATAZ did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should reflect the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatrics (from 6 to 18 years of age)

Dosage is based on body weight not to exceed the adult dose (See DOSAGE AND ADMINISTRATION). There are no dosing recommendations for pediatric patients less than 6 years of age.

CONTRAINDICATIONS

Patients with previously demonstrated clinically significant hypersensitivity (eg. Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any component of the product or container, including atazanavir. For a complete listing see (DOSAGE FORMS, COMPOSITION AND PACKAGING).

Coadministration of REYATAZ is contraindicated with drugs that are highly dependent on CYP3A4 and/or UGT1A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 1.

Table 1 : Drugs That Are Contraindicated with REYATAZ ¹

| Drug Class | Drugs within class that are contraindicated with REYATAZ |
|------------------------------|---|
| Benzodiazepines | orally administered midazolam ² , triazolam |
| Ergot Derivatives | dihydroergotamine, ergotamine, ergonovine, methylergonovine |
| GI Motility Agent | cisapride ³ |
| HMG-CoA Reductase Inhibitors | lovastatin, simvastatin |
| Neuroleptic | pimozide |
| Antiarrhythmics | quinidine |
| Calcium Channel Blockers | bepidil ³ |
| Antimycobacterials | rifampin |
| Antineoplastics | irinotecan |
| Herbal Products : | St. John's wort (<i>Hypericum perforatum</i>) |
| Protease Inhibitors | indinavir |

¹ See Table 13 for more detailed information.

² Oral formulation of midazolam is not marketed in Canada. See Table 14 for parenterally administered midazolam.

³ Not marketed in Canada

WARNINGS AND PRECAUTIONS

General

ALERT : Find out about medicines that should NOT be taken with REYATAZ. (See CONTRAINDICATIONS and DRUG INTERACTIONS.)

Atazanavir should always be used in combination with other antiretroviral agents. Atazanavir should not be added as a single agent when antiretrovirals are changed due to loss of virologic response.

Antiretroviral Treatment-Experienced Patients

Atazanavir 400 mg once daily has been shown to be inferior to lopinavir/ritonavir in antiretroviral experienced patients. There are limited safety data from controlled trials for REYATAZ plus ritonavir regimens without tenofovir. (See DRUG INTERACTIONS, DOSAGE AND ADMINISTRATION and CLINICAL TRIALS.)

Carcinogenesis and Mutagenesis

The incidence of benign hepatocellular adenomas was increased in high-dose female mice at systemic exposures approximately 7-fold higher than those in humans at the recommended 400 mg clinical dose. There was no increase in the incidence of tumors in male mice or in male or female rats at any dose tested. The clinical significance of the carcinogenic findings in female mice is unknown as the benign hepatic tumors occurred only at doses that induced liver toxicity. (see TOXICOLOGY - Carcinogenicity and Mutagenicity).

Cardiovascular

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 limited to first degree AV block with some exceptions (see OVERDOSAGE). There have been post-marketing reports of second-degree AV block, third-degree AV block, QTc prolongation, Torsades de Pointes and other conduction abnormalities in patients treated with REYATAZ (see ADVERSE REACTIONS – Post-Market Adverse Drug Reactions). In clinical trials, asymptomatic first-degree AV block was observed in 5.9% of atazanavir-treated patients (n = 920), 3.0% of efavirenz treated patients (n = 329), 5.2% of lopinavir/ritonavir treated patients (n = 252) and 10.4% of nelfinavir treated patients (n = 48). In study AI424-045 asymptomatic first degree AV block was observed in 5% (6/118) of REYATAZ/ritonavir-treated patients and 5% (6/116) of lopinavir/ritonavir-treated patients who had on-study electrocardiogram measurements. Because of limited clinical experience, atazanavir should be used with caution in patients with preexisting conduction system disease (e.g., marked first-degree AV block or second or third-degree AV block).

Dose related asymptomatic prolongations in PR interval with REYATAZ have been observed in clinical studies. Caution should be used with medicinal products known to induce PR prolongations. In patients with pre-existing 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. Particular caution should be used when prescribing REYATAZ in association with medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances). (See ACTION AND CLINICAL PHARMACOLOGY.)

In a pharmacokinetic study between atazanavir 400 mg once daily and diltiazem 180 mg once daily, a CYP3A substrate, there was a 2-fold increase in the diltiazem plasma concentration and an additive effect on the PR interval. When used in combination with atazanavir, a dose reduction of diltiazem by one half should be considered and ECG monitoring is recommended. In a pharmacokinetic study between atazanavir 400 mg once daily and atenolol 50 mg once daily,

there was no substantial additive effect of atazanavir and atenolol on the PR interval. When used in combination with atazanavir, there is no need to adjust the dose of atenolol. (See DRUG INTERACTIONS.)

Pharmacokinetic studies between atazanavir and other drugs that prolong the PR interval including beta blockers (other than atenolol), verapamil and digoxin have not been performed. An additive effect of atazanavir and these drugs cannot be excluded; therefore, caution should be exercised when atazanavir is given concurrently with these drugs, especially those that are metabolized by CYP3A4 (e.g., verapamil). (See DRUG INTERACTIONS.)

Endocrine and Metabolism

Diabetes mellitus/Hyperglycemia : New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing 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.

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.

Hematologic

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.

Hepatic/Biliary

Hepatic Impairment and Toxicity : REYATAZ is principally metabolized by the liver; caution should be exercised when administering this drug to patients with hepatic impairment because atazanavir concentrations may be increased (see DOSAGE AND ADMINISTRATION). Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. In these patients, test for liver enzymes before initiating therapy with REYATAZ and monitor liver enzymes during treatment. REYATAZ should not be administered to patients with severe hepatic impairment. REYATAZ/ritonavir is not recommended for use in

patients with hepatic impairment.

Immune Reconstitution: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including REYATAZ. During the initial phase of treatment, a patient whose immune system responds to therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP and TB), which may necessitate further evaluation and treatment.

Hyperbilirubinemia : Most patients taking atazanavir experience elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT). This hyperbilirubinemia is generally reversible upon discontinuation of REYATAZ. If hepatic transaminase elevations occur with hyperbilirubinemia while a patient is receiving atazanavir, consideration should be given to also evaluating alternative etiologies. No long-term safety data are available for patients experiencing persistent elevations in total bilirubin > 5 x ULN. Alternative antiretroviral therapy to REYATAZ may be considered if jaundice or scleral icterus associated with bilirubin elevations present 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.)

There have been post-marketing reports of cholelithiasis, cholecystitis, and cholestasis in patients treated with atazanavir with ritonavir as part of their ART regimen (see ADVERSE REACTIONS – Post-Market Adverse Drug Reactions).

Renal

In healthy subjects, approximately 7% of the dose of atazanavir is eliminated unchanged in the urine. 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 impact of renal impairment on atazanavir elimination for patients without hemodialysis is anticipated to be low. Moderate increases in atazanavir clearance and decreased exposure levels were seen in patients managed with hemodialysis. REYATAZ should not be administered to HIV-treatment-experienced patients with end stage renal disease managed with hemodialysis. (See DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Cases of nephrolithiasis were reported during post-marketing surveillance in HIV-infected patients receiving atazanavir therapy. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made. If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of therapy may be considered.

Resistance / Cross-Resistance

Resistance

In vitro HIV-1 isolates with a decreased susceptibility to ATV have been selected *in vitro* and obtained from patients treated with ATV or atazanavir/ritonavir (ATV/RTV). HIV-1 isolates that were 93- to 183-fold resistant to ATV from three different viral strains were selected *in vitro* by 5 months. The mutations in these HIV-1 viruses that contributed to ATV resistance included I50L,

N88S, I84V, A71V, and M46I. Changes were also observed at the protease cleavage sites following drug selection. Recombinant viruses containing the I50L mutation were growth impaired and displayed increased *in vitro* susceptibility to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). The I50L and I50V substitutions yielded selective resistance to ATV and amprenavir, respectively, and did not appear to be cross-resistant.

Both genotypic and phenotypic resistances have developed during clinical studies (see MICROBIOLOGY, Resistance).

Cross Resistance

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

Genotypic and/or phenotypic analysis of baseline virus may aid in determining ATV susceptibility before initiation of ATV/RTV therapy.

Overall, both the number and type of baseline PI mutations affected response rates in treatment-experienced patients (see MICROBIOLOGY, Cross-Resistance).

Sexual Function/Reproduction

In a fertility and early embryonic development study in rats, atazanavir altered estrus cycling with no effects on mating, fertility or early embryonic development. Systemic drug exposure levels were equal (in male rats) or two times (in female rats) those at the human clinical dose (400 mg/day).

Skin

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 $\geq 2\%$) are presented for the individual clinical studies (see ADVERSE REACTIONS). 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 have been reported in patients receiving

REYATAZ. (See CONTRAINDICATIONS.)

Special Populations

Pregnant Women : There are no adequate and well-controlled studies in pregnant women. Cases of lactic acidosis, sometimes fatal, and symptomatic hyperlactatemia have been reported in patients (including pregnant women) receiving REYATAZ in combination with nucleoside analogues, which are known to be associated with increased risk of lactic acidosis. Female gender and obesity are also known risk factors for lactic acidosis syndrome. The contribution of REYATAZ to the risk of development of lactic acidosis syndrome has not been established.

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

No teratogenic effects were observed at maternally toxic doses in rats or rabbits. Systemic drug exposure levels were equal to (in rabbits) or two times (in rats) those at the human clinical dose (400 mg once daily). In the pre-and post-natal development assessment in rats, atazanavir produced a transient reduction in body weight in the offspring at maternally toxic drug exposure levels two times those at the human clinical dose.

REYATAZ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See WARNINGS AND PRECAUTIONS : Endocrine and Metabolism.)

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

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

Pediatrics (from 6 to 18 years of age) :

REYATAZ should not be administered in pediatric patients below the age of 3 months due to the risk of kernicterus. 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 TRIALS). The safety profile in pediatric patients was comparable to that observed in adults (see ADVERSE REACTIONS). The safety, activity, and pharmacokinetic profiles of REYATAZ in pediatric patients ages 3 months to less than 6 years have not been established.

Geriatrics (> 65 years of age) : Clinical studies of REYATAZ did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. 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.

Lactose : Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Drug Interaction

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

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 the complete prescribing information for NORVIR[®] for information on other potential drug interactions with ritonavir. Clinically significant interactions are not expected between atazanavir and substrates of CYP2C19, CYP2C9, CYP2D6, CYP2B6, CYP2A6, CYP1A2, or CYP2E1 (see DRUG INTERACTIONS).

ADVERSE REACTIONS

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximate rates.

Clinical Trial Experience in Adults

REYATAZ has been evaluated for safety and tolerability in combination therapy with other antiretroviral medications in controlled clinical trials in 1806 adult patients receiving REYATAZ 400 mg once daily (1151 patients, 52 weeks median duration and 152 weeks maximum duration), or REYATAZ 300 mg once daily plus ritonavir 100 mg once daily (655 patients, 96 weeks median duration and 108 weeks maximum duration).

The more frequent adverse events of any severity with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs were nausea (20%), diarrhea (10%) and jaundice (13%).

Jaundice was reported within a few days to a few months after the initiation of treatment and resulted in discontinuation of treatment in <1% of patients. Discontinuation of treatment due to adverse reactions was 5% in treatment-naïve patients and 5% in treatment-experienced patients.

Lipodystrophy, of moderate intensity or greater, was reported in regimens containing REYATAZ and one or more NRTIs as shown in Tables 3 and 4 below (see WARNINGS AND PRECAUTIONS).

Treatment-Emergent Adverse Events in Antiretroviral Treatment-Naïve Patients

Drug-related clinical adverse events of moderate or severe intensity in $\geq 2\%$ of treatment-naïve patients receiving combination therapy including REYATAZ 300 mg with ritonavir 100 mg and REYATAZ 400 mg (without ritonavir) are presented in Table 2 and 3, respectively.

Table 2: Selected Treatment-Emergent Adverse Events^a of Moderate or Severe Intensity Reported in $\geq 2\%$ of Adult Treatment-Naïve Patients^b, Study AI424-138

| | Phase III Study AI424-138 | |
|----------------------------|---|--|
| | 96 weeks ^c REYATAZ 300 mg plus ritonavir 100 mg (once daily) and tenofovir plus emtricitabine ^d N = 441 | 96 weeks ^c lopinavir 400 mg plus ritonavir 100 mg (twice daily) and tenofovir plus emtricitabine ^d N = 437 |
| Digestive System | | |
| Nausea | 4% | 8% |
| Jaundice/ scleral icterus | 5% | * |
| Diarrhea | 2% | 12% |
| Skin and Appendages | | |
| Rash | 3% | 2% |

* 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.

Table 3: Treatment-Emergent Adverse Events^a of Moderate or Severe Intensity Reported in $\geq 2\%$ of Adult Treatment-Naive Patients^b, Studies AI424-034, AI424-007 and AI424-008

| | Phase III Study AI424-034 | | Phase II Studies AI424-007, -008 | |
|---|--|---|---|---|
| | 64 weeks ^c REYATAZ 400 mg once daily + lamivudine + zidovudine ^e N = 404 | 64 weeks ^c efavirenz 600 mg once daily + lamivudine + zidovudine ^e N = 401 | 120 weeks ^{c,d} REYATAZ 400 mg once daily + stavudine / lamivudine or + stavudine / didanosine N = 279 | 73 weeks ^{c,d} nelfinavir 750 mg TID or 1250 mg BID + stavudine + lamivudine or + stavudine + didanosine N = 191 |
| Body as a Whole | | | | |
| Headache | 6% | 6% | 1% | 2% |
| Digestive System | | | | |
| Diarrhea | 1% | 2% | 3% | 16% |
| Dyspepsia | 2% | 2% | < 1% | <1% |
| Scleral icterus | 2% | * | 2% | * |
| Jaundice | 5% | * | 5% | * |
| Nausea | 14% | 12% | 6% | 4% |
| Abdominal pain | 4% | 4% | 4% | 2% |
| Vomiting | 4% | 7% | 3% | 3% |
| Metabolic and Nutritional System | | | | |
| Lipodystrophy | 1% | 1% | 7% | 3% |
| 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% |

* Not reported in this treatment arm.

^a Includes adverse events of possible, probable, certain, or unknown relationship to treatment regimen. Assessments of relationship refer to regimens containing REYATAZ or comparator.

^b Based on regimen(s) containing REYATAZ.

^c Median time on therapy. In study AI424-034 efficacy analyses are based on 48 week data. Safety data are derived from a 64 week safety update report.

^d Includes long-term follow-up.

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

Treatment-Emergent Adverse Events in Antiretroviral Treatment-Experienced Patients

Drug related clinical adverse events of moderate or severe intensity in $\geq 2\%$ of treatment-experienced patients receiving combination therapy including REYATAZ are presented in Table 4.

Table 4: Treatment-Emergent Adverse Events^a of Moderate or Severe Intensity Reported in ≥ 2% of Adult Treatment-Experienced Patients^b, Studies AI424-043 and AI424-045

| | Phase III Study AI424-043 | | Phase III Study AI424-045** | |
|---|---|--|---|--|
| | 48 weeks ^c REYATAZ 400 mg once daily + 2 NRTIs N = 144 | 48 Weeks ^c lopinavir + ritonavir (400/100 mg) BID ^d + 2 NRTIs N = 146 | 48 weeks ^c REYATAZ 300 mg once daily + ritonavir 100 mg once daily + tenofovir + NRTI N = 119 | 48 weeks ^c lopinavir + ritonavir (400/100 mg) BID ^d + tenofovir + NRTI N = 118 |
| Body as a Whole | | | | |
| Headache | 4% | 3% | < 1% | <1% |
| fever | - | - | 2% | * |
| Digestive System | | | | |
| Diarrhea | 2% | 4% | 3% | 11% |
| Scleral icterus | * | * | 3% | * |
| Jaundice | 3% | * | 6% | * |
| Nausea | 3% | 4% | 3% | 2% |
| Vomiting | 2% | 2% | * | <1% |
| Pain abdomen | 3% | 2% | 2% | 2% |
| Metabolic and Nutritional System | | | | |
| Lipodystrophy | 6% | 1% | 5% | 4% |
| Weight decreased | 2% | <1% | * | 2% |
| Musculoskeletal System | | | | |
| Myalgia | * | * | 4% | * |
| Nervous System | | | | |
| Peripheral neurologic symptom | 2% | 5% | < 1% | 3% |
| Depression | - | - | 2* | * |
| Skin and Appendages | | | | |
| Rash | 2% | * | * | <1% |

** NOTE : There are limited safety data from controlled trials for REYATAZ plus ritonavir regimens without tenofovir. (See DRUG INTERACTIONS.)

* Not reported in this treatment arm.

^a Includes adverse events of possible, probable, certain, or unknown relationship to treatment regimen. Assessments of relationship refer to regimens containing REYATAZ or comparator.

^b Based on regimen(s) containing REYATAZ.

^c Median time on therapy.

^d As a fixed dose combination.

^e Soft gelatin capsules.

Less Common Clinical Trial Adverse Drug Reactions (< 2%)

Treatment-Emergent Adverse Events in all REYATAZ-Treated Patients

Treatment-emergent adverse events of at least moderate intensity occurring in less than 2% of adult patients receiving REYATAZ in all phase II/III clinical trials with at least a possible relationship to treatment with REYATAZ-containing regimens, and not listed in Tables 2, 3 or 4 are listed below by body system.

| | |
|--|---|
| <i>Body as a Whole :</i> | allergic reaction, asthenia, chest pain, fatigue, malaise |
| <i>Cardiovascular System :</i> | hypertension, palpitation, syncope, edema |
| <i>Digestive System :</i> | abdominal distension, aphthous stomatitis, dysgeusia, flatulence, gastritis, hepatitis, hepatosplenomegaly, pancreatitis, dry mouth |
| <i>Immune System</i> | allergic reaction |
| <i>Metabolic and Nutritional Disorders :</i> | weight gain, anorexia, appetite increased, weight decreased |
| <i>Musculoskeletal System :</i> | arthralgia, muscle atrophy, myopathy |
| <i>Nervous System :</i> | abnormal dream, abnormal gait, amnesia, anxiety, confusion, , sleep disorder, somnolence |
| <i>Respiratory System :</i> | dyspnea |
| <i>Skin and Appendages :</i> | alopecia, eczema, pruritus, urticaria, vesiculobullous rash, vasodilatation |
| <i>Urogenital System</i> | gynecomastia, hematuria, kidney pain, proteinuria, pollakiuria, nephrolithiasis |

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Abnormalities

The percentages of adult treatment-naive and treatment-experienced patients treated with combination therapy including REYATAZ 300 mg with ritonavir 100 mg and REYATAZ 400 mg (without ritonavir) with Grade 3-4 laboratory abnormalities are presented in Tables 5, 6 and 7. The most frequently reported laboratory abnormality in patients receiving regimens containing REYATAZ and one or more NRTIs was elevated bilirubin. Elevations in bilirubin were reported predominantly as elevated indirect [unconjugated] bilirubin.

In clinical studies, the observed magnitude of dyslipidemia was less with REYATAZ than with comparators. However, the clinical impact of such findings has not been demonstrated.

Table 5: Grade 3-4 Laboratory Abnormalities Reported in $\geq 2\%$ of Adult Treatment-Naïve Patients^a, Studies AI424-138

| Variable | Limit ^c | Treatment-Naïve Patients | |
|-------------------|-------------------------------|--|--|
| | | Phase III Studies AI424-138 | |
| | | 96 weeks ^b REYATAZ 300 mg plus ritonavir 100 mg (once daily) and tenofovir plus emtricitabine ^d N = 441 | 96 weeks ^b lopinavir 400 mg plus ritonavir 100 mg (twice daily) and tenofovir plus emtricitabine ^d N = 437 |
| Chemistry | High | | |
| SGOT/AST | $\geq 5.1 \times \text{ULN}$ | 3% | 1% |
| SGPT/ALT | $\geq 5.1 \times \text{ULN}$ | 3% | 2% |
| Total Bilirubin | $\geq 2.6 \times \text{ULN}$ | 44% | <1% |
| Lipase | $\geq 2.1 \times \text{ULN}$ | 2% | 2% |
| Creatine Kinase | $\geq 5.1 \times \text{ULN}$ | 8% | 7% |
| Total Cholesterol | $\geq 240 \text{ mg/dL}$ | 11% | 25% |
| Hematology | Low | | |
| Neutrophils | $< 750 \text{ cells/mm}^3$ | 5% | 2% |
| Prothrombin Time | $\geq 1.51 \times \text{ULN}$ | 2% | 6% |

^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 6: Selected Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Treatment-Naive Patients^a, Studies AI424-034, AI424-007 and AI424-008

| Variable | Limit ^d | Treatment-Naive Patients | | | |
|-----------------|----------------------------|---|---|--|--|
| | | Phase III Study AI424-034 | | Phase II Studies AI424-007, -008 | |
| | | 64 weeks ^b REYATAZ 400 mg once daily + lamivudine + zidovudine ^e N = 404 | 64 weeks ^b efavirenz 600 mg once daily + lamivudine + zidovudine ^e N = 401 | 120 weeks ^{b,c} REYATAZ 400 mg once daily + stavudine + lamivudine or + stavudine + didanosine N = 279 | 73 weeks ^{b,c} nelfinavir 750 mg TID or 1250 mg BID + stavudine + lamivudine or + stavudine + didanosine N = 191 |
| Chemistry | High | | | | |
| AST | ≥ 5.1 X ULN | 2% | 2% | 7% | 5% |
| ALT | ≥ 5.1 X ULN | 4% | 3% | 9% | 7% |
| Total Bilirubin | ≥ 2.6 X ULN | 35% | <1% | 47% | 3% |
| Amylase | ≥ 2.1 X ULN | * | * | 14% | 10% |
| Lipase | ≥ 2.1 X ULN | <1% | 1% | 4% | 5% |
| Creatine Kinase | ≥ 5.1 X ULN | 6% | 6% | 11% | 9% |
| Hematology | Low | | | | |
| Hemoglobin | <8.0 g/L | 5% | 3% | <1% | 4% |
| Neutrophils | <750 cells/mm ³ | 7% | 9% | 3% | 7% |

** NOTE : There are limited safety data from controlled trials for REYATAZ plus ritonavir regimens without tenofovir. (See DRUG INTERACTIONS.)

* Not reported in this treatment arm.

^a Based on regimen(s) containing REYATAZ.

^b Median time on therapy. In Study AI424-034 efficacy analyses are based on 48 week data. Safety data are derived from a 64 week safety update report.

^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.

^f Soft gelatin capsules.

^g As a fixed dose combination.

Table 7: Selected Grade 3-4 Laboratory Abnormalities Reported in $\geq 2\%$ of Adult Treatment-Experienced Patients^a, Studies AI424-043 and AI424-045

| Variable | Limit ^d | Treatment-Experienced Patients | | | |
|-----------------|----------------------------------|---|---|--|--|
| | | Phase III Study AI424-043 | | Phase III Studies AI424-045 ^{**} | |
| | | 48 weeks ^b | | 48 weeks ^b | 48 weeks ^b |
| | | REYATAZ 400 mg once daily + 2NRTIs N = 144 | lopinavir + ritonavir (400/100 mg) BID ^g + 2NRTIs N = 146 | REYATAZ 300 mg once daily + ritonavir 100 mg once daily + tenofovir + NRTI N = 119 | lopinavir + ritonavir (400/100 mg) BID ^g + tenofovir + NRTI N = 118 |
| Chemistry | High | | | | |
| AST | $\geq 5.1 \times \text{ULN}$ | 3% | 3% | 3% | 3% |
| ALT | $\geq 5.1 \times \text{ULN}$ | 7% | 3% | 4% | 3% |
| Total Bilirubin | $\geq 2.6 \times \text{ULN}$ | 25% | <1% | 49% | <1% |
| Lipase | $\geq 2.1 \times \text{ULN}$ | 4% | 3% | 5% | 6% |
| Creatine Kinase | $\geq 5.1 \times \text{ULN}$ | 8% | 6% | 8% | 8% |
| Hematology | Low | | | | |
| Platelets | $<50,000/\text{mm}^3$ | * | * | 2% | 3% |
| Neutrophils | $<750 \text{ cells}/\text{mm}^3$ | 6% | 5% | 7% | 8% |

**** NOTE :** There are limited safety data from controlled trials for REYATAZ plus ritonavir regimens without tenofovir. (See DRUG INTERACTIONS.)

* Not reported in this treatment arm.

^a Based on regimen(s) containing REYATAZ.

^b Median time on therapy. In Study AI424-034 efficacy analyses are based on 48 week data. Safety data are derived from a 64 week safety update report.

^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.

^f Soft gelatin capsules.

^g As a fixed dose combination.

Lipids – Treatment-Naïve Patients

Tables 8 and 9 present the changes in lipids, insulin and glucose for the treatment-naive studies.

Table 8: Lipid, Glucose and Insulin Mean Values, Study AI424-138

| | REYATAZ/ritonavir ^{a,b} | | | | | Lopinavir/ritonavir ^{b,c} | | | | |
|--------------------------------|--|---|--|---|--|--|---|--|---|--|
| | Baseline mmol/L ^h N = 428 ^e | Week 48 mmol/L ^h N = 372 ^e | Week 48 Change ^{d,g} N = 372 ^e | Week 96 mmol/L ^h N = 342 ^e | Week 96 Change ^{d,g} N = 342 ^e | Baseline mmol/L ^h N = 424 ^e | Week 48 mmol/L ^h N = 335 ^e | Week 48 Change ^{d,g} N = 335 ^e | Week 96 mmol/L ^h N = 291 ^e | Week 96 Change ^{d,g} N = 291 ^e |
| Total-Cholesterol ^f | 3.86 | 4.36 | +13% | 4.38 | +13% | 3.88 | 4.84 | +25% | 4.81 | +25% |
| HDL-Cholesterol ^f | 0.95 | 1.2 | +29% | 1.14 | +21% | 0.93 | 1.24 | +37% | 1.19 | +29% |
| LDL-Cholesterol ^f | 2.38 | 2.70 | +14% | 2.72 | +14% | 2.4 | 2.87 | +19% | 2.84 | +17% |
| Triglycerides ^f | 1.42 | 1.63 | +15% | 1.58 | +13% | 1.46 | 2.2 | +52% | 2.08 | +50% |
| Insulin | 57.7 | 76.6 | + 18.1 | 58.9 | +1.1 | 59.9 | 61.1 | +1.2 | 51.8 | -5.5 |
| Glucose | 4.77 | 4.86 | +0.12 | 4.97 | +0.22 | 4.88 | 4.9 | +0.01 | 4.96 | +0.05 |

^a REYATAZ 300 mg plus 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. Use of serum lipid-reducing agents was more common in the lopinavir/ritonavir treatment arm (8%) than in the REYATAZ/ritonavir arm (2%). 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 plus ritonavir 100mg 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.

^g Absolute changes are reported for insulin and glucose levels

^h Units are pmol/L for insulin

Table 9: Lipid, Insulin, and Glucose Mean Values From Study AI424-034*

| | REYATAZ ^a | | | Efavirenz ^b | | |
|---------------------------------------|--|--|--|--|--|--|
| | Baseline | Week 48 | | Baseline | Week 48 | |
| | mmol/L ^c (n = 383 ^e) | mmol/L ^c (n = 283 ^e) | % Change ^{c,f} (n = 272 ^e) | mmol/L ^c (n = 378 ^e) | mmol/L ^c (n = 264 ^e) | % Change ^{c,f} (n = 253 ^e) |
| Total Cholesterol | 4.24 | 4.34 | + 2% | 4.19 | 5.04 | + 21% |
| HDL-Cholesterol | 1.01 | 1.11 | + 13% | 0.98 | 1.19 | + 24% |
| LDL-Cholesterol ^g | 2.53 | 2.53 | + 1% | 2.53 | 2.95 | + 18% |
| Triglycerides ^g | 1.56 | 1.4 | - 9% | 1.46 | 1.9 | + 23% |
| Total-to-HDL Cholesterol Ratio < 3 | 13% | 17% | | 9% | 14% | |
| Insulin ^{d, g} | 81.1 | 88.3 | +9.3 | 71 | 82.5 | +10.1 |
| Glucose ^{d, g} | 5 | 5.2 | +0.17 | 5 | 5.2 | +0.33 |

* No multivariate analyses were performed on these data.

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

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

^c Units are pmol/mL for insulin levels.

^d Absolute changes are reported for insulin and glucose levels.

^e Number of patients with LDL cholesterol measured.

^f 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.

^g, Fasting

Lipids – Treatment-Experienced Patients

Tables 10, 11 and 12 present the changes from baseline in lipids, insulin and glucose for the treatment-experienced studies.

Table 10: Lipid, Insulin, and Glucose Mean Values From Study AI424-043*

| | REYATAZ ^a | | | Lopinavir + ritonavir ^b | | |
|--------------------------------------|--|--|--|--|---|---|
| | Baseline | Week 48 | | Baseline | Week 48 | |
| | mmol/L ^c (n = 143 ^e) | mmol/L ^c (n = 101 ^e) | % Change ^{d,g} (n = 101 ^e) | mmol/L ^c (n = 144 ^e) | mmol/L ^c (n = 99 ^e) | % Change ^{d,g} (n = 99 ^e) |
| Total Cholesterol | 4.68 | 4.50 | - 2% | 4.53 | 5.02 | + 12% |
| HDL-Cholesterol | 1.01 | 1.06 | + 9% | 0.96 | 1.11 | + 10% |
| LDL-Cholesterol ^{f, h} | 2.74 | 2.56 | - 6% ^f | 2.66 | 2.79 | + 3% |
| Triglycerides ^h | 2.17 | 4.50 | + 1% | 2.17 | 6.52 | + 53% |
| Total-to-HDL Cholesterol Ratio <3 | 7% | 12% | | 7% | 10% | |
| Insulin ^h | 76.1 | 86.1 | +14.4 | 71.0 | 78.9 | +7.9 |
| Glucose ^h | 4.9 | 5.1 | +0.17 | 5 | 5.0 | -0.6 |

* No multivariate analyses were performed on these data.

^a REYATAZ 400 mg once daily + 2 NRTIs.

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

^c Units are pmol/mL for insulin levels.

^d Absolute changes are reported for insulin and glucose levels.

^e Number of patients with LDL cholesterol measured.

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

^g 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.

^h Fasting

Table 11: Lipid and Glucose Mean Values from Study AI424-045*

| | ATV 300/RTV ^a | | | LPV/RTV ^b | | |
|---|-----------------------------------|----------------------------------|----------------------|-----------------------------------|----------------------------------|----------------------|
| | Baseline | Week 48 | | Baseline | Week 48 | |
| | mmol/L (n = 112 ^c) | mmol/L (n = 75 ^c) | % Change (n = 74) | mmol/L (n = 108 ^c) | mmol/L (n = 76 ^c) | % Change (n = 73) |
| Total Cholesterol | 4.86 | 4.40 | -8% | 4.68 | 4.83 | 6% |
| HDL-Cholesterol | 1.03 | 1.00 | -7% | 1.01 | 1.06 | 2% |
| LDL-Cholesterol ^e | 2.82 | 2.53 | -10% | 2.69 | 2.66 | 1% |
| Triglycerides | 2.43 | 4.16 | -4% | 2.21 | 5.79 | 30% |
| Total-to-HDL Cholesterol Ratio <3 | 9% | 13% | | 12% | 13% | |
| Glucose ^{d, e} | 5.27 | 5.49 | +0.22 | 5.00 | 5.10 | +0.06 |

* There are limited safety data from controlled trials for REYATAZ plus ritonavir regimens without tenofovir. (See DRUG INTERACTIONS.)

No multivariate analyses were performed on these data.

^a REYATAZ 300 mg + ritonavir 100 mg once daily + tenofovir + 1 NRTI

^b Lopinavir + ritonavir (400/100 mg) BID + tenofovir + 1 NRTI.

^c Number of patients with LDL cholesterol measured.

^d Absolute changes are reported for glucose levels.

^e Fasting

Table 12: Lipid, Insulin and Glucose Values from Study AI424-044 (Nelfinavir patients in study AI424-008 who switched to REYATAZ^a in the long term AI424-044 study)*

| | Baseline Study AI424-008 | Entry Study AI424-044 | Week 12 Study AI424-044 | |
|------------------------------|---|---|---|---|
| | mmol/L ^a (n = 54 ^b) | mmol/L ^a (n = 33 ^b) | mmol/L ^a (n = 41 ^b) | % Change ^c (n = 29 ^b) |
| Total Cholesterol | 4.34 | 5.53 | 4.53 | -16% |
| HDL-Cholesterol | 1.09 | 1.19 | 1.24 | +5% |
| LDL-Cholesterol ^d | 2.53 | 3.57 | 2.69 | -21% |
| Triglycerides ^d | 1.19 | 1.77 | 1.22 | -28% |
| Insulin ^d | - | 70.3 | 66.7 | - |
| Glucose ^d | - | 4.77 | 4.88 | - |

* No multivariate analyses were performed on these data.

^a Units are pmol/mL for insulin levels.

^b Number of patients with LDL cholesterol measured.

^c The change from entry is the mean of within patient changes from entry for patients with both entry and Week 12 values and is not a simple difference of the entry and Week 12 mean values.

^d Fasting

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. Use of REYATAZ in pediatric patients less than 6 years of age is under investigation.

The safety profile of REYATAZ in pediatric patients (6 to less than 18 years of age) was comparable to that observed in clinical studies of REYATAZ in adults. The most common Grade 2–4 adverse events ($\geq 5\%$, regardless of causality) reported in pediatric patients were cough (21%), fever (19%), rash (14%), jaundice/scleral icterus (13%), diarrhea (8%), vomiting (8%), headache (7%), and rhinorrhea (6%). Asymptomatic second-degree atrioventricular block was reported in 2% of patients. The most common Grade 3–4 laboratory abnormality was elevation of total bilirubin (≥ 3.2 mg/dL) which occurred in 49% of pediatric patients. All other Grade 3–4 laboratory abnormalities occurred with a frequency of less than 3%. Both the frequency and severity of cardiac conduction abnormalities were greater in pediatric patients in this study than observed in clinical studies in adults.

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 (see WARNINGS AND PRECAUTIONS : Hepatic/Biliary).

In studies AI424-008 and AI424-034, 74 patients treated with 400 mg of REYATAZ once daily, 58 who received efavirenz, and 12 who received nelfinavir were seropositive for hepatitis B and/or C at study entry. AST levels >5 times the upper limit of normal (ULN) developed in 9% of the REYATAZ-treated patients, 5% of the efavirenz-treated patients, and 17% of the nelfinavir-treated patients. ALT levels >5 times ULN developed in 15% of the REYATAZ-treated patients, 14% 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.

Post-market Adverse Drug Reactions

The following events have been identified during post approval use of REYATAZ. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, or causal connection to REYATAZ, or a combination of these factors.

Body as a whole: edema

Cardiac disorders and vascular disorders: second-degree AV block, third-degree AV block, QTc prolongation, Torsades de Pointes, left bundle branch block

Gastrointestinal system: pancreatitis

Hepatic system: hepatic function abnormalities

Metabolism and nutrition disorders: hyperglycemia, diabetes mellitus

Musculoskeletal system: arthralgia

Renal system: nephrolithiasis

Skin and appendages: pruritus, alopecia, maculopapular rash

Hepatobiliary disorders: cholelithiasis, cholecystitis, cholestasis

DRUG INTERACTIONS

Serious Drug Interactions

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.

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

- Refer to CONTRAINDICATIONS
- Refer to Table 13 for Drugs That Are Contraindicated or Not Recommended for Coadministration with REYATAZ.
- Refer to Table 14 for Established and Other Potentially Significant Drug Interactions

Overview

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 ($K_i=1.9 \mu\text{M}$).

Co-administration of atazanavir and drugs primarily metabolized by CYP3A4 (e.g., calcium channel blockers, HMG CoA reductase inhibitors, immunosuppressants and phosphodiesterase (PDE5) inhibitors) or UGT1A1 (e.g., irinotecan) may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse effects.

Co-administration of atazanavir and drugs that induce CYP3A4, such as rifampin, may decrease atazanavir plasma concentrations and reduce its therapeutic effect. Co-administration of atazanavir and drugs that inhibit CYP3A4 may increase atazanavir plasma concentrations. (See Tables 13 and 14, DRUG INTERACTIONS.)

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

Atazanavir should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A or UGT1A1 (see CONTRAINDICATIONS).

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

Particular caution should be used when prescribing phosphodiesterase (PDE5) inhibitors for erectile dysfunction (eg, sildenafil, tadalafil) in patients receiving protease inhibitors, including REYATAZ. Co-administration of a protease inhibitor with a PDE5 inhibitor is expected to substantially increase PDE5 inhibitor concentrations and may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, visual changes, and priapism. (See PRECAUTIONS, Information for Patients, and the complete Product Monograph for sildenafil, and tadalafil.). Vardenafil should not be coadministered with REYATAZ (with and without ritonavir) (see Tables 13 and 14).

Simvastatin and lovastatin are contraindicated with REYATAZ (see Table 13). Caution should be exercised if HIV protease inhibitors, including REYATAZ, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A pathway. Use the lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with REYATAZ (with and without ritonavir). The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including REYATAZ, are used in combination with these drugs.

Midazolam is extensively metabolized by CYP3A4. Although not studied, coadministration of midazolam with REYATAZ may cause a large increase in the concentration of this benzodiazepine. Increases in benzodiazepine concentration are expected to be significantly higher with oral administration of the benzodiazepine, relative to parenteral. Therefore, REYATAZ should not be coadministered with orally administered midazolam, whereas caution should be used with coadministration of REYATAZ and parenteral midazolam. If REYATAZ is

coadministered with parenteral midazolam, a close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.

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

The magnitude of CYP3A4-mediated drug interactions (effect on atazanavir or effect on coadministered drug) may change when REYATAZ is coadministered with ritonavir, a potent CYP3A4 inhibitor. The Product Monograph for ritonavir should be consulted for information on drug interactions with ritonavir.

Atazanavir has the potential to prolong the PR interval of the electrocardiogram in some patients. Caution should be used when co-administering REYATAZ with medicinal products known to induce PR interval prolongation (eg, atenolol, diltiazem).

The exposure to buprenorphine and the active metabolite, norbuprenorphine, were significantly increased when co-administered with atazanavir (with or without ritonavir), due to CYP3A4 and UGT1A1 inhibition. Co-administration of buprenorphine and REYATAZ/ritonavir warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered. There was no significant effect on atazanavir plasma concentration when REYATAZ plus ritonavir were coadministered with buprenorphine. Coadministration of buprenorphine and REYATAZ without ritonavir may substantially decrease atazanavir plasma concentrations. REYATAZ without ritonavir should not be coadministered with buprenorphine.

A drug interaction study in healthy subjects has shown that ritonavir significantly increases plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Concomitant use of REYATAZ with ritonavir and fluticasone propionate is expected to produce the same effects. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression, have been reported during post-marketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Therefore, coadministration of fluticasone propionate and REYATAZ/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Exposure to rifabutin was significantly increased when co-administered with atazanavir (with or without ritonavir). Increased monitoring for neutropenia should be performed if these drugs are co-administered. Dosage reduction of rifabutin is recommended (see Table 14).

Drugs that are contraindicated or not recommended for coadministration with REYATAZ are included in Table 13. Drugs with established and other potentially significant drug interactions are included in Table 14. 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 13: Drugs That Are Contraindicated or Not Recommended for Coadministration with REYATAZ

| Drug Class : Specific Drugs | Clinical Comment |
|---|---|
| Antiarrhythmics : quinidine | REYATAZ/ritonavir : CONTRAINDICATED if REYATAZ is coadministered with ritonavir due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias. |
| Antineoplastics : irinotecan | Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan resulting in increased irinotecan toxicities. |
| Antimycobacterials : rifampin | Rifampin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect and development of resistance. |
| Benzodiazepines : orally administered midazolam ¹ , triazolam | CONTRAINDICATED due to potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression. |
| Ergot Derivatives : dihydroergotamine, ergotamine, ergonovine, methylergonovine | CONTRAINDICATED due to potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues. |
| GI Motility Agent : cisapride ² | CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias. |
| Proton Pump Inhibitors omeprazole | <p>Co-administration of omeprazole (40 mg once daily) with REYATAZ and ritonavir (300/100 mg once daily) resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C_{max}, and C_{min}). Co-administration of omeprazole (20 mg once daily) with an increased dose of REYATAZ and ritonavir (400/100 mg once daily) in healthy volunteers resulted in a decrease of approximately 30% in the AUC, C_{max} and C_{min} of atazanavir relative to REYATAZ and ritonavir (300/100 mg once daily) without omeprazole. This decrease in AUC, C_{max} and C_{min} was not mitigated when an increased dose of REYATAZ and ritonavir (400/100 mg once daily) was temporally separated from omeprazole by 12 hours. Although not studied, similar results are expected with other proton pump inhibitors. This decrease in atazanavir exposure might negatively impact the efficacy of atazanavir.</p> <p>Co-administration of REYATAZ with proton pump inhibitors is not recommended. If the combination of REYATAZ with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of REYATAZ to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded.</p> |
| HMG-CoA Reductase Inhibitors : lovastatin, simvastatin | CONTRAINDICATED due to potential for serious reactions such as myopathy including rhabdomyolysis. |
| Neuroleptic : pimozide | CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias. |
| Protease Inhibitors : indinavir | Both REYATAZ and indinavir are associated with indirect (unconjugated) hyperbilirubinemia. Combinations of these drugs have not been studied and coadministration of REYATAZ and indinavir is not recommended. |

| Drug Class : Specific Drugs | Clinical Comment |
|--|---|
| Herbal Products : St. John's wort (<i>Hypericum perforatum</i>) | CONTRAINDICATED Patients taking REYATAZ should not use products containing St. John's wort (<i>Hypericum perforatum</i>) because coadministration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance. |
| Calcium Channel Blockers : bepridil ² | Potential for serious and/or life-threatening adverse event. CONTRAINDICATED if REYATAZ is coadministered with ritonavir. |
| Erectile dysfunction agents (PDE5 inhibitors) : Vardenafil | Vardenafil should not be coadministered with REYATAZ (with and without ritonavir). |

¹ Oral formulation of midazolam is not marketed in Canada. See Table 14 for parenterally administered midazolam.

² Not marketed in Canada.

Table 14: Established and Other Potentially Significant Drug Interactions : Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions^a

| Concomitant Drug Class : Specific Drugs | Effect on Concentration of REYATAZ or Concomitant Drug | Clinical Comment |
|---|---|---|
| HIV Antiviral Agents | | |
| Nucleoside Reverse Transcriptase Inhibitors (NRTIs) : <ul style="list-style-type: none"> • didanosine buffered formulations | ↓ atazanavir | Coadministration with REYATAZ did not alter exposure to didanosine; however, exposure to atazanavir was markedly decreased by coadministration of REYATAZ with didanosine buffered tablets (presumably due to the increase in gastric pH caused by buffers in the didanosine tablets). Atazanavir should be given with food, 2 hours before or 1 hour after didanosine buffered formulations (which are given on an empty stomach). |
| | <ul style="list-style-type: none"> • didanosine EC formulation | ↓ atazanavir ↓ didanosine |

| Concomitant Drug Class : Specific Drugs | Effect on Concentration of REYATAZ or Concomitant Drug | Clinical Comment |
|---|--|--|
| Nucleotide Reverse Transcriptase Inhibitors (NRTIs) : tenofovir DF | ↓ atazanavir ↑ tenofovir | REYATAZ as a single PI, without ritonavir, may be less effective due to decreased atazanavir concentrations in patients taking REYATAZ and tenofovir DF (see Table 23, DETAILED PHARMACOLOGY, Drug-Drug Interactions). If REYATAZ is to be coadministered with tenofovir DF, it is recommended that REYATAZ 300 mg with ritonavir 100 mg be coadministered with tenofovir DF 300 mg (see DOSAGE AND ADMINISTRATION). Reyataz without ritonavir should not be co-administered with tenofovir. Atazanavir increases tenofovir concentrations. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving atazanavir and tenofovir should be monitored for tenofovir-associated adverse events. No dose adjustment for tenofovir is recommended. |
| Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) : • efavirenz • nevirapine | ↓ atazanavir ↓ atazanavir | Efavirenz decreases atazanavir exposure (see Table 23, DETAILED PHARMACOLOGY, Drug-Drug Interactions). For 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 should be administered on an empty stomach, preferably at bedtime. For Treatment-experience patients: Do not coadminister REYATAZ with efavirenz in treatment-experienced patients due to decreased atazanavir exposure. Nevirapine, an inducer of CYP3A4, substantially decreases atazanavir exposure. There is a potential risk for nevirapine associated toxicity due to the increased nevirapine exposures. Do not coadminister REYATAZ with nevirapine. |

| Concomitant Drug Class : Specific Drugs | Effect on Concentration of REYATAZ or Concomitant Drug | Clinical Comment |
|---|---|---|
| Protease Inhibitor PIs : <ul style="list-style-type: none"> • saquinavir (soft gelatin capsules) • ritonavir • Other protease inhibitors | ↑ saquinavir ↑ atazanavir ↑ Other PIs | <p>The safety and efficacy of this combination 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 a nucleoside reverse transcriptase inhibitor did not provide adequate efficacy (see CLINICAL TRIALS).</p> <p>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 DOSAGE AND ADMINISTRATION). See the complete product monograph for NORVIR® (ritonavir) for information on drug interactions with ritonavir.</p> <p>Although not studied, the coadministration of REYATAZ plus ritonavir with other protease inhibitors would be expected to increase exposure to the other protease inhibitor and is not recommended.</p> |
| 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, 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. Quinidine is contraindicated when REYATAZ is coadministered with ritonavir. |
| Anticoagulants : | ↑ warfarin | Coadministration with REYATAZ has the potential to produce serious and/or life-threatening bleeding and has not been studied. It is recommended that INR (International Normalized Ratio) be monitored. |
| Antidepressants : | ↑ tricyclic antidepressants ↑ trazodone | <p>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.</p> <p>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.</p> |

| Concomitant Drug Class : Specific Drugs | Effect on Concentration of REYATAZ or Concomitant Drug | Clinical Comment |
|---|---|---|
| Antifungals : <ul style="list-style-type: none"> • ketoconazole, itraconazole • voriconazole | ↑ atazanavir ↑ ritonavir ↑ ketoconazole ↑ itraconazole Effect is unknown | 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 with caution with REYATAZ/ritonavir. Coadministration of voriconazole with REYATAZ, with or without ritonavir has not been studied. However, administration of voriconazole with ritonavir 400 mg every 12 hours decreased voriconazole steady-state AUC by an average of 82%. The effect of lower ritonavir doses on voriconazole is not known at this time. Until data are available, voriconazole should not be administered to patients receiving REYATAZ/ritonavir. Coadministration of voriconazole with REYATAZ (without ritonavir) may increase atazanavir concentrations; however, no data are available. |
| Antimycobacterials : | ↑ rifabutin | A rifabutin dose reduction of up to 75% (eg, 150 mg every other day or 3 times per week) is recommended. Concomitant use of REYATAZ with or without ritonavir and rifabutin may result in decreased neutrophil count or neutropenia. Increased monitoring for neutropenia should be performed if these drugs are co-administered. Further dosage reduction of rifabutin may be necessary. |
| Benzodiazepines: Parenterally administered midazolam ^b | ↑ midazolam | If REYATAZ is coadministered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered. |
| Calcium channel blockers : | ↑ diltiazem and desacetyl-diltiazem ↑ felodipine, nifedipine, nicardipine, and verapamil | A dose reduction of diltiazem by 50% should be considered. Caution is warranted. Coadministration of 400 mg atazanavir once daily and diltiazem 180 mg once daily had an added effect on the PR interval. ECG monitoring is recommended. Coadministration of REYATAZ/ritonavir with diltiazem has not been studied. Caution is warranted. Dose titration of the calcium channel blocker should be considered. ECG monitoring is recommended. |
| Erectile dysfunction agents (PDE5 inhibitors) : | ↑ sildenafil ↑ tadalafil ↑ vardenafil | Coadministration is expected to substantially increase the PDE5 inhibitor concentration and may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, visual changes and priapism. Reduced doses are recommended (sildenafil, 25 mg every 48 hours; tadalafil, 10 mg every 72 hours; with increased monitoring for adverse events. Vardenafil should not be coadministered with REYATAZ (with and without ritonavir). |

| Concomitant Drug Class : Specific Drugs | Effect on Concentration of REYATAZ or Concomitant Drug | Clinical Comment |
|---|--|--|
| H ₂ -Receptor Antagonists | ↓ atazanavir | <p>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. Although not studied, similar results are expected with other H₂-receptor antagonists.</p> <p>In treatment-naïve patients: The H₂-receptor antagonist dose should not exceed a 40 mg dose equivalent of famotidine twice daily. REYATAZ 300 mg with ritonavir 100 mg once daily (all as a single dose with food) should be administered simultaneously with, and/or at least 10 hours after, the dose of the H₂-receptor antagonist.</p> <p>In treatment-experienced patients: The H₂-receptor antagonist dose should not exceed a dose equivalent 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 H₂-receptor antagonist.</p> <ul style="list-style-type: none"> ▪ REYATAZ 300 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with an H₂-receptor ▪ REYATAZ 400 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with both tenofovir and an H₂-receptor antagonist. |
| HMG-CoA Reductase Inhibitors : | ↑ atorvastatin ↑ rosuvastatin | The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including REYATAZ, are used in combination with these drugs. Caution should be exercised. Use the lowest possible dose with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with REYATAZ (with and without ritonavir). |
| Immunosuppressants : | ↑ cyclosporin, sirolimus, tacrolimus | Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with REYATAZ. |

| Concomitant Drug Class : Specific Drugs | Effect on Concentration of REYATAZ or Concomitant Drug | Clinical Comment |
|--|--|---|
| Inhaled/nasal corticosteroids (interaction with ritonavir) | ↑ fluticasone propionate | In healthy volunteers, ritonavir significantly increased plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Concomitant use of REYATAZ/ritonavir with fluticasone propionate is expected to produce the same effects. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported when ritonavir was coadministered with inhaled or intranasally administered fluticasone propionate. These effects could also occur with other corticosteroids metabolized via the cytochrome P450 3A pathway, eg, budesonide. Therefore, concomitant use of REYATAZ/ritonavir and fluticasone propionate or other glucocorticoids that are metabolized by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. 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. |
| Macrolide Antibiotics : | ↑ clarithromycin ↓ 14-OH clarithromycin ↑ atazanavir | Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a dose reduction of clarithromycin by 50% should be considered when it is coadministered with REYATAZ. In addition, concentrations of the active metabolite 14-OH clarithromycin are significantly reduced; consider alternative therapy for indications other than infections due to <i>Mycobacterium avium</i> complex. Caution is advised during coadministration as a high incidence of rash (20%) was observed in the pharmacokinetic trial in healthy volunteers. Coadministration of REYATAZ/ritonavir with clarithromycin has not been studied. |

| Concomitant Drug Class : Specific Drugs | Effect on Concentration of REYATAZ or Concomitant Drug | Clinical Comment |
|---|---|--|
| Oral Contraceptives : ethinyl estradiol and norgestimate or norethindrone | ↑ ethinyl estradiol ↑ norethindrone ^d ↓ ethinyl estradiol ↑ norgestimate ^c | <p>Mean concentrations of ethinyl estradiol and norethindrone, when coadministered with REYATAZ, are increased.</p> <p>Administration of REYATAZ/ritonavir with ethinyl estradiol and norgestimate decreases the mean concentration of ethinyl estradiol, and increases the mean concentration of 17-deacetyl norgestimate, the active metabolite of norgestimate. If an oral contraceptive is administered with REYATAZ plus ritonavir, it is recommended that the oral contraceptive contain at least 30 mcg of ethinyl estradiol. If REYATAZ is administered without ritonavir, the oral contraceptive should contain no more than 30 mcg of ethinyl estradiol.</p> <p>Use with caution as the effect of increases in concentration of the progestational agent are unknown and could increase the risk of acne, dyslipidemia, and insulin resistance.</p> <p>Coadministration of REYATAZ or REYATAZ /ritonavir with other hormonal contraceptives (eg, contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestagens other than norethindrone or norgestimate, or less than 25 mcg of ethinyl estradiol have not been studied; therefore alternative methods of contraception are recommended.</p> |

^a For magnitude of interactions see DETAILED PHARMACOLOGY : Drug-Drug Interactions.

^b See Table 13 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.

Based on known metabolic profiles, clinically significant drug interactions are not expected between REYATAZ and fluvastatin, pravastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin or erythromycin. Coadministration of methadone and REYATAZ in subjects chronically treated with methadone did not result in clinically relevant interactions. REYATAZ does not interact with substrates of CYP2D6 (eg, nortriptyline, desipramine, metoprolol). Additionally, no clinically significant drug interaction was observed when REYATAZ was coadministered with fluconazole or acetaminophen.

Refer to Norvir® Product Monograph for drug interaction of ritonavir with these drugs before prescribing REYATAZ 300 mg with ritonavir 100 mg.

DOSAGE AND ADMINISTRATION

Recommended Adult Dose

Therapy-Naïve Patients

- REYATAZ 300 mg once daily taken with ritonavir 100 mg once daily taken with food.
OR
- REYATAZ 400 mg (two 200-mg capsules) once daily (without ritonavir) taken with food, for patients who are unable to tolerate ritonavir.

Therapy-Experienced Patients

- REYATAZ 300 mg once daily taken with ritonavir 100 mg once daily taken with food.

Capsules should not be opened, they should be swallowed whole with water.

Recommended Pediatric Dose (from 6 to 18 years of age)

The recommended dosage of REYATAZ 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 for any of the following: (1) patients less than 6 years of age, (2) without ritonavir in patients less than 13 years of age, and (3) treatment-experienced pediatric patients with body weight less than 25 kg.

Therapy-Naive Pediatric Patients

The recommended dosage of REYATAZ with ritonavir in treatment-naive patients at least 6 years of age is shown in Table 15.

For treatment-naive patients at least 13 years of age and at least 39 kg, who are unable to tolerate ritonavir, the recommended dose is REYATAZ 400 mg (without ritonavir) once daily with food.

Table 15: Dosage for Treatment-Naive Pediatric Patients (6 to less than 18 years of age) for REYATAZ Capsules with ritonavir

| Body Weight | | REYATAZ dose ^{a,b} | ritonavir dose ^b |
|--------------------|--------------------|-----------------------------|-----------------------------|
| (kg) | (lbs) | (mg) | (mg) |
| 15 to less than 25 | 33 to less than 55 | 150 | 80 ^c |
| 25 to less than 32 | 55 to less than 70 | 200 | 100 ^d |
| 32 to less than 39 | 70 to less than 86 | 250 | 100 ^d |
| at least 39 | at least 86 | 300 | 100 ^d |

^a The recommended dosage of REYATAZ can be achieved using a combination of commercially available capsule strengths.

^b The dosage of REYATAZ and ritonavir was calculated as follows:

- 15 kg to less than 20 kg: REYATAZ 8.5 mg/kg with ritonavir 4 mg/kg once daily with food.
- at least 20 kg: REYATAZ 7 mg/kg with ritonavir 4 mg/kg once daily with food not to exceed REYATAZ 300 mg and ritonavir 100 mg.

^c Ritonavir liquid.

^d Ritonavir capsule or liquid.

Therapy-Experienced Pediatric Patients

The recommended dosage of REYATAZ with ritonavir in treatment-experienced patients at least 6 years of age is shown in Table 16.

Table 16: Dosage for Treatment-Experienced Pediatric Patients (6 to less than 18 years of age) for REYATAZ Capsules with ritonavir

| Body Weight | | REYATAZ dose ^{a,b} (mg) | ritonavir dose ^b (mg) |
|--------------------|--------------------|-------------------------------------|-------------------------------------|
| (kg) | (lbs) | | |
| 25 to less than 32 | 55 to less than 70 | 200 | 100 ^c |
| 32 to less than 39 | 70 to less than 86 | 250 | 100 ^c |
| at least 39 | at least 86 | 300 | 100 ^c |

^a The recommended dosage of REYATAZ can be achieved using a combination of commercially available capsule strengths.

^b The dosage was calculated as REYATAZ 7 mg/kg with ritonavir 4 mg/kg once daily with food not to exceed REYATAZ 300 mg and ritonavir 100 mg.

^c Ritonavir capsule or liquid.

Dosing Considerations

Concomitant Therapy : (See ACTION AND CLINICAL PHARMACOLOGY : Drug-Drug Interactions, WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS.)

Ritonavir : There are limited safety data from controlled trials for REYATAZ plus ritonavir regimens without tenofovir. (See WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS.)

Efavirenz - Therapy-Naïve 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 should be administered on an empty stomach, preferably at bedtime.

Efavirenz - Therapy-Experienced Patients:

Do not coadminister REYATAZ with efavirenz in treatment-experienced patients due to decreased atazanavir exposure.

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

Tenofovir DF : If coadministered with tenofovir DF, it is recommended that 300 mg of REYATAZ and ritonavir 100 mg be given with tenofovir 300 mg (together as single daily doses with food). There are limited safety data from controlled trials for REYATAZ plus ritonavir regimens without tenofovir. REYATAZ without ritonavir should not be coadministered with tenofovir. (See DRUG INTERACTIONS.)

Dose Adjustments:

Patients With 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, with or without ritonavir, should not be used in antiretroviral-treatment experienced patients with end stage renal disease managed with hemodialysis. REYATAZ without ritonavir should not be administered to patients managed with hemodialysis. (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY : Special Populations and Conditions).

Patients With Hepatic Impairment

REYATAZ should be used with caution in patients with mild-to-moderate hepatic impairment. For patients with moderate hepatic impairment (Child-Pugh Class B) who have not experienced prior virologic failure, a dose reduction to 300 mg once daily should be considered. REYATAZ should not be used in patients with severe hepatic impairment (Child-Pugh Class C). REYATAZ/ritonavir has not been studied in subjects with hepatic impairment and is not recommended. (See WARNINGS AND PRECAUTIONS, Hepatic/Biliary.)

Missed Dose

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.

OVERDOSAGE

| |
|--|
| For management of a suspected drug overdose, please contact your regional Poison Control Centre. |
|--|

Administration of activated charcoal may be used to aid in removal of unabsorbed drug. Treatment of overdose with atazanavir should consist of general supportive measures, including monitoring of vital signs and ECG, and observations of the patient's clinical status. There is no specific antidote for overdose with atazanavir. 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.

Human experience of acute overdose with atazanavir is limited. Single doses up to 1200 mg have been taken by healthy volunteers without symptomatic untoward effects. A single self-administered overdose of 58.4 g of atazanavir in an HIV-infected patient (146 times the 400 mg recommended dose) was associated with asymptomatic bilateral bundle branch 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 cardiac conduction abnormalities, including PR and/or QT interval prolongations, may be observed. (See WARNINGS AND PRECAUTIONS : Cardiovascular, and DETAILED PHARMACOLOGY : Electrocardiogram.)

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

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.

Table 17: Steady-State Pharmacokinetics of Atazanavir in Healthy Adult Subjects or HIV-Infected Patients in the Fed State

| Parameter | 400 mg once daily | | 300 mg with ritonavir 100 mg once daily | |
|----------------------|------------------------------|--------------------------------------|--|--------------------------------------|
| | Healthy Subjects (n = 14) | HIV-Infected Patients (n = 13) | Healthy Subjects (n = 28) | HIV-Infected Patients (n = 10) |
| C_{max} (ng/mL) | | | | |
| Geometric mean (CV%) | 5199 (26) | 2298 (71) | 6129 (31) | 4422 (58) |
| Mean (SD) | 5358 (1371) | 3152 (2231) | 6450 (2031) | 5233 (3033) |
| T_{max} (h) | | | | |
| Median | 2.5 | 2.0 | 2.7 | 3.0 |
| AUC (ng·h/mL) | | | | |
| Geometric mean (CV%) | 28132 (28) | 14874 (91) | 57039 (37) | 46073 (66) |
| Mean (SD) | 29303 (8263) | 22262 (20159) | 61435 (22911) | 53761 (35294) |
| T-half (h) | | | | |
| Mean (SD) | 7.9 (2.9) | 6.5 (2.6) | 18.1 (6.2) ^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

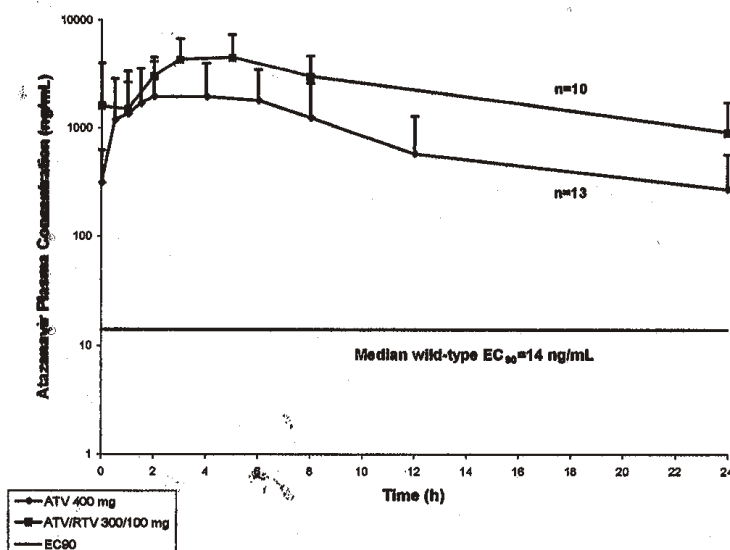
^b n = 12

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.

Figure 1 displays the mean plasma concentrations of atazanavir on Day 29 (steady state) following atazanavir 400 mg once daily (as two 200-mg capsules) with a light meal and after atazanavir 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



Food Effect

Administration of a single 400-mg dose of atazanavir 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 atazanavir 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. Thus, REYATAZ is taken with food in order to enhance its bioavailability and reduce the pharmacokinetic variability.

Coadministration of REYATAZ and ritonavir with food optimizes the bioavailability of atazanavir. Coadministration of a single 300-mg dose of REYATAZ and a 100-mg dose of ritonavir with a light meal (336 total kcal, 5.1 g fat, 9.3 g protein and 63.3 g carbohydrates) 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 total kcal, 54.7 g fat, 35.9 g protein and 77.9 g carbohydrates) 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 atazanavir 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

Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that atazanavir is principally metabolized by CYP3A4 isozyme to oxygenated metabolites, which are then excreted in the bile as either free or glucuronidated metabolites. Additional minor metabolic pathways consist of N-dealkylation, hydrolysis and oxygenation with dehydrogenation.

Two minor metabolites of atazanavir in plasma have been characterized. Neither metabolite demonstrated *in vitro* antiviral activity.

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.

Electrocardiogram : Effect on PR and QT intervals

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 pre-dose 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 pharmacodynamic interaction in humans between atazanavir and other drugs that prolong the PR interval of the electrocardiogram (see WARNINGS AND PRECAUTIONS).

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

Special Populations and Conditions

Age/Gender/Race

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

Pediatrics (from 6 to 18 years of age)

The pharmacokinetic data from pediatric patients receiving REYATAZ Capsules with ritonavir based on body surface area are presented in Table 18.

Table 18: Steady-State Pharmacokinetics of Atazanavir with ritonavir in HIV Infected Pediatric Patients (6 to 18 years of age) in the Fed State

| | 205 mg/m ² atazanavir with 100 mg/m ² ritonavir once daily | |
|------------------------|--|-----------------------------|
| | Age range (years) | |
| | At least 6 to 13 (n=17) | At least 13 to 18 (n=10) |
| Dose mg | | |
| Median | 200 | 400 |
| [min-max] | [150-400] | [250-500] |
| C _{max} ng/mL | | |
| Geometric Mean (CV%) | 4451 (33) | 3711 (46) |
| AUC ng•h/mL | | |
| Geometric Mean (CV%) | 42503 (36) | 44970 (34) |
| C _{min} ng/mL | | |
| Geometric Mean (CV%) | 535 (62) | 1090 (60) |

Renal impairment

In healthy subjects, approximately 7% of the dose of atazanavir is eliminated unchanged in the urine. 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. Subjects on hemodialysis appeared to display lower exposures as compared to healthy subjects and renally-impaired subjects without hemodialysis. The geometric means for ATV AUC, Cmax and Cmin, for REYATAZ administered immediately following dialysis in subjects on hemodialysis (n=10) were 42%, 37% and 54% lower, respectively, relative to subjects with normal renal function. When REYATAZ was administered 2 hours before a 4-hour hemodialysis session, the geometric means for ATV AUC, Cmax and Cmin in hemodialysis subjects were 28%, 25% and 43% lower, respectively, than subjects with normal renal function. The mechanism of this decrease is unknown. (See DOSAGE AND ADMINISTRATION.)

Impaired hepatic function

Atazanavir is metabolized and eliminated primarily by the liver. Atazanavir has been studied in adult patients with moderate to severe hepatic impairment (14 Child-Pugh B and 2 Child-Pugh C) after a single 400-mg dose. The mean AUC(0-∞) was 42% greater in patients with impaired hepatic function than in healthy volunteers. The mean half-life of atazanavir in hepatically impaired patients 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 PRECAUTIONS and DOSAGE AND ADMINISTRATION).

STORAGE AND STABILITY

REYATAZ capsules should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

REYATAZ (atazanavir sulfate) Capsules are available for oral administration in strengths containing atazanavir sulfate equivalent to 150 mg, 200 mg or 300 mg of atazanavir and the following inactive ingredients : crospovidone, lactose monohydrate, and magnesium stearate. The capsule shells contain the following inactive ingredients: gelatin, FD&C Blue #2, and titanium dioxide (for all strengths), black iron oxide, red iron oxide and yellow iron oxide (300 mg only). REYATAZ capsules are supplied in HDPE bottles containing 60 capsules (150 mg and 200 mg) and 30 capsules (300 mg).

150 mg capsule

Blue opaque cap and powder-blue opaque body, hard gelatin capsule printed in white with “BMS”, “150 mg”, and in blue “3624”.

200 mg capsule

Blue opaque cap and body, hard gelatin capsule printed in white with “BMS”, “200 mg”, and “3631”.

300 mg capsule

Red opaque cap and blue opaque body, hard gelatin capsule printed in white with “BMS”, “300 mg”, and “3622”.

PART II : SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

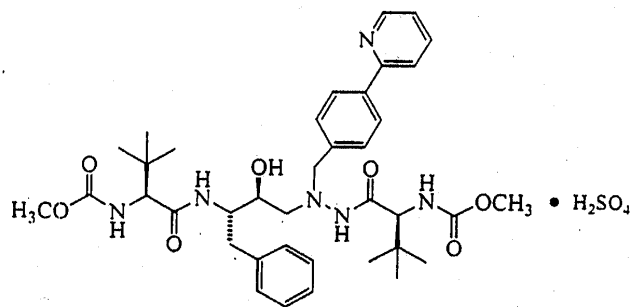
Drug Substance

Proper Name : Atazanavir sulfate

Chemical Name : (3S,8S,9S,12S)-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)

Empirical Formula : $C_{38}H_{52}N_6O_7 \cdot H_2SO_4$

Structural Formula :



Molecular Weight : 802.9 (sulfuric acid salt)
704.9 (free base)

Physicochemical Properties

Description : REYATAZ (atazanavir sulfate) is an azapeptide inhibitor of HIV-1 protease. Atazanavir sulfate is a white to pale yellow powder.

Solubility: It is slightly soluble in water (4-5 mg/mL, free base equivalent).

pH: The pH of a saturated solution in water being about 1.9 at $24 \pm 3^\circ C$.

CLINICAL TRIALS

Antiretroviral Treatment-Naive Adult Patients

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 plus ritonavir (400/100 mg twice daily), each in combination with fixed-dose tenofovir plus emtricitabine (300/200 mg once daily), in 883 antiretroviral treatment-naive patients. Patients had a mean age of 36 years (range 19–72), 48% were Caucasian, 18% Black, 9% Asian, 24% Hispanic/Mestizo/mixed race and 69% were male. The median baseline plasma CD4+ cell count was 205 cells/mm³ (range 2 to 810 cells/mm³) and the mean baseline plasma HIV-1 RNA level was 4.94 log₁₀ copies/mL (range: 2.60 to 5.88 log₁₀ copies/mL). Treatment response and outcomes through Week 48 and Week 96 are presented in Table 19.

Table 19: Outcomes of Randomized Treatment Through Week 48 and Week 96 (Study AI424-138)

| Outcome | REYATAZ 300 mg + ritonavir 100 mg (once daily) with tenofovir/emtricitabine (once daily) ^a (n = 440) | | Lopinavir 400 mg + ritonavir 100 mg (twice daily) with tenofovir/emtricitabine (once daily) ^a (n = 443) | |
|--|--|------------------|---|------------------|
| | 48 Weeks | 96 Weeks | 48 Weeks | 96 Weeks |
| Responder ^b | 78% ^c | 75% ^d | 76% ^c | 69% ^d |
| Virologic failure ^e | 13% | 9% | 10% | 11% |
| Rebound | 4% | 7% | 4% | 9% |
| Never suppressed through Week 48 or Week 96 | 9% | 2% | 6% | 1% |
| Death | 1% | 1% | <1% | <1% |
| Discontinued due to adverse event | 2% | 3% | 3% | 5% |
| Discontinued for other reasons ^f | 6% | 12% | 9% | 15% |

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

^b Patients achieved confirmed HIV RNA <50 copies/mL at Week 48. Roche Amplicor[®], v1.5 ultra-sensitive assay.

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

^d Pre-specified ITT analysis 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 48 and Week 96, respectively.

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

The proportion of responders among patients with high viral loads (ie, baseline HIV RNA $\geq 100,000$ copies/mL) were comparable for the REYATAZ/ritonavir (164 of 223 patients, 74% at 48 weeks and 165 of 223 patients, 74% at 96 weeks) and lopinavir/ritonavir 161 of 222 patients, 73% at 48 weeks and 149 of 222 patients, 67% at 96 weeks) arms. The median increase from baseline in CD4+ cell count was 191 (48 weeks) and 261 (96 weeks) cells/mm³ for the REYATAZ/ritonavir arm and 200 (48 weeks) and 273 (96 weeks) cells/mm³ for the lopinavir/ritonavir arm.

Study AI424-034 : REYATAZ (atazanavir) 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) (n=405) to efavirenz (600 mg once daily) (n=405), 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-naïve 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/mm³ (range : 64 to 1424 cells/mm³) and the mean baseline plasma HIV-1 RNA level was 4.8 log₁₀ copies/mL (range : 2.2 to 5.9 log₁₀ copies/mL).

The primary endpoint for this study was the proportion of treated patients who achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.

Through 48 weeks of therapy, there was a similar proportion of patients with HIV RNA <400 copies/mL in the REYATAZ arm compared to the efavirenz arm (67% vs. 63%, respectively). Virologic failure was the most frequent reason for treatment failure on both regimens (20% vs. 19% respectively). Few subjects on either regimen did not achieve viral suppression through Week 48 (7% on both regimens) and virologic failure was mainly due to viral rebound (13% and 11%, respectively). Discontinuation due to adverse events (AEs) and due to other reasons was slightly higher on EFV than on atazanavir (9% vs. 6% for discontinuation due to AEs, and 9% vs. 7% for discontinuation due to other reasons). Results for the proportion of patients in the REYATAZ arm compared to the efavirenz arm with HIV RNA <50 copies/mL were 31% vs. 36%, respectively. The mean increase from baseline in CD4 cell count was 176 cells/mm³ for the REYATAZ arm and 160 cells/mm³ for the efavirenz arm.

Table 20: 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 by TRWPF analysis ^a LOQ<400 copies/mL (< 50 copies/mL) | 67% (31%) | 63% (36%) |
| Virologic failure ^b | 20% | 19% |
| Rebound | 13% | 11% |
| Never suppressed through Week 48 | 7% | 7% |
| Death or Disease Progression | <1% | <1% |
| Discontinued due to adverse event | 6% | 9% |
| Discontinued for other reasons ^c | 6% | 9% |

^a The TRWPF defined as responders patients who achieved and maintained confirmed HIV RNA <400 copies/mL (< 50 copies/mL) through week 48 without intervening replicated rebound, CDC Class C AIDS events, or treatment discontinuation. ATV-EFV (95% CI) : 3.8 (-2.8, 10.3); ATV is similar to EFV as the lower 95% confidence interval is > -12%, the pre-defined criteria for similarity. Roche Amplicor[®] HIV-1 Monitor[™] Assay, test version 1.0 or 1.5 as geographically appropriate.

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

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

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

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, open-label, multicenter trial, blinded to dose of REYATAZ, comparing REYATAZ at two dose levels (400 mg and 600 mg once daily) (n=181 and n=195, respectively), to nelfinavir (1250 mg twice daily) (n=91), each in combination with stavudine (40 mg) and lamivudine (150 mg) given twice daily, in 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/mm³ (range : 4 to 1003 cells/mm³) and the mean baseline plasma HIV-1 RNA level was 4.7 log₁₀ copies/mL (range : 1.8 to 5.9 log₁₀ copies/mL).

Table 21: 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 by TRWPF ^a | 65% (31%) | 59% (38%) |
| Virologic failure ^b | 23% | 35% |
| Rebound | 11% | 14% |
| Never suppressed through Week 48 | 12% | 21% |
| Death or disease progression | 2% | - |
| Discontinued due to adverse event | 4% | 3% |
| Discontinued for other reasons ^c | 4% | 2% |

^a TRWPF defined responders as patients who achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48 without intervening replicated rebound, CDC Class C AIDS events, or treatment discontinuation. Roche Amplicor[®] HIV-1 Monitor[™] Assay, test version 1.0 or 1.5 as geographically appropriate.

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

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

Through 48 weeks of treatment, the proportion of patients with HIV RNA <400 (<50) copies/mL was 65% (31%) for the REYATAZ 400-mg arm and 59% (38%) for the nelfinavir arm. The mean increase from baseline in CD4 cell count was 234 cells/mm³ for the REYATAZ 400-mg arm and 211 cells/mm³ for the nelfinavir arm. Virologic failure was comparable across all study regimens and was due to approximately equal numbers of subjects who never achieved virologic suppression (12% on ATV 400, 13% on ATV 600 and 21% on NFV).

Antiretroviral Treatment-Experienced Adult Patients

Study AI424-043 : REYATAZ once daily compared to lopinavir + ritonavir twice daily, each in combination with two nucleosides

Study AI424-043 is 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 randomized subjects who experienced virologic failure to only one prior PI containing regimen. The mean time of prior exposure to antiretrovirals was 141 weeks for PIs, 181 weeks for NRTIs, and 93 weeks for NNRTIs (14% of patients had prior exposure to NNRTIs). The mean age was 38 years (range: 20 to 65); 51% were Hispanic, 42% were Caucasian, and 79% were male. The mean baseline CD4 cell count was 323 cells/mm³ (range: 54 to 1210 cells/mm³) and the mean baseline plasma HIV-1 RNA level was 4.14 log₁₀ copies/mL (range: 2.60 to 5.87 log₁₀ copies/mL). Based on results of the Week 24 analysis, patients in the REYATAZ treatment arm were offered alternative treatment after 24 weeks of study therapy.

The co-primary endpoints for this study were the time-averaged difference in change from baseline in HIV RNA levels through Week 48 (efficacy) and the Week 48 percentage change from baseline in fasting LDL cholesterol (safety). Through 48 weeks of therapy, 57% of patients treated with REYATAZ has > 1 log₁₀ virologic suppression (or < 400 copies/mL) compared to

75% of patients treated with lopinavir/ritonavir. There was a greater proportion of patients with HIV RNA <400 copies/mL and HIV RNA <50 copies/mL in the lopinavir/ritonavir arm compared to the REYATAZ arm (67% vs. 45% and 51% vs. 32%).

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.

Study AI424-043 also compared changes from baseline in LDL-cholesterol. Through 48 weeks, REYATAZ resulted in significantly lower fasting LDL-cholesterol (co-primary endpoint), total cholesterol, and fasting triglyceride concentrations than lopinavir + ritonavir, as assessed by change from baseline. HDL cholesterol rose modestly and comparably between baseline to week 48 on both regimens. (For more details, see ADVERSE REACTIONS, Table 10.)

Antiretroviral Treatment- Experienced Adult Patients (Salvage)

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, open-label, multicenter trial comparing REYATAZ (300 mg once daily) taken with ritonavir (100 mg once daily) and REYATAZ (400 mg once daily) in combination with saquinavir soft gelatin capsules (1200 mg once daily), to lopinavir + ritonavir (400/100 mg fixed dose combination twice daily), each in combination with tenofovir and one NRTI, in 358 randomized subjects with virologic failure on HAART regimens containing PIs, NRTIs, and NNRTIs. The mean time of prior antiretroviral exposure was 138 weeks for PIs, 281 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 337 cells/mm³ (range : 14 to 1543 cells/mm³) and the mean baseline plasma HIV-1 RNA level was 4.40 log₁₀ copies/mL (range : 2.6 to 5.9 log₁₀ copies/mL). The primary endpoint for this study was the time-averaged difference in change from baseline in HIV RNA through 48 weeks.

There are limited safety data from controlled clinical trials for REYATAZ plus ritonavir regimens without tenofovir.

The similarity (non-inferiority) of the antiviral efficacy of the ATV 300/RTV and LPV/RTV regimens was demonstrated for the primary efficacy endpoint through Week 48 (TAD [97.5% CI] for ATV 300/RTV - LPV/RTV was 0.13 [-0.12, 0.39]). In contrast, the antiviral efficacy of the ATV 400/SQV regimen was lower than that of the LPV/RTV regimen (TAD [97.5% CI] ATV 400/SQV - LPV/RTV was 0.31 [0.07, 0.55] 0.33 [0.07, 0.60]). At Week 48, HIV RNA levels declined from baseline by a mean of 1.93 log₁₀ c/mL for ATV 300/RTV, and 1.87 log₁₀ c/mL for LPV/RTV.

The comparability of the ATV 300/RTV regimen relative to the LPV/RTV regimen was supported by the analyses which included the proportion of subjects with HIV RNA levels < 400 c/mL. Response rates at Week 48 were comparable between the ATV 300/RTV and LPV/RTV treatment groups. Using the TRWPF definition, response rates were 53% for ATV

300/RTV and 54% for LPV/RTV.

Study AI424-045, however was not large enough to reach a definite conclusion that REYATAZ/ritonavir and lopinavir/ritonavir are equivalent on the secondary endpoint of proportions below the HIV RNA lower limit of detection.

Table 22: Outcomes of Treatment Through 48 Weeks in Study AI424-045 (Patients with Prior Antiretroviral Experience)*^a

| Outcome | REYATAZ 300 mg once daily + ritonavir 100 mg once daily + tenofovir + NRTI N = 120 | lopinavir + ritonavir (400/100 mg) BID + tenofovir + NRTI N = 123 |
|---|---|---|
| HIV RNA Mean Change from Baseline (log ₁₀ copies/mL) ^{a,b,c} | -1.93 | -1.87 |
| CD4 Mean Change from Baseline (cell/mm ³) ^d | 110 | 121 |
| Percent of Randomized Patients Responding ^e | | |
| HIV RNA <400 copies/mL ^a | 53% | 54% |
| HIV RNA <50 copies/mL ^a | 36% | 42% |

* There are limited safety data from controlled trials for REYATAZ plus ritonavir regimens without tenofovir. (See DRUG INTERACTIONS.)

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

^b Based on patients with baseline and Week 48 HIV-1 RNA measurements (REYATAZ + ritonavir, n=90; lopinavir + ritonavir, n=99).

^c Protocol-defined primary efficacy outcome measure.

^d Based on patients with baseline and Week 48 CD4 cell count measurements (REYATAZ + ritonavir, n=83; lopinavir + ritonavir, n=94).

^e TRWPF defined as responders patients who achieved and maintained confirmed HIV RNA <400 copies/mL (< 50 copies/mL) through week 48 without intervening replicated rebound, CDC Class C AIDS events, or treatment discontinuation.

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, 182 patients (83 antiretroviral-naive and 99 antiretroviral-experienced) received once daily REYATAZ, with or without ritonavir, in combination with two NRTIs.

Ninety-nine patients (6 to less than 18 years of age) treated with the REYATAZ capsule formulation, with or without ritonavir, were evaluated. In this cohort, the overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <400 copies/mL at week 24 were 68% (28/41) and 33% (19/58), respectively. The overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <50 copies/mL at week 24 were 59% (24/41) and 24% (14/58), respectively. The median increase from baseline in absolute CD4 count at 20 weeks of

therapy was 171 cells/mm³ in antiretroviral-naive patients and 116 cells/mm³ in antiretroviral-experienced patients. The efficacy of REYATAZ in the pediatric population beyond 24 weeks has not yet been established.

DETAILED PHARMACOLOGY

Electrocardiogram : Effect on PR and QT intervals

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 pre-dose 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 pharmacodynamic interaction in humans between atazanavir and other drugs that prolong the PR interval of the electrocardiogram (see WARNINGS AND PRECAUTIONS).

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

Drug-Drug Interactions

See also CONTRAINDICATIONS and DRUG INTERACTIONS.

Atazanavir is metabolized in the liver by the cytochrome P450 enzyme system and inhibits CYP3A4 and UGT1A1 at clinically relevant concentrations with Ki of 2.35 μM (CYP3A4 isoform) and 1.9 μM. Atazanavir should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4 (see CONTRAINDICATIONS). Drugs that induce CYP3A4 activity would be expected to increase the clearance of atazanavir, resulting in lowered plasma concentrations. Coadministration of atazanavir and other drugs that inhibit CYP3A4 may increase atazanavir plasma concentrations.

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

Atazanavir has been shown *in vivo* not to induce its own metabolism, nor to increase the biotransformation of some drugs metabolized by CYP3A4. In a multiple-dose study, atazanavir decreased the urinary ratio of endogenous 6β-OH cortisol to cortisol versus baseline, indicating

that CYP3A4 production was not induced.

Drug interaction studies were performed with atazanavir and other drugs likely to be coadministered and some drugs commonly used as probes for pharmacokinetic interactions.

The effects of coadministered drugs on the AUC, C_{max} and C_{min} of atazanavir are summarized in Table 23.

Table 23: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs

| Coadministered Drug | Coadministered Drug Dose/Schedule | Atazanavir Dose/Schedule | N ^a | Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00 | | |
|--|---|---|----------------|---|----------------------|----------------------|
| | | | | C_{max} | AUC | C_{min} |
| Atenolol | 50 mg once daily, d 7-11 and d19-23 | 400 mg once daily, d 1-11 | 19 | 1.00 (0.89, 1.12) | 0.93 (0.85,1.01) | 0.74 (0.65, 0.86) |
| clarithromycin | 500 mg BID, d 7-10 and d 18-21 | 400 mg once daily, d 1-10 | 29 | 1.06 (0.93, 1.20) | 1.28 (1.16, 1.43) | 1.91 (1.66, 2.21) |
| didanosine (ddI) (buffered tablets) plus stavudine (d4T) | ddI : 200 mg x 1 dose, d4T : 40 mg x 1 dose | 400 mg x 1 dose simultaneously with ddI and d4T | 31 | 0.11 (0.06, 0.18) | 0.13 (0.08, 0.21) | 0.16 (0.10, 0.27) |
| | ddI : 200 mg x 1 dose, d4T : 40 mg x 1 dose | 400 mg x 1 dose 1 hour after ddI + d4T | 31 | 1.12 (0.67, 1.18) | 1.03 (0.64, 1.67) | 1.03 (0.61, 1.73) |
| didanosine (ddI) (enteric-coated [EC] capsules) ^b | 400 mg d 8 (fed) | 400 mg once daily d 2-8 | 34 | 1.03 (0.93, 1.14) | 0.99 (0.91, 1.08) | 0.98 (0.89, 1.08) |
| | 400 mg d 19 (fed) | 300 mg/ritonavir 100 mg once daily d 9-19 | 31 | 1.04 (1.01, 1.07) | 1.00 (0.96, 1.03) | 0.87 (0.82, 0.92) |
| diltiazem | 180 mg once daily, d 7-11 and d 19-23 | 400 mg once daily, d 1-11 | 30 | 1.04 (0.96, 1.11) | 1.00 (0.95, 1.05) | 0.98 (0.90, 1.07) |
| efavirenz | 600 mg once daily, d 7-20 | 400 mg once daily, d 1-20 | 27 | 0.41 (0.33, 0.51) | 0.26 (0.22, 0.32) | 0.07 (0.05, 0.10) |
| efavirenz and ritonavir | efavirenz 600 mg once daily 2 h after REYATAZ and ritonavir 100 mg once daily simultaneously with REYATAZ, d 7-20 | 400 mg once daily, d 1-6 then 300 mg once daily d 7-20 | 13 | 1.14 (0.83, 1.58) | 1.39 (1.02, 1.88) | 1.48 (1.24, 1.76) |
| efavirenz and ritonavir | 600 mg once daily, d 11-24 (pm) | 300 mg once daily / ritonavir 100 mg once daily, d 1-10 (pm), then 400 mg once daily / ritonavir 100 mg once daily, d 11-24 (pm), (simultaneous with efavirenz) | 14 | 1.17 (1.08, 1.27) | 1.00 (0.91, 1.10) | 0.58 (0.49, 0.63) |

| Coadministered Drug | Coadministered Drug Dose/Schedule | Atazanavir Dose/Schedule | N ^a | Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00 | | |
|---------------------|--------------------------------------|--|----------------|---|----------------------|----------------------|
| | | | | C _{max} | AUC | C _{min} |
| famotidine | 40 mg BID d 7-12 ^c | 400 mg once daily d 1-12 ^c | 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 ^d | 400 mg once daily (pm) d 1-6, d 7-12 ^d | 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 ^{c,e} | 300 mg once daily / ritonavir 100 mg once daily d 1-20 ^{c,e} | 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 | 300 mg once daily /ritonavir 100 mg once daily /tenofovir 300 mg once daily, d 1-10 (am), then 300 mg once daily /ritonavir 100 mg once daily /tenofovir 300 mg once daily, d 11-17 (am) (simultaneous administration with am famotidine) ^{m,n} | 18 | 0.91 (0.84, 0.99) | 0.90 (0.82, 0.98) | 0.81 (0.69, 0.94) |
| | 40 mg once daily (pm), d 18-24 | 300 mg once daily /ritonavir 100 mg once daily /tenofovir 300 mg once daily, d 1-10 (am), then 300 mg once daily /ritonavir 100 mg once daily /tenofovir 300 mg once daily, d 18-24 (am) (12h after pm famotidine) ⁿ | 20 | 0.89 (0.81, 0.97) | 0.88 (0.80, 0.96) | 0.77 (0.63, 0.93) |
| | 40 mg BID, d 18-24 | 300 mg once daily /ritonavir 100 mg once daily /tenofovir 300 mg once daily, d 1-10 (am), then 300 mg once daily /ritonavir 100 mg once daily /tenofovir 300 mg once daily, d 18-24 (am) (10h after pm famotidine and 2h before am famotidine) ⁿ | 18 | 0.74 (0.66, 0.84) | 0.79 (0.70, 0.88) | 0.72 (0.63, 0.83) |

| Coadministered Drug | Coadministered Drug Dose/Schedule | Atazanavir Dose/Schedule | N ^a | Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00 | | |
|--------------------------|---------------------------------------|--|------------------------|---|--|--|
| | | | | C _{max} | AUC | C _{min} |
| fluconazole | 200 mg once daily, d 11-20 | 300 mg once daily /ritonavir 100 mg once daily, d 1-10, then 300 mg once daily /ritonavir 100 mg once daily, d 11-20 | 29 | 1.03 (0.95, 1.11) | 1.04 (0.95, 1.13) | 0.98 (0.85, 1.13) |
| ketoconazole | 200 mg once daily, d 7-13 | 400 mg once daily, d 1-13 | 14 | 0.99 (0.77, 1.28) | 1.10 (0.89, 1.37) | 1.03 (0.53, 2.01) |
| nevirapine ^{fg} | 200 mg BID, d 1-23 | 300 mg once daily / ritonavir 100 mg once daily, d 4-13, then 400 mg once daily / ritonavir 100 mg once daily, d 14-23 | 23, 22 ^h | 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 once daily d 7-12 ⁱ | 400 mg once daily d 1-12 | 16 | 0.04 (0.04, 0.05) | 0.06 (0.05, 0.07) | 0.05 (0.03, 0.07) |
| | 40 mg once daily d 11-20 ⁱ | 300 mg once daily/ritonavir 100 mg once daily d 1-20 | 15 | 0.28 (0.24, 0.32) | 0.24 (0.21, 0.27) | 0.22 (0.19, 0.26) |
| | 20 mg once daily, d 17-23 (am) | 300 mg once daily /ritonavir 100 mg once daily, d 7-16 (pm), then 300 mg once daily /ritonavir 100 mg once daily, d 17-23 (pm) ^{o, p} | 13 | 0.61 (0.46, 0.81) | 0.58 (0.44, 0.75) | 0.54 (0.41, 0.71) |
| | 20 mg once daily, d 17-23 (am) | 300 mg once daily /ritonavir 100 mg once daily, d 7-16 (am), then 400 mg once daily /ritonavir 100 mg once daily, d 17-23 (am) ^{q, r} | 14 | 0.69 (0.58, 0.83) | 0.70 (0.57, 0.86) | 0.69 (0.54, 0.88) |
| rifabutin | 150 mg once daily, d 15-28 | 400 mg once daily, d 1-28 | 7 | 1.34 (1.14, 1.59) | 1.15 (0.98, 1.34) | 1.13 (0.68, 1.87) |
| rifampin | 600 mg once daily d 17-26 | 300 mg once daily/ritonavir 100 mg once daily d 7-26 | 16 | 0.47 (0.41, 0.53) | 0.28 (0.25, 0.32) | 0.02 (0.02, 0.03) |
| ritonavir ^j | 100 mg once daily, d 11-20 | 300 mg once daily, d 1-20 | 28 | 1.86 (1.69, 2.05) | 3.38 (3.13, 3.63) | 11.89 (10.23, 13.82) |

| Coadministered Drug | Coadministered Drug Dose/Schedule | Atazanavir Dose/Schedule | N ^a | Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00 | | |
|--------------------------------------|--|---|----------------|---|-----------------------------------|-----------------------------------|
| | | | | C _{max} | AUC | C _{min} |
| tenofovir ^k | 300 mg once daily with food d 9-16 | 400 mg once daily with food d 1-16 | 34 | 0.79 (0.73, 0.86) | 0.75 (0.70, 0.81) | 0.60 (0.52, 0.68) |
| tenofovir ^k and ritonavir | tenofovir ^k 300 mg once daily d 15-42 | 300 mg once daily with ritonavir 100 mg once daily d 1-42 | 10 | 0.72 ^l (0.50, 1.05) | 0.75 ^l (0.58, 0.97) | 0.77 ^l (0.54, 1.10) |

^a N = number of subjects

^b 400 mg ddi EC and REYATAZ were administered together with food on Days 8 and 19.

^c Simultaneous administration

^d 10 hr after, 2 hr before famotidine

^e 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.

^f Study was conducted in HIV-infected individuals.

^g 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.

^h Parallel group design; n for atazanavir/ritonavir plus nevirapine, n for atazanavir 300 mg/ritonavir 100 mg without nevirapine. Subjects were treated with nevirapine prior to study entry.

ⁱ Omeprazole was administered on an empty stomach 2 hours before REYATAZ.

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

^k Tenofovir disoproxil fumarate. Note that similar results were observed in studies where administration of tenofovir and REYATAZ was separated by 12 hours.

^l 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 ^g).

^m 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.

ⁿ Atazanavir/ritonavir/tenofovir was administered after a light meal.

^o 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.

^p 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).

^q Omeprazole 20 mg was given 30 min 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.

^r 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).

The effects of coadministration of atazanavir on the AUC, C_{max}, and C_{min} of other drugs are summarized in Table 24.

Table 24: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Atazanavir

| Coadministered Drug | Coadministered Drug Dose/Schedule | Atazanavir Dose/Schedule | N ^a | Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Atazanavir; No Effect = 1.00 | | |
|--|--|--|----------------|---|---|--|
| | | | | C _{max} | AUC | C _{min} |
| acetaminophen | 1 gm BID, d 1-20 | 300 mg once daily /ritonavir 100 mg once daily, d 11-20 | 10 | 0.87 (0.77, 0.99) | 0.97 (0.91, 1.03) | 1.26 (1.08, 1.46) |
| atenolol | 50 mg once daily, d 7-11 and d 19-23 | 400 mg once daily, d 1-11 | 19 | 1.34 (1.26, 1.42) | 1.25 (1.16, 1.34) | 1.02 (0.88, 1.19) |
| buprenorphine | 16 mg once daily naloxone 4 mg once daily | 300 mg once daily/ritonavir 100 mg once daily x 5 days | 10 | buprenorphine: 1.37 norbuprenorphine: 16.1 | buprenorphine: 1.67 norbuprenorphine: 2.05 | buprenorphine: 1.69 norbuprenorphine: 2.01 |
| | once daily stable maintenance dose with naloxone | 400 mg once daily x 5 days | 10 | buprenorphine: 1.64 norbuprenorphine: 1.36 | buprenorphine: 1.93 norbuprenorphine: 1.76 | buprenorphine: 1.99 norbuprenorphine: 1.64 |
| clarithromycin | 500 mg BID, d 7-10 and d 18-21 | 400 mg once daily, d 1-10 | 21 | 1.50 (1.32, 1.71) OH-clarithromycin : 0.28 (0.24, 0.33) | 1.94 (1.75, 2.16) OH-clarithromycin : 0.30 (0.26, 0.34) | 2.60(2.35, 2.88) OH-clarithromycin : 0.38 (0.34, 0.42) |
| didanosine (ddI) (buffered tablets) plus stavudine (d4T) | ddI : 200 mg x 1 dose d4T : 40 mg x 1 dose | 400 mg x 1 dose simultaneous with ddI and d4T | 31 | ddI : 0.92 (0.84, 1.02) d4T : 1.08 (0.96, 1.22) | ddI : 0.98 (0.92, 1.05) d4T : 1.00 (0.97, 1.03) | NA d4T : 1.04 (0.94, 1.16) |
| didanosine (ddI) (enteric coated [EC] capsules) ^b | 400 mg d 1 (fasted), 8 (fed) | 400 mg once daily, d 2-8 | 34 | 0.64 (0.55, 0.74) | 0.66 (0.60, 0.74) | 1.13 (0.91, 1.41) |
| | 400 mg d 1 (fasted), 19 (fed) | 300 mg once daily/ritonavir 100 mg once daily, d 9-19 | 31 | 0.62 (0.52, 0.74) | 0.66 (0.59, 0.73) | 1.25 (0.92, 1.69) |
| diltiazem | 180 mg once daily, d 7-11 and d 19-23 | 400 mg once daily, d 1-11 | 28 | 1.98 (1.78, 2.19) desacetyl-diltiazem : 2.72 (2.44, 3.03) | 2.25 (2.09, 2.16) desacetyl-diltiazem : 2.65 (2.45, 2.87) | 2.42 (2.14, 2.73) desacetyl-diltiazem : 2.21 (2.02, 2.42) |

| Coadministered Drug | Coadministered Drug Dose/Schedule | Atazanavir Dose/Schedule | N ^a | Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Atazanavir; No Effect = 1.00 | | |
|--|--|--|----------------|---|--|--|
| | | | | C _{max} | AUC | C _{min} |
| ethinyl estradiol & norethindrone ^c | Ortho-Novum® 7/7/7 once daily, d 1-29 | 400 mg once daily, d 16-29 | 19 | ethinyl estradiol : 1.15 (0.99, 1.32) norethindrone : 1.67 (1.42, 1.96) | ethinyl estradiol : 1.48 (1.31, 1.68) norethindrone : 2.10 (1.68, 2.62) | Ethinyl estradiol : 1.91 (1.57, 2.33) norethindrone : 3.62 (2.57, 5.09) |
| ethinyl estradiol & norgestimate ^d | Tri-Cyclen® once daily, d 1-28, then Tri-Cyclen® LO once daily, d 29-42 ^e | 300 mg once daily /ritonavir 100 mg once daily, d 29-42 | 13 | ethinyl estradiol: 0.84 (0.74, 0.95) 17-deacetyl norgestimate: ^f 1.68 (1.51, 1.88) | ethinyl estradiol: 0.81 (0.75, 0.87) 17-deacetyl norgestimate: ^f 1.85 (1.67, 2.05) | ethinyl estradiol: 0.63 (0.55, 0.71) 17-deacetyl norgestimate: ^f 2.02 (1.77, 2.31) |
| fluconazole | 200 mg once daily, d 1-20 | 300 mg once daily /ritonavir 100 mg once daily, d 11-20 | 30 | 1.05 (0.99, 1.10) | 1.08 (1.02, 1.15) | 1.07 (1.00, 1.15) |
| methadone | stable maintenance dose, d 1-15 | 400 mg once daily, d 2-15 | 16 | (R)-methadone: ^g 0.91 (0.84, 1.0) total: 0.85 (0.78, 0.93) | (R)-methadone: ^g 1.03 (0.95, 1.10) total: 0.94 (0.87, 1.02) | (R)-methadone: ^g 1.11 (1.02, 1.20) total: 1.02 (0.93, 1.12) |
| nevirapine ^{hi} | 200 mg BID, d 1-23 | 300 mg once daily / ritonavir 100 mg once daily, d 4-13, then 400 mg once daily / ritonavir 100 mg once daily, d 14-23 | 23 | 1.17 (1.09, 1.25) 1.21 (1.11, 1.32) | 1.25 (1.17, 1.34) 1.26 (1.17, 1.36) | 1.32 (1.22, 1.43) 1.35 (1.25, 1.47) |
| omeprazole ^j | 40 mg single dose d 7 and d 20 | 400 mg once daily d 1-12 | 16 | 1.24 (1.04, 1.47) | 1.45 (1.20, 1.76) | NA |
| rifabutin | 300 mg once daily, d 1-10 then 150 mg once daily, d 11-20 | 600 mg once daily ^k d 11-20 | 3 | 1.18 (0.94, 1.48) 25-O-desacetyl-rifabutin : 8.20 (5.90, 11.40) | 2.10 (1.57, 2.79) 25-O-desacetyl-rifabutin : 22.01 (15.97, 30.34) | 3.43 (1.98, 5.96) 25-O-desacetyl-rifabutin : 75.6 (30.1, 190.0) |

| Coadministered Drug | Coadministered Drug Dose/Schedule | Atazanavir Dose/Schedule | N ^a | Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Atazanavir; No Effect = 1.00 | | |
|------------------------------------|--|---|----------------|---|---|---|
| | | | | C _{max} | AUC | C _{min} |
| | 150 mg twice weekly, d 1-15 | 300 mg once daily / ritonavir 100 mg once daily, d 1-17 | 7 | 2.49 ¹ (2.03, 3.06) 25-O-desacetyl-rifabutin: 7.77 (6.13, 9.83) | 1.48 ¹ (1.19, 1.84) 25-O-desacetyl-rifabutin: 10.90 (8.14, 14.61) | 1.40 ¹ (1.05, 1.87) 25-O-desacetyl-rifabutin: 11.45 (8.15, 16.10) |
| rosiglitazone ^m | 4 mg single dose, d 1, 7, 17 | 400 mg once daily D 2-7, then 300 mg once daily / ritonavir 100 mg once daily, d 8-17 | 14 | 1.08 (1.03, 1.13) 0.97 (0.91, 1.04) | 1.35 (1.26, 1.44) 0.83 (0.77, 0.89) | NA NA |
| saquinavir (soft gelatin capsules) | 1200 mg once daily, d 1-13 | 400 mg once daily, d 7-13 | 7 | 4.39 (3.24, 5.95) | 5.49 (4.04, 7.47) | 6.86 (5.29, 8.91) |
| tenofovir ⁿ | 300 mg once daily with food d 9-16 and d 24-30 | 400 mg once daily with food d 1-16 | 33 | 1.14 (1.08, 1.20) | 1.24 (1.21, 1.28) | 1.22 (1.15, 1.30) |
| | 300 mg once daily d 1-7 (pm) d 25-34 (pm) ⁿ | 300 mg once daily/ritonavir 100 mg once daily d 25-34 (am) ^o | 12 | 1.34 (1.20, 1.51) | 1.37 (1.30, 1.45) | 1.29 (1.21, 1.36) |
| lamivudine + zidovudine | 150 mg lamivudine + 300 mg zidovudine BID d 1-12 | 400 mg once daily, d 7-12 | 19 | lamivudine : 1.04 (0.92, 1.16) Zidovudine : 1.05 (0.88, 1.24) Zidovudine glucuronide : 0.95 (0.88, 1.02) | Lamivudine : 1.03 (0.98, 1.08) Zidovudine : 1.05 (0.96, 1.14) Zidovudine glucuronide : 1.00 (0.97, 1.03) | Lamivudine : 1.12 (1.04, 1.21) zidovudine : 0.69 (0.57, 0.84) zidovudine glucuronide : 0.82 (0.62, 1.08) |

^a N = number of subjects

^b 400 mg ddi EC and REYATAZ were administered together with food on Days 8 and 19.

^c 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.

^d 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.

^e 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.

- ^f 17-deacetyl norgestimate is the active component of norgestimate.
- ^g (R)-methadone is the active isomer of methadone.
- ^h Study was conducted in HIV-infected individuals.
- ⁱ Subjects were treated with nevirapine prior to study entry.
- ^j 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.
- ^k Not the recommended therapeutic dose of atazanavir.
- ^l When compared to rifabutin 150 mg once daily alone d1-10 (n=14). Total of rifabutin + 25-O-desacetyl-rifabutin: AUC 2.19 (1.78, 2.69).
- ^m Rosiglitazone used as a probe substrate for CYP2C8.
- ⁿ Tenofovir disoproxil fumarate. Note that similar results were observed in studies where administration of tenofovir and REYATAZ was separated by 12 hours.
- ^o Administration of tenofovir and REYATAZ was temporally separated by 12 hours.

MICROBIOLOGY

Antiviral activity *in vitro*

Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC₅₀) 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 EC₅₀ values above the EC₅₀ values of failure isolates. Two-drug combination studies with ATV showed additive to antagonistic antiviral activity *in vitro* with abacavir and the NNRTIs (delavirdine, efavirenz, and nevirapine) and additive antiviral activity *in vitro* with the PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), NRTIs (didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine), the HIV-1 fusion inhibitor enfuvirtide, and two compounds used in the treatment of viral hepatitis, adefovir and ribavirin, without enhanced cytotoxicity.

Resistance

Clinical Studies of Treatment-Naive Patients: Receiving REYATAZ 400 mg Without Ritonavir: ATV-resistant clinical isolates from treatment-naive patients who experienced virologic failure developed an I50L mutation (after an average of 50 weeks of ATV therapy), often in combination with an A71V mutation. In treatment-naive patients, viral isolates that developed the I50L mutation showed phenotypic resistance to ATV but retained *in vitro* susceptibility to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir); however, there are no clinical data available to demonstrate the effect of the I50L mutation on the efficacy of subsequently administered PIs.

Clinical Studies of Treatment-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 ≥ 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 virologic failure isolate had a 56-fold decrease in ATV susceptibility emerge on therapy with the development of PI substitutions L10F, V32I, K43T,

M46I, A71I, G73S, I85I/V, and L90M. Five of the treatment failure isolates in the ATV/RTV arm developed emtricitabine resistance with the emergence of either the M184I (1 patient) or the M184V (4 patients) substitution on therapy. In the LPV/RTV arm, one virologic failure isolate had a 69-fold decrease in LPV susceptibility emerge on therapy with the development of PI substitutions L10V and V11I in addition to baseline PI substitutions V32I, I54I/V, V82A, L90M, L10I, A71I, G73S and L89V. Six of the failure isolates in the LPV/RTV arm developed emtricitabine resistance with the emergence of the M184V substitution.

Clinical Studies of Treatment-Experienced Patients: In contrast, from studies of treatment-experienced patients treated with ATV or ATV/RTV, most ATV-resistant isolates from patients who experienced virologic failure developed mutations that were associated with resistance to multiple PIs and displayed decreased susceptibility to multiple PIs. The most common protease mutations to develop in the viral isolates of patients who failed treatment with ATV 300 mg once daily and RTV 100 mg once daily (together with tenofovir and an NRTI) included V32I, L33F/V/I, E35D/G, M46I/L, I50L, F53L/V, I54V, A71V/T/I, G73S/T/C, V82A/T/L, I85V, and L89V/Q/M/T. Other mutations that developed on ATV/RTV treatment including E34K/A/Q, G48V, I84V, N88S/D/T, and L90M occurred in less than 10% of patient isolates. Generally, if multiple PI resistance mutations were present in the HIV-1 of the patient at baseline, ATV resistance developed through mutations associated with resistance to other PIs and could include the development of the I50L mutation. The I50L mutation has been detected in treatment-experienced patients experiencing virologic failure after long-term treatment. Protease cleavage site changes also emerged on ATV treatment but their presence did not correlate with the level of ATV resistance.

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 25.

Table 25: 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.

Cross-Resistance

An association between virologic response at 48 weeks and the number and type of primary PI-resistance-associated mutations detected in baseline HIV-1 isolates from antiretroviral-experienced patients receiving ATV/RTV once daily or lopinavir (LPV)/RTV twice daily in Study AI424-045 is shown in Table 26.

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

Table 26: HIV RNA Response by Number and Type of Baseline PI Mutation, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

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

Table 26: HIV RNA Response by Number and Type of Baseline PI Mutation, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

- ^a Primary mutations include any change at D30, V32, M36, M46, I47, G48, I50, I54, A71, G73, V77, V82, I84, N88, and L90.
^b Results should be interpreted with caution because the subgroups were small.
^c There were insufficient data (n<3) for PI mutations V32I, I47V, G48V, I50V, and F53L.

The response rates of antiretroviral-experienced patients in Study AI424-045 were analyzed by baseline phenotype (shift in *in vitro* susceptibility relative to reference, Table 27). 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 27: Baseline Phenotype by Outcome, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

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

- ^a Fold change in *in vitro* susceptibility relative to the wild-type reference.
^b Results should be interpreted with caution because the subgroups were small.

TOXICOLOGY

Acute Toxicity

The single-dose oral toxicity of atazanavir was evaluated in mice and rats at doses of 200 to 1600 mg/kg. In mice, doses of 800 and 1600 mg/kg produced death; clinical signs including tremors, hypoactivity, ptosis, scant stool, and/or urogenital staining; and transient group mean body weight loss (males). Additional clinical signs observed at 1600 mg/kg included loss of righting reflex, recumbency, and labored respiration. Clinical signs were generally first noted on Day 2 and resolved within 2 to 3 days. Doses up to 400 mg/kg were well tolerated in mice with only transient scant stool observed at 400 mg/kg. The no-effect dose in mice was 200 mg/kg. In rats, no atazanavir-related effects were observed after administration of single oral doses up to 1600 mg/kg.

Short- and Long-Term Toxicity

Repeat-dose oral toxicity studies were conducted in rats for 2 weeks to 6 months, and in dogs for 2 weeks to 9 months to evaluate the short- and long-term toxicity of atazanavir. Atazanavir-related findings were generally confined to the liver and included increases in serum total bilirubin in both species and liver enzymes in dogs, and hepatocellular vacuolation and hypertrophy in rats. These liver changes were observed at systemic exposures (AUC) of atazanavir that were 0.4 to 4 times in rats and 0.2 to 20 times in dogs the exposure in humans given atazanavir at 400 mg once daily. Similar liver changes were also observed in a 3-month oral toxicity study in mice at exposures 0.4 to 12 times the exposure in humans given 400 mg once daily. Additionally in mice, cytotoxic liver changes were observed in males (increased transaminases) and females (increased transaminases and single-cell necrosis) at exposures equivalent to and 12 times, respectively, that observed in humans given 400 mg once daily, whereas no effects were observed at exposures of 0.4 and 4 times, respectively, human exposure. Serum cholesterol and glucose were minimally to mildly increased in rats but not in mice. Similar increases were observed in an initial 2-week oral toxicity study performed in dogs. Subsequent 2-week and 9-month oral toxicity studies in dogs showed no drug-related changes in serum cholesterol and glucose.

Cardiotoxicity

Atazanavir minimally increased the duration of the rabbit Purkinje fiber action potential, weakly inhibited sodium and potassium IKr (HERG-encoded) and IKs currents ($IC_{50} > 30 \mu M$), and moderately inhibited calcium current ($IC_{50} = 10.4 \mu M$) *in vitro*. Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of QRS complex) were observed only in an initial 2-week oral toxicity study performed in dogs and were considered secondary to the marked clinical toxicity and not a direct drug effect. Subsequent 2-week and 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes.

Reproduction and Teratology

In a fertility and early embryonic development study in rats, atazanavir altered oestrus cycling with no effects on mating or fertility. No teratogenic effects were observed in rats or rabbits at maternally toxic doses. In the pre- and postnatal development assessment in rats, atazanavir produced a transient reduction in body weight in the offspring at a maternally toxic dose. Systemic exposure to atazanavir at doses that resulted in maternal toxicity was at least equal to or slightly greater than that observed in humans given 400 mg once daily.

Carcinogenicity and Mutagenicity

Carcinogenicity studies with atazanavir were conducted in mice and rats. Mice were administered doses of 20, 40, and 80 mg/kg/day in males and 40, 120, and 360 mg/kg/day in females. In female mice, there was an increase in the incidence of benign hepatocellular adenomas at the highest dose. The exposure in female mice at the high dose is approximately seven times exposure in humans given atazanavir 400 mg once daily. No increase in the incidence of tumors was observed in female mice at lower doses or male mice at any dose.

Exposures in male and female mice at nontumorigenic doses are approximately four times human exposure at 400 mg/day. In rats administered doses of 100, 350, and 1200 mg/kg/day, there was no increased incidence of any tumor type. Exposures in rats at the high dose are approximately two (males) and six (females) times exposure in humans given atazanavir 400 mg once daily. The clinical significance of benign hepatocellular adenomas in high-dose female mice is unknown as these benign tumors occurred in mice only at exposures (approximately seven times human exposure at 400 mg/day) causing significant liver damage. 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).

REFERENCES

1. Bartlett JA, Benoit SL, Johnson VA, et al. Lamivudine plus zidovudine compared with zalcitabine plus zidovudine in patients with HIV infection. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 1996; 125 :161-172.
2. Cramer JA, Mattson RH, Prevey MI, et al. How Often is Medication Taken as Prescribed? A Novel Assessment Technique. *JAMA* 1989; 261 :3273-3277.
3. Eldred LJ, Wu AW, Chaisson RE, Moore RD. Adherence to Antiretroviral and Pneumocystis Prophylaxis in HIV Disease. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* 1998, 18 :117-125.
4. Gulick RM, Mellors JW, Havfir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med.* 1997; 337 :734-739.
5. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogs plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic milliliter or less. *N Engl J Med.* 1997;337 :725-733.
6. Holmberg SD, Moorman AC, Williamson JM, Tong TC, Ward DJ, Wood KC, Greenberg AE, Janssen RS, the HIV Outpatient Study (HOPS) investigators. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *The Lancet*, Vol. 360, November 30, 2002.
7. Holtzer CD, Roland M. The Use of Combination Antiretroviral Therapy in HIV-Infected Patients. *Ann Pharmacother* 1999; 33 :198-209.
8. Panel On Clinical Practices for the Treatment of HIV Infection Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, August 13, 2001.
9. Raffi F, Reliquet V, Auger S, et al. Efficacy and safety of stavudine and didanosine combination therapy in antiretroviral-experienced patients. *AIDS.* 1998; 12 :1999-2005.
10. Hirsch M, Steigbigel R, Staszewski S, et al. A randomized, controlled trial of indinavir, zidovudine, and lamivudine in adults with advanced human immunodeficiency virus type 1 infection and prior antiretroviral therapy. *J Infect Dis.* 1999;180 :659-665.
11. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection : Recommendations of an International AIDS Society-USA panel. *JAIDS* 31 : 257-275, 2002.
12. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, ATP III). *JAMA*, 2001, 285 :2486.

13. Sanne I et al. Results of a Phase 2 Clinical Trial at 48 Weeks (AI424-007) : A Dose-Ranging, Safety, and Efficacy Comparative Trial of Atazanavir at Three Doses in Combination with Didanosine and Stavudine in Antiretroviral-Naive Subjects. JAIDS 2003; 32(1) : 18-29.
14. Johnson M et al. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. AIDS 2005, 19:685-694.

PART III : CONSUMER INFORMATION

Pr **REYATAZ** *
(atazanavir sulfate)

This leaflet is Part III of a three-part “Product Monograph” published when REYATAZ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about REYATAZ. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

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

What the medication is used for :

REYATAZ is a prescription medicine used in combination with antiviral drugs to treat patients who are infected with HIV (the human immunodeficiency virus), the virus that causes AIDS. HIV infection destroys CD4 (T) cells, which are important to the immune system. The immune system helps fight infection. After a large number of T cells are destroyed, AIDS develops. REYATAZ helps to block HIV protease, an enzyme that is needed for the HIV virus to multiply. REYATAZ may lower the amount of HIV in your blood, helps your body keep its supply of CD4 (T) cells, and reduce the risk of death and illness associated with HIV.

What it does :

REYATAZ belongs to a family of medicines called protease inhibitors that control HIV infection by blocking a protease enzyme that HIV needs to multiply. Protease inhibitors work in two ways : they lower the number of HIV viruses in your body and allow the number of your CD4 T-cells that fight infection in your body to increase.

Your doctor prescribed REYATAZ for you because you are infected by the HIV virus that causes AIDS. REYATAZ helps by reducing the amount of HIV virus in your body and, therefore, reducing the risk of developing illnesses associated with HIV disease.

REYATAZ is prescribed together with other anti-viral medicines that also fight HIV infection. Your doctor will determine which combination of these medicines with REYATAZ is best for you.

You should know that REYATAZ is not a cure for HIV infection and that you may continue to develop infections or other illnesses associated with HIV infection. You should, therefore, remain under the care of your doctor while taking REYATAZ.

Treatment with REYATAZ does not reduce the risk of transmission of HIV to others through sexual contact or blood contamination. It is important to continue safe sex practices and not to share needles.

When it should not be used :

- If you know that you are allergic to atazanavir or any of the other ingredients of REYATAZ (See “What the non-medicinal ingredients are”).
 - If you have, or have had a severe liver disease.
 - If you take rifampin (RIFADIN*, RIFATER*, or ROFACT*), midazolam (when taken by mouth), triazolam, or ergot alkaloids (ex. dihydroergotamine, MIGRANAL NS*), irinotecan (CAMPTOSAR*), cisapride (PROPULSID*)[♦], lovastatin (MEVACOR*), simvastatin (ZOCOR*), pimozide (ORAP*), indinavir (CRIXIVAN*), bepridil[♦], quinidine (BIQUIN*) and vardenafil (LEVITRA*).
 - If you take medicinal products containing St. John’s wort (*Hypericum perforatum*) as this may result in loss of efficacy and development of resistance to REYATAZ.
 - If you are taking REYATAZ and ritonavir (KALETRA*, NORVIR*) together, do not take voriconazole (VFEND*.)
 - If you take VIRAMUNE* (nevirapine, used for HIV infection). NC 131741
- [♦] cisapride and bepridil are not marketed in Canada

What the medicinal ingredient is :

Each capsule contains amounts of atazanavir sulfate corresponding to 150, 200 and 300 mg of atazanavir free base.

What the important non-medicinal ingredients are :

The non-medicinal ingredients include crospovidone, lactose monohydrate, and magnesium stearate.

What dosage forms it comes in :

Capsules for oral use.

WARNINGS AND PRECAUTIONS

BEFORE you use REYATAZ, talk to your doctor or pharmacist :

- If you suffer from liver disease because the dose of REYATAZ may need to be reduced.
- If you are intolerant to lactose because REYATAZ capsules contain small quantities of lactose. These small quantities are unlikely to induce specific symptoms of intolerance.
- If you are pregnant or planning to become pregnant, or breast feeding.
- If you have a heart problem.

Discuss the use of REYATAZ with your doctor because some conditions may require special attention before or while taking this medicine. In particular because :

- There have been changes in the way the heart beats (heart rhythm changes). Call your healthcare provider right away if you get dizzy or lightheaded. These could be symptoms of a heart problem.
- There is a possibility of increased bleeding if you have a type A or B haemophilia.
- There have been reports of increased sugar in the blood and development or worsening of diabetes mellitus when using protease inhibitors.
- Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck, breasts and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause or long-term health effects of these conditions are not known at this time.
- There have been reports of kidney stones. If you develop signs or symptoms of kidney stones (pain in your side, blood in your urine, pain when you urinate) call your healthcare provider right away.

See section on SIDE EFFECTS, for more information.

Can I take REYATAZ during pregnancy and breast-feeding?

Pregnant and breast-feeding mothers should not take REYATAZ unless specifically directed by their doctor.

It is not known if REYATAZ can harm your unborn baby.

Pregnant women have experienced serious side effects when taking REYATAZ with other HIV medicines called nucleoside analogues.

There have been reports of a condition called lactic acidosis syndrome (excess of lactic acid in the blood) with the use of REYATAZ in combination with other medicines used to treat HIV infection. This serious side effect has occasionally been fatal. Lactic acidosis occurs more often in women, particularly if very overweight. Frequent nausea, vomiting and stomach pain might indicate the development of lactic acidosis. Ask your doctor for advice if you get pregnant or think you are pregnant or if you want to breast-feed. It is recommended that women infected by HIV do not breast-feed in order to avoid transmission of HIV to their infant through the breast milk.

Can REYATAZ be used in children?

REYATAZ capsules can be used in children 6 years of age and older. Dosing recommendations are not available for children from 3 months to less than 6 years of age. REYATAZ should not be used in babies under the age of 3 months.

INTERACTIONS WITH THIS MEDICATION

REYATAZ may interact with other drugs, including those you take without a prescription. You must tell your doctor or pharmacist about all drugs, including prescription and non-prescription drugs, herbal products and supplements and street drugs, you are taking or planning to take before you take REYATAZ. REYATAZ should be taken in combination with other antiretroviral agents. Clinical trials have found that combination antiviral therapy is more effective than one drug alone at reducing the amount of HIV in the blood and at reducing the development of resistance.

REYATAZ should not be taken with indinavir (CRIXIVAN[®]) as both REYATAZ and CRIXIVAN[®] sometimes cause increased levels of bilirubin in the blood. (Increased levels of bilirubin can cause yellowing of the skin and the white part of the eyes).

Please see section “When it should not be used”.

If you are taking didanosine (VIDEX[®]) buffered tablets or antacids, take REYATAZ with a meal one

hour after or more than two hours before you take these medicines. Taking them together causes lower amounts of REYATAZ in the blood making it less effective.

The following medicines may require your healthcare provider to either monitor your therapy more closely or to change the dose or dose schedule of either REYATAZ or the other medicine:

- The anticoagulant warfarin (COUMADIN^{*}).
- Corticosteroids, given by nose or inhaled, such as fluticasone propionate (ADVAIR^{*}, FLONASE^{*} or FLOVENT^{*}). Your doctor may choose not to keep you on fluticasone, especially if you are also taking ritonavir (KALETRA^{*}, NORVIR^{*}).
- Medicines to prevent organ transplant rejection: cyclosporine (SANDIMMUNE^{*}, NEORAL^{*}), tacrolimus (PROGRAF^{*}) and sirolimus (RAPAMUNE^{*}).
- Medicines for abnormal heart rhythm: lidocaine and quinidine (also known as BIQUIN^{*}), amiodarone (CORDARONE^{*}).
- The antidepressant trazodone (DESYREL^{*}).
- Tricyclic antidepressant such as amitriptyline (ELAVIL^{*}), desipramine, imipramine (TOFRANIL^{*}).
- Rifabutin (MYCOBUTIN^{*})
- Calcium channel blockers such as diltiazem (CARDIZEM^{*} or TIAZAC^{*}), felodipine (PLENDIL^{*}), verapamil (COVERA-HS^{*} or ISOPTIN SR^{*}).
- Oral contraceptives; REYATAZ may affect the safety and effectiveness of hormonal contraceptives such as birth control pills. **Talk to your healthcare provider about choosing an effective method of contraception.** Hormonal contraceptives do not prevent the spread of HIV to others.
- Stomach acid reducing agents (eg, famotidine, also known as PEPCID AC^{*}).
- Proton-pump inhibitors used for indigestion, heart burn or ulcers (ex. omeprazole, also known as LOSEC^{*}).
- The antifungals ketoconazole (NIZORAL^{*}) and itraconazole (SPORANOX^{*}) if you are taking REYATAZ with ritonavir.
- efavirenz
- midazolam (when injected)
- Atorvastatin (LIPITOR^{*}); there is an increased chance of serious side effects if you take REYATAZ with this cholesterol-lowering medicine.
- Sildenafil (VIAGRA^{*}), tadalafil (CIALIS^{*}), or vardenafil (LEVITRA^{*}): Before you take sildenafil, tadalafil or vardenafil with REYATAZ, talk to your doctor about possible drug interactions and side

- effects. Your doctor may lower your dose of sildenafil or tadalafil if you are taking REYATAZ. Vardenafil should not be co-administered with REYATAZ. If you take sildenafil or tadalafil and REYATAZ together, you may be at increased risk of side effects of sildenafil or tadalafil such as low blood pressure, visual changes, and penile erection lasting more than 4 hours. If you experience any of these side effects you should seek immediate medical assistance.
- Medicine to treat opioid dependence: buprenorphine (SUBOXONE^{*}).
 - The antibiotic clarithromycin (BIAXIN^{*}).

Other medicines may interact with REYATAZ. Remember to tell your healthcare provider all the medicines (prescription, non-prescription) and herbal supplements you are taking or planning to take.

PROPER USE OF THIS MEDICATION

Usual dose :

For adults, who have never taken anti-HIV medicines before, the recommended dose of REYATAZ is

- 300 mg (one 300-mg capsule or two 150-mg capsules) once daily taken with ritonavir 100 mg once daily taken with food.

OR

- 400 mg (two 200-mg capsules), or as prescribed by physician, once a day with food (without ritonavir).

For adults who have taken anti-HIV medicines in the past, the usual dose is

- 300 mg (one 300-mg capsule or two 150-mg capsules) once daily taken with ritonavir 100 mg once daily taken with food.

For children from 6 to 18 years of age, the recommended dose is based on weight. Your child's physician will provide you with the correct dosing instructions. **Do not exceed the adult dose.**

It is important that you take REYATAZ with food to achieve higher, more consistent REYATAZ levels. REYATAZ capsules should not be opened, they should be swallowed whole with water.

REYATAZ must be taken every day exactly as your doctor prescribes because it gives you the best chance to slow down resistance to the medicine. Therefore do not change or stop your daily dose of REYATAZ without first asking your doctor.

REYATAZ should always be taken with other antiretrovirals.

REYATAZ should be taken at about the same time each day with a meal.

If a side effect prevents you from taking REYATAZ as directed, tell your doctor right away.

Always keep REYATAZ on hand so you don't run out. When you travel or need to stay in the hospital, make sure you will have enough REYATAZ to last until you can get a new supply.

Overdose :

If you have accidentally taken too much REYATAZ, you should contact your doctor, pharmacist or local poison control centre and ask for their advice. If you cannot reach them, go to the hospital with this medicine and any other medicines you are taking.

Missed Dose :

It is important to take the daily dose prescribed by your doctor to ensure that you get maximum benefit. If you forget to take a dose, take the dose you missed as soon as possible with some food, and then return to your normal schedule. However, if a dose is skipped, do not double the next dose. Continue as normal with your next dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, REYATAZ can have side effects.

When treating HIV infection, it is not always easy to tell what side effects are caused by REYATAZ, by the other medicines you take, or by the HIV infection itself. For this reason, it is important that you inform your doctor of any change in your health.

Some of the most common side effects of REYATAZ taken with other anti-HIV medicines include nausea, headache, rash, abdominal pain, and yellowing of the skin or whites of the eyes.

REYATAZ can cause the following side effects :

- **Yellowing of the skin or eyes.** These effects may be due to increases in bilirubin levels in the blood. Call your healthcare provider if your skin or the white part of your eyes turn yellow. Although these effects may not be damaging to your liver,

skin, or eyes, it is important to tell your healthcare provider promptly if they occur.

- **If you have liver disease** including hepatitis B or C, your liver disease may get worse when you take anti-HIV medicines like REYATAZ.
- **Rash.** Rash (redness and itching) sometimes occurs in patients taking REYATAZ, most often in the first few weeks after the medicine is started. Tell your healthcare provider if rash occurs. If severe rash occurs, seek immediate medical attention.
- **Diabetes and high blood sugar (hyperglycemia)** sometimes happen in patients taking protease inhibitor medicines like REYATAZ. Some patients had diabetes before taking protease inhibitors while others did not. Some patients may need changes in their diabetes medicine.
- **A change in the way your heart beats (heart rhythm change).** Call your healthcare provider right away if you get dizzy or lightheaded. These could be symptoms of a heart problem.
- **Gallbladder disorders** (which may include gallstones and gallbladder inflammation) have been reported in patients taking REYATAZ.

Other side effects may occur with REYATAZ. Ask your doctor or pharmacist for more information about side effects. Inform your doctor promptly about these or any other symptoms. If the condition persists or worsens, seek medical attention.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

This summary does not include everything there is to know about REYATAZ. If you have questions or concerns, or want more information about REYATAZ, your physician and pharmacist have the complete prescribing information upon which this leaflet was based. You may want to read it and discuss it with your doctor or other healthcare professional. Remember, no written summary can replace careful discussion with your doctor.

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|--|--|-------------------------------------|--------------|---|
| Symptom/effect | | Talk with your doctor or pharmacist | | Stop taking drug & call Your doctor or pharmacist |
| | | Only if severe | In all cases | |
| Common | Rash (redness & itching) | ✓ | - | - |
| | Yellowing of the skin or eyes | - | ✓ | - |
| Uncommon | Frequent nausea, vomiting & stomach pain (occurs more often in women, particularly if very overweight) | - | ✓ | - |
| Postmarket- ing cases of unknown frequency | Diabetes and high blood sugar | - | ✓ | - |
| Postmarket- ing cases of unknown frequency | Heart rhythms changes | - | ✓ | - |
| Postmarket- ing cases of unknown frequency | Gall bladder disorders | ✓ | - | - |
| Postmarket- ing cases of unknown frequency | Kidney stones (pain in your side, blood in your urine, pain when you urinate) | - | - | ✓ |

This is not a complete list of side effects. If you have any unexpected effects while taking REYATAZ, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach of children.
Do not store above 25°C. Protect from moisture.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Bristol-Myers Squibb Canada, at :
1-866-463-6267.

This leaflet was prepared by Bristol-Myers Squibb Canada.

Last revised : 06 November 2009

REYATAZ*, VIDEX*, COUMADIN* and DESYREL* are trademarks of Bristol-Myers Squibb Company used under licence by Bristol-Myers Squibb Canada. Other brands listed are trademarks of their respective owners and are not trademarks of Bristol-Myers Squibb Company.