Attachment 1: Product information for AusPAR Reyataz Atazanavir Bristol-Myers Squibb Australian Pty. Ltd. PM-2012-01034-3-2 Final 21 October 2013. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

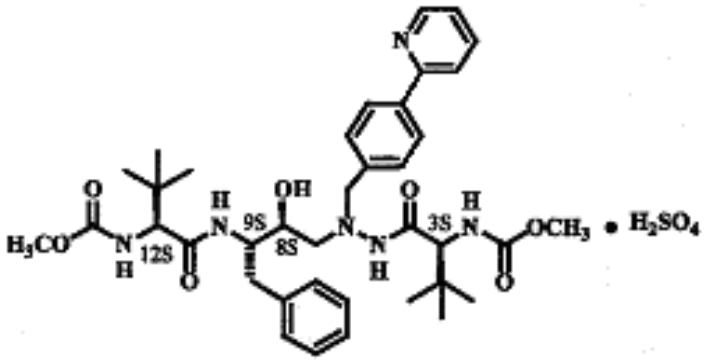
REYATAZâ

(atazanavir sulfate)

CAPSULES

NAME OF THE MEDICINE

Chemically atazanavir sulfate is (3*S*,8*S*,9*S*,12*S*)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-phenylmethyl-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate (1:1), it is an azapeptide HIV-1 protease inhibitor with the following structure:



CAS Registry No: 229975-97-7
Molecular formula: $C_{38}H_{52}N_6O_7.H_2SO_4$
Molecular mass: 802.9 (sulfate); 704.9 (free base).

DESCRIPTION

Atazanavir sulfate is an off-white to pale yellow crystalline powder.

Reyataz capsules contain atazanavir sulfate equivalent to 100 mg, 150 mg or 200 mg or 300mg atazanavir. Inactive ingredients are lactose, crospovidone, and magnesium stearate. The capsule shells contain gelatin and titanium dioxide, and are coloured with Indigo carmine CI73015 the 300mg capsule shell also contains red iron oxide, black iron oxide and yellow iron oxide.

PHARMACOLOGY

Pharmacokinetics:
The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected adult and paediatric patients.

Healthy adult volunteers and HIV-infected patients
The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients after administration of Reyataz 400 mg once daily and after administration of Reyataz 300 mg with ritonavir 100 mg once daily (see Table 1).

Table 1. Steady-State Pharmacokinetics of Atazanavir in Healthy Adult Subjects or HIV-Infected Adult 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.
Cmax – maximum plasma drug concentration during a dosing interval; Cmin – minimum plasma drugconcentration during a dosing interval; AUC – total area under the plasma drug concentration-time curve; Tmax – time to maximum concentration; T-half – Half life; CV% - percent coefficient of variation; SD - standard deviation.

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

Food effect: Administration of Reyataz with food enhances bioavailability and reduces pharmacokinetic variability. Administration of a single 400 mg dose of Reyataz with a light meal (357 kcal, 8.2 g fat, 10.6 g protein) (i.e., toast with jam, low fat margarine, orange juice and skim milk) resulted in a 70% increase in AUC and a 57% increase in C_{max} compared to the fasting state. Administration of a single 400 mg dose of Reyataz (as two 200 mg capsules)

with a meal high in calories, fat, and protein (721 kcal, 37.3 g fat, 29.4 g protein) resulted in a mean increase in AUC of 35% and no change in C_{max} compared to administration in the fasting state. Administration of Reyataz with either a light meal or a high fat meal decreased the coefficient of variation of AUC and C_{max} approximately one-half compared to the fasting state.

Coadministration of a single 300mg dose of Reyataz and a 100mg dose of ritonavir with a light meal (336 kcal, 5.1 g fat, 9.3 g protein) resulted in a 33% increase in the AUC and a 40% increase in both the C_{max} and the 24-hour concentration of atazanavir relative to the fasting state. Coadministration with a high-fat meal (951 kcal, 54.7 g fat, 35.9 g protein) did not affect the AUC of atazanavir relative to fasting conditions and the C_{max} was within 11% of fasting values. The 24-hour concentration following a high-fat meal was increased by approximately 33% due to delayed absorption; the median T_{max} increased from 2.0 to 5.0 hours. Coadministration of REYATAZ with ritonavir with either a light or a high-fat meal decreased the coefficient of variation of AUC and C_{max} by approximately 25% compared to the fasting state.

Distribution: atazanavir was approximately 86% bound to human serum proteins over a concentration range of 100 to 10,000 ng/ml. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively, at 1,000 ng/ml).

Metabolism: studies in humans and *in vitro* studies using human liver microsomes have demonstrated that atazanavir is principally metabolised 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 and hydrolysis. Two metabolites of atazanavir, possessing no anti-HIV activity, have been detected in the systemic circulation.

Elimination: following a single 400 mg dose of ^{14}C-atazanavir, 79% and 13% of the total radioactivity was recovered in the faeces and urine, respectively. Approximately 26% of the radioactivity in the faeces was due to parent drug, corresponding to 20% of the dose, and 44% of the radioactivity in the urine was due to parent drug, corresponding to 7% of the dose. The mean elimination half-life of atazanavir in healthy volunteers and HIV-infected patients adult patients was approximately 7 hours at steady state following a dose of 400mg daily with a light meal.

Special populations

***Impaired renal function*:** in healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. Reyataz has been studied in adult subjects with severe renal impairment (n=20), including those on haemodialysis, at multiple doses of 400mg 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 haemodialysis (n=10), than in age, weight, and gender matched subjects with normal renal function. Atazanavir was not appreciably cleared during haemodialysis. In a 4-hour dialysis session, 2.1% of the administered dose was removed. When atazanavir was administered either prior

to, or following haemodialysis (n=10), the geometric means for C_{max} were 25% and 37% lower, AUC were 28% and 42% lower, and C_{min} were 43% and 54% lower, respectively, compared to subjects with normal renal function. The mechanism of this decrease is unknown (see DOSAGE and ADMINISTRATION).

***Impaired hepatic function*:** atazanavir is metabolised and eliminated primarily by the liver. Atazanavir has been studied in adult patients with moderate to severe hepatic impairment 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 (see CONTRAINDICATIONS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Age/Gender: a study of the pharmacokinetics of atazanavir was performed in 59 healthy male and female adult subjects (29 young, 30 elderly). There were no clinically significant differences in AUC or Cmax based on age or gender in this study.

Paediatric Patient Pharmacokinetics

Children and adolescents (6 – 18 years of age):

The pharmacokinetic data from paediatric patients receiving REYATAZ Capsules with ritonavir based on body surface area are presented in Table 2.

Table 2: Steady-State Pharmacokinetics of Atazanavir with ritonavir in HIV-Infected Paediatric 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 [min-max]	200 [150–400]	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)

Table 3 presents the pharmacokinetics for atazanavir at steady state in paediatric patients predicted by a pharmacokinetic model, summarised by weight ranges that correspond to the recommended doses (see DOSAGE AND ADMINISTRATION: Recommended Paediatric Dosing).

Table 3. Predicted Steady-State Pharmacokinetics of Atazanavir (Capsule Formulation) with Ritonavir in HIV-Infected Paediatric Patients

Parameter	**atazanavir 150 mg/ ritonavir 100 mg Body weight (range in kg) 15 - <20**	**atazanavir 200 mg/ ritonavir 100 mg Body weight (range in kg) 20 - <40**	**atazanavir 300 mg/ ritonavir 100 mg Body weight (range in kg) ≥40**
C_{max} ng/mL Geometric Mean (CV%)	5213 (78.7%)	4954 (81.7%)	5040 (84.6%)
AUC ng•h/mL Geometric Mean (CV%)	42902 (77.0%)	42999 (78.5%)	46777 (80.6%)

C_{min} ng/mL Geometric Mean (CV%)	504 (99.5%)	562 (98.9%)	691 (98.5%)

Atazanavir exposures were predicted based on observed data in 167 paediatric patients and 60 adult patients treated with atazanavir with or without ritonavir. See PRECAUTIONS regarding inter-patient variability in atazanavir exposure parameters.

Children less than 6 years of age

There are no dosing recommendations for Reyataz in paediatric patients less than 8 years of age as there is insufficient data to recommend a dose. Reyataz should not be administered to paediatric patients below 3 months of age due to the risk of kernicterus.

Pregnancy

The pharmacokinetic data from HIV-infected pregnant women receiving Reyataz capsules with ritonavir are presented in Table 4.

Table 4. Steady-State Pharmacokinetics of Atazanavir with Ritonavir in HIV-Infected Pregnant Women in the Fed State

	atazanavir 300mg with ritonavir 100 mg			
Pharmacokinetic Parameter	**2nd Trimester (n=9)**	**3rd Trimester (n=20)**	**Historical Non-Pregnant[a] (n=23)**	**Postpartum[b] (n=36)**
C_{max} ng/mL Geometric Mean (CV%)	3729.09 (39)	3291.46 (48)	4485.18 (32)	5649.10 (31)
AUC ng•h/mL Geometric Mean (CV%)	34399.1 (37)	34251.5 (43)	43888.06 (42)	60532.7 (33)
C_{min} ng/mL[c] Geometric Mean (CV%)	663.78 (36)	668.48 (50)	661.50 (67)	1420.64 (47)

[a]Atazanavir peak concentration and AUCs were found to be approximately 17-27% lower during pregnancy relative to those observed historically in HIV-infected, non-pregnant patients. Atazanavir plasma trough concentrations were similar when compared to those observed historically in HIV-infected, non-pregnant patients.

[b]Atazanavir peak concentrations and AUCs were found to be approximately 26-40% higher during postpartum period (4-12 weeks) than those observed historically in HIV-infected, non-pregnant patients. Atazanavir plasma trough concentrations were approximately 2-fold higher during postpartum period when compared to those observed historically in HIV-infected, non-pregnant patients.

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

Drug interactions:

Atazanavir is metabolized in the liver by CYP3A. Atazanavir inhibits CYP3A4 and UGT1A1 at clinically relevant concentrations with K_i of 2.35 μM (CYP3A4 isoform) and 1.9 μM, respectively. 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 1.0mM. Atazanavir is also a direct inhibitor for UGT1A1 (K_i=1.9mM) and CYP2C8 (K_i=2.1mM). Reyataz should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A, or UGT1A1 (see also CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES**).**

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 indicies (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 CYP3A. In a multiple-dose study, Reyataz decreased the urinary ratio of endogenous 6b-OH cortisol to cortisol versus baseline, indicating that CYP3A production was not induced.

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

Drug interaction studies were performed with Reyataz and other drugs likely to be coadministered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of Reyataz on the AUC, C_{max}, and C_{min} are summarized in Tables 5 and 6. For information regarding clinical recommendations, see CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES.

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

Coadministered Drug	Coadministered Drug Dose/Schedule	Reyataz Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}
atenolol	50 mg once daily, d 7-11 (n=19) and d 19-23	400 mg once daily, d 1-11 (n=19)	1.00 (0.89, 1.12)	0.93 (0.85, 1.01)	0.74 (0.65, 0.86)
clarithromycin	500 mg BID, d 7-10 (n=29) and d 18-21	400 mg once daily, d 1-10 (n=29)	1.06 (0.93, 1.20)	1.28 (1.16, 1.43)	1.91 (1.66, 2.21)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)[b]	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose (n=31)	400 mg x 1 dose simultaneously with ddI and d4T (n=31)	0.11 (0.06, 0.18)	0.13 (0.08, 0.21)	0.16 (0.10, 0.27)
	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose (n=32)	400 mg x 1 dose 1 hour after ddI + d4T (n=32)	1.12 (0.67, 1.18)	1.03 (0.64, 1.67)	1.03 (0.61, 1.73)
didanosine (ddI) (enteric-coated capsules)[c]	400mg d 8 (fed) (n=34) 400mg d 19 (fed) (n=31)	400 mg once daily d 2-8 (n=34) 300mg/ritonavir 100mg once daily d 9-19 (n=31)	1.03 (0.93, 1.14) 1.04 (1.01, 1.07)	0.99 (0.91, 1.09) 1.00 (0.96, 1.03)	0.98 (0.89, 1.08 0.87 (0.82, 0.92)
diltiazem	180 mg once daily, d 7-11 (n=30) and d 19-23	400 mg once daily, d 1-11 (n=30)	1.04 (0.96, 1.11)	1.00 (0.95, 1.05)	0.98 (0.90, 1.07)
efavirenz	600 mg once daily, d 7-20 (n=27)	400 mg once daily, d 1-20 (n=27)	0.41 (0.33, 0.51)	0.26 (0.22, 0.32)	0.07 (0.05, 0.10)
	600 mg once daily d 7-20 (n=13)	400 mg once daily, d 1-6 (n=23) then 300 mg/ritonavir 100 mg once daily, 2 h before efavirenz, d 7-20 (n=13)	1.14 (0.83, 1.58)	1.39 (1.02, 1.88)	1.48 (1.24, 1.76)
	600 mg once daily, d 11–24 (pm) (n=14)	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) (n=14)	1.17 (1.08, 1.27)	1.00 (0.91, 1.10)	0.58 (0.49, 0.69)

Attachment 1: Product information for AusPAR Reyataz Atazanavir Bristol-Myers Squibb Australian Pty. Ltd. PM-2012-01034-3-2 Final 21 October 2013. This Product Information was approved at the time this AusPAR was published.

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

Coadministered Drug	Coadministered Drug Dose/Schedule	Reyataz Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}
famotidine	40 mg BID d 7-12 (n=15)	400 mg once daily d 1-6 (n=45), d 7-12 (simultaneous administration) (n=15)	0.53 (0.34, 0.82)	0.59 (0.40, 0.87)	0.58 (0.37, 0.89)
	40 mg BID d 7-12 (n=14)	400 mg once daily (pm) d 1-6 (n=45), d 7-12 (10 hr after, 2 hr before famotidine) (n=14)	1.08 (0.82, 1.41)	0.95 (0.74, 1.21)	0.79 (0.06, 1.04)
	40 mg BID d 11-20 (n=14)[d]	300 mg once daily/ ritonavir 100mg once daily d 1- 10 (n=46), d11-20[d] (simultaneous administration) (n=14)	0.86 (0.79, 0.94)	0.82 (0.75, 0.89)	0.72 (0.64, 0.81)
	20mg BID, d 11-17 (n=18)	300mg once daily/ritonavir 100mg once daily/tenofovir 300mg once daily, d 1-10 (am) (n=39), d 11-17 (am) simultaneous administration with am famotidine) (n=18) [e,f]	0.91 (0.84, 0.99)	0.90 (0.82, 0.98)	0.81 (0.69, 0.94)
	40mg once daily (pm), d18-24 (n=20)	300mg once daily/ritonavir 100mg once daily/tenofovir 300mg once daily d 1-10 (am) (n=39), d 18-24 (am) (12 h after pm famotidine) (n=20) [f]	0.89 (0.81, 0.97)	0.88 (0.80, 0.96)	0.77 (0.63, 0.93)
	40mg BID, d 18-24 (n=18	300mg once daily/ritonavir 100mg once daily/tenofovir 300mg once daily, d 1-10 (am) (n=39), d 18-24 (am) (10 h after pm famotidine and 2 h before am famotidine) (n=18) [f]	0.74 (0.66, 0.84)	0.79 (0.70, 0.88)	0.72 (0.63, 0.83)
	40mg BID d 11-20 (n=15)	300mg once daily/ritonavir 100mg once daily, d 1-10 (am) (n=46), then 400mg once daily/ritonavir 100 mg once daily, d 11-20 (am) (n=15)	1.02 (0.87, 1.18)	1.03 (0.86, 1.22)	0.86 (0.68, 1.08)

Attachment 1: Product information for AusPAR Reyataz Atazanavir Bristol-Myers Squibb Australian Pty. Ltd. PM-2012-01034-3-2 Final 21 October 2013. This Product Information was approved at the time this AusPAR was published.

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

Coadministered Drug	Coadministered Drug Dose/Schedule	Reyataz Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}
fluconazole	200 mg once daily, d 11–20 (n=29)	300 mg once daily/ritonavir 100 mg once daily, d 1–10, then 300 mg once daily/ritonavir 100 mg one daily, d 11–20 (n=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 (n=14)	400 mg once daily, d 1-13 (n=14)	0.99 (0.77, 1.28)	1.10 (0.89, 1.37)	1.03 (0.53, 2.01)
nevirapine[g,h]	200 mg BID, d 1–23 (n=23)	300 mg once daily/ritonavir 100 mg once daily , d 4–13 (n=23), then 400 mg once daily/ ritonavir 100 mg once daily, d 14–23, (n=23 [i])	0.72 (0.60, 0.86)	0.58 (0.48, 0.71)	0.28 (0.20, 0.40)
			1.02 (0.85, 1.24)	0.81 (0.65, 1.02)	0.41 (0.27, 0.60)
omeprazole	40 mg once daily d 7-12 (n=16)[j]	400 mg once daily d 1-6 (n=48), d 7-12 (n=16)	0.04 (0.04, 0.05	0.06 (0.05, 0.07)	0.05 (0.03, 0.07)
	40 mg once daily d 11-20 (n=15)[j]	300 mg once daily/ ritonavir 100 mg once daily d 1-20 (n=15)	0.28 (0.24, 0.32)	0.24 (0.21, 0.27)	0.22 (0.19, 0.26)
	20mg once daily, d17-23 (am) (n=13)	300mg once daily/ritonavir 100mg once daily, d7-16 (pm) (n=27), d 17-23 (pm) (n=13) [k,l]	0.61 (0.46, 0.81)	0.58 (0.44, 0.75)	0.54 (0.41, 0.71)
	20mg once daily, d 17-23 (am) (n=14)	300mg once daily/ritonavir 100mg once daily, d 7-16 (am) (n=27), then 400mg once daily/ritonavir 100mg once daily, d 17-23 (am) (n=14) [m,n]	0.69 (0.58, 0.83)	0.70 (0.57, 0.86)	0.69 (0.54, 0.88)
rifabutin	150 mg once daily, d 15-28 (n=7)	400 mg once daily, d 1-28 (n=7)	1.34 (1.14, 1.59)	1.15 (0.98, 1.34)	1.13 (0.68, 1.87)

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

Coadministered Drug	Coadministered Drug Dose/Schedule	Reyataz Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}
rifampin	600 mg once daily d 17-26 (n=16)	300 mg once daily/ ritonavir 100 mg once daily d 7-16 (n=48), d 17-26 (n=16)	0.47 (0.41, 0.53)	0.28 (0.25, 0.32)	0.02 (0.02, 0.03)
ritonavir[o]	100 mg once daily, d 11-20 (n=28)	300 mg once daily, d 1-20 (n=28)	1.86 (1.69, 2.05)	3.38 (3.13, 3.63)	11.89 (10.23, 13.82)
tenofovir [p,q]	300 mg once daily with food d 9-16 (n=34)	400 mg once daily with food d 2-16 (n=34)	0.79 (0.73, 0.86)	0.75 (0.70, 0.81)	0.60 (0.52, 0.68)
tenofovir[p,q]	tenofovir 300 mg once daily d 15-42 (n=10)	300 mg once daily with ritonavir 100 mg once daily d 1-42 (n=10)	0.72 [r] (0.50, 1.05)	0.75 [r] (0.58, 0.97)	0.77 [r] (0.54, 1.10)
voriconazole[s] (subjects with at least one functional CYP2C19 allele)	200 mg BID, d2-3, 22-30; 400 mg BID, d 1, 21 (n = 20)	300 mg/ritonavir 100 mg QD, d 11-30 (n = 20)	0.87 (0.80, 0.96)	0.88 (0.82, 0.95)	0.80 (0.72, 0.90)
voriconazole[s] (subjects without a functional CYP2C19 allele)	50 mg BID, d 2-3, 22-30; 100 mg BID, d 1, 21 (n = 8)	300 mg/ritonavir 100 mg QD, d 11-30 (n = 8)	0.81 (0.66, 1.00)	0.80 (0.65, 0.97)	0.69 (0.54, 0.87)

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

[b] All drugs were given under fasted conditions.

[c] 400mg didanosine enteric-coated capsules and Reyataz were administered together with food on days 8 and 19.

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

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

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

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

Attachment 1: Product information for AusPAR Reyataz Atazanavir Bristol-Myers Squibb Australian Pty. Ltd. PM-2012-01034-3-2 Final 21 October 2013. This Product Information was approved at the time this AusPAR was published.

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

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

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

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

[l] Reyataz 300mg plus ritonavir 100mg once daily separated by 12 hours from omeprazole 20mg 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 400mg once daily in the absence of omeprazole (study days 1-6).

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

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

[o] 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.

[p] tenofovir disoproxil fumarate

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

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

[s] Refer also to Table 12 (INTERACTIONS WITH OTHER MEDICINES)

AUC = area under the [concentration-time] curve; BID = twice daily; Cmax = maximum plasma concentration; Cmin = minimum plasma concentration; d = day; h = hour;
mg = milligram; n = number.

Attachment 1: Product information for AusPAR Reyataz Atazanavir Bristol-Myers Squibb Australian Pty. Ltd. PM-2012-01034-3-2 Final 21 October 2013. This Product Information was approved at the time this AusPAR was published.

Table 6. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Reyataz[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	Reyataz Dose/ Schedule	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Reyataz; No effect = 1.00		
			C_{max}	AUC	C_{min}
paracetamol	1 gm BID, d 1-20 (n=10)	300 mg once daily/ ritonavir 100 mg once daily, d 11-20 (n=10)	0.87 (0.77, 0.99)	0.97 (0.91, 1.03)	1.26 (1.08, 1.46)
atenolol	50 mg once daily, d 7-11 (n=19) and d 19-23	400 mg once daily, d 1-11 (n=19)	1.34 (1.26, 1.42)	1.25 (1.16, 1.34)	1.02 (0.88, 1.19)
clarithromycin	500 mg BID, d 7-10 (n=21) and d 18-21	400 mg once daily, d 1-10 (n=21)	1.50 (1.32, 1.71) OH-clarithromycin: 0.28 (0.24, 0.33)	1.94 (1.75, 2.16) OH-clarithromycin: 0.30 (0.26, 0.34)	0.38 (0.35, 0.43) OH-clarithromycin: 2.64 (2.36, 2.94)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)[b]	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose (n=31)	400 mg x 1 dose simultaneous with ddI and d4T (n=31)	ddI: 0.92 (0.84, 1.02) d4T: 1.08 (0.96, 1.22)	ddI: 0.98 (0.92, 1.05) d4T: 1.00 (0.97, 1.03)	NA d4T: 1.04 (0.94, 1.16)
didanosine enteric coated capsules[c]	400 mg d 1 (fasted), 8 (fed) (n=34)	400 mg once daily d 2-8 (n=34)	0.64 (0.55, 0.74)	0.66 (0.60, 0.74)	1.13 (0.91, 1.41)
	400mg d 1 (fasted) 19 (fed) (n=31)	300 mg once daily/ ritonavir 100mg once daily d 9-19 (n=31)	0.62 (0.52, 0.74)	0.66 (0.59, 0.73)	1.25 (0.92, 1.69)
diltiazem	180 mg once daily, d 7-11 (n=28) and d 19-23	400 mg once daily, d 1-11 (n=28)	1.98 (1.78, 2.19) desacetyl-diltiazem: 2.72 (2.44, 3.03)	2.25 (2.09, 2.16) desacetyl-diltiazem: 2.65 (2.45, 2.87)	0.41 (0.37, 0.47) desacetyl-diltiazem: 0.45 (0.41, 0.49)
ethinyl estradiol & norethindrone	Ortho-NovumÒ 7/7/7 once daily, d 1-29 (n=19)	400 mg once daily, d 16-29 (n=19)	ethinyl estradiol: 1.15 (0.99, 1.32) norethindrone: 1.67 (1.42, 1.96)	ethinyl estradiol: 1.48 (1.31, 1.68) norethindrone: 2.10 (1.68, 2.62)	ethinyl estradiol: 1.91 (1.57, 2.33) norethindrone: 3.62 (2.57, 5.09)
fluconazole	200 mg once daily, d 1–10 (n=11) and 200mg once daily, d 11-20 (n=29)	300 mg once daily/ritonavir 100 mg once daily, d 11–20 (n=29)	1.05 (0.99, 1.10)	1.08 (1.02, 1.15)	1.07 (1.00, 1.15)

Attachment 1: Product information for AusPAR Reyataz Atazanavir Bristol-Myers Squibb Australian Pty. Ltd. PM-2012-01034-3-2 Final 21 October 2013. This Product Information was approved at the time this AusPAR was published.

Table 6. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Reyataz[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	Reyataz Dose/ Schedule	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Reyataz; No effect = 1.00		
			C_{max}	AUC	C_{min}
methadone	stable maintenance dose, d 1-15 (n=16)	400 mg once daily d 2-15 (n=16)	(R)-methadone[d] 0.91 (0.84, 1.0) total: 0.85 (0.78, 0.93)	(R)-methadone[d] 1.03 (0.95, 1.10) total: 0.94 (0.87, 1.02)	(R)-methadone[d] 1.11 (1.02, 1.20) total: 1.02 (0.93, 1.12)
Nevirapine[e,f]	200 mg BID, d 1–23 (n=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 (n=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[g]	40mg single dose d 7 and d 20 (n=16)	400 mg once daily d 1-12 (n=16)	1.24 (1.04, 1.47)	1.45 (1.20, 1.76)	N/A
rifabutin	300 mg once daily, d 1-10 then 150 mg once daily, d 11-20 (n=3)	600 mg once daily [h], d 11-20 (n=3)	1.18 (0.94, 1.48) 25-O-desacetyl-rifabutin: 8.20 (5.90, 11.40)	2.10 (1.57, 2.79) 25-O-desacetyl-rifabutin: 22.01 (15.97, 30.34	3.43 (1.98, 5.96) 25-O-desacetyl-rifabutin: 75.6 (30.1, 190.0)
rosiglitazone[i]	4 mg single dose, d 1, 7, 17 (n=14)	400 mg once daily d 2-7, then 300 mg once daily/ ritonavir 100 mg once daily, d 8-17 (n=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)[j]	1200 mg once daily, d 1-13 (n=7)	400 mg once daily, d 7-13 (n=7)	4.39 (3.24, 5.95)	5.49 (4.04, 7.47)	6.86 (5.29, 8.91)
tenofovir[k]	300 mg once daily with food d 9-16 (n=33) and d 24-30 (n=33)	400 mg once daily with food d 2-16 (n=33)	1.14 (1.08, 1.20)	1.24 (1.21, 1.28)	1.22 (1.15, 1.30)
	300mg once daily, d 1-7 (pm) (n=14) d25-34 (pm) (n=12)[k]	300 mg once daily/ritonavir 100mg once daily, d 25-34 (am) (n=12)[k]	1.34 (1.20, 1.51)	1.37 (1.30, 1.45)	1.29 (1.21, 1.36)

Table 6. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Reyataz[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	Reyataz Dose/ Schedule	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Reyataz; No effect = 1.00		
			C_{max}	AUC	C_{min}
voriconazole[l] (subjects with at least one functional CYP2C19 allele)	200 mg BID, d2-3, 22-30; 400 mg BID, d 1, 21 (n = 20)	300 mg/ritonavir 100 mg QD, d 11-30 (n = 20)	0.90 (0.78, 1.04)	0.67 (0.58, 0.78)	0.61 (0.51, 0.72)
voriconazole[l] (subjects without a functional CYP2C19 allele)	50 mg BID, d 2-3, 22-30; 100 mg BID, d 1, 21 (n = 8)	300 mg/ritonavir 100 mg QD, d 11-30 (n = 8)	4.38 (3.55, 5.39)	5.61 (4.51, 6.99)	7.65 (5.71, 10.2)
lamivudine + zidovudine	150 mg lamivudine + 300 mg zidovudine BID, d 1-12 (n=19)	400 mg once daily, d 7-12 (n=19)	lamivudine: 1.04 (0.92, 1.16) zidovudine: 1.05 (0.88, 1.24) zidovudine glucuronide: 0.95 (0.88, 1.02)	lamivudine: 1.03 (0.98, 1.08) zidovudine: 1.05 (0.96, 1.14) zidovudine glucuronide: 1.00 (0.97, 1.03)	lamivudine: 1.12 (1.04, 1.21) zidovudine: 0.69 (0.57, 0.84) zidovudine glucuronide: 0.82 (0.62, 1.08)

[a] Data provided are under fed conditions unless otherwise noted.
[b] All drugs were given under fasted conditions.
[c] 400mg didanosine enteric-coated capsules and Reyataz were administered together with food on Days 8 and 19
[d] (R)-methadone is the active isomer of methadone.
[e] Study was conducted in HIV-infected individuals.
[f] Subjects were treated with nevirapine prior to study entry.
[g] 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.
[h] Not the recommended therapeutic dose of atazanavir.
[i] Rosiglitazone used as a probe substrate for CYP2C8.
[j] The combination of atazanavir and saquinavir 1200 mg once daily produced daily saquinavir exposures similar to the values produced by the standard therapeutic dosing of saquinavir at 1200 mg TID. However, the C_{max} is about 79% higher than that for the standard dosing of saquinavir (soft gelatin capsules) alone at 1200 mg TID.
[k] Administration of tenofovir disproxil fumarate and Reyataz was temporally separated by 12 hours.
[l] Refer also to Table 12 (INTERACTIONS WITH OTHER MEDICINES)

AUC = area under the [concentration-time] curve; BID = twice daily; Cmax = maximum plasma concentration; Cmin = minimum plasma concentration; d = day; h = hour; mg = milligram; n = number.
NA = not available.

Effects on Electrocardiogram:

Concentration- and dose-dependent prolongation of the PR interval in the electrocardiogram has been observed in healthy volunteers receiving atazanavir in a clinical pharmacology study (study 076), in which oral doses of 400mg and 800mg were compared with placebo in 72 healthy subjects. The mean (±SD) maximum change in PR interval from the predose value was 24 (±15) msec following oral dosing with 400mg of atazanavir (n=65) and 60 (±25) msec following oral dosing with 800mg of atazanavir (n=65) compared to 13 (±11) msec following dosing with placebo (n=67). The PR interval prolongations in this study were asymptomatic. There is limited information on the potential for a pharmacodynamic interaction in humans between atazanavir and other drugs that prolong the PR interval of the electrocardiogram. (see PRECAUTIONS). In the placebo-controlled study 076, there was no concentration-dependent effect of atazanavir on the QTc interval (using Fridericia's correction). For HIV-

infected patients in study 045 treated with Reyataz + ritonavir, Reyataz + saquinavir, or lopinavir + ritonavir, each with tenofovir and an NRTI (see PHARMACOLOGY – Clinical Trials), no female patients had a QTc interval >470 msec and two male patients has a QTc interval of 450-500 msec. No patients receiving atazanavir + ritonavir, 2 (2%) patients receiving atazanavir + saquinavir, and 1 (<1%) patient receiving lopinavir + ritonavir had an on-study change in QTc > 60 msec. No atazanavir-treated healthy subject or HIV-infected patient had a QTc interval > 500 msec.

Pharmacological Actions:

Mechanism of action: atazanavir is an azapeptide HIV-1 protease inhibitor. The compound selectively inhibits the virus-specific processing of viral gag-pol proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells.

Antiviral activity in vitro: atazanavir exhibits anti-HIV-1 activity (EC_{50} of 2.6 to 5.3 nM) against a variety of HIV isolates in the absence of human serum. Reyataz administered 400 mg once daily results in a mean (SD) C_{min} of 250 (175) ng/ml. The estimated protein-adjusted (in 40% human serum) C_{min} is approximately 17 to 98 fold higher than a representative EC_{50}. Combinations of atazanavir with stavudine, didanosine, lamivudine, zidovudine, nelfinavir, indinavir, ritonavir, saquinavir, or amprenavir in HIV-infected peripheral blood mononuclear cells yielded additive antiviral effects. Combinations of drug pairs did not result in antagonistic anti-HIV activity or enhanced cytotoxic effects at the highest concentrations used for antiviral evaluation.

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

Cross-resistance: Atazanavir susceptibility was evaluated *in vitro* using a diverse panel of 551 clinical isolates from patients without prior atazanavir exposure. The isolates exhibited resistance to at least one approved protease inhibitor, with resistance defined as ³ 2.5-fold change in EC_{50} relative to a reference strain. Greater than 80% of the isolates resistant to 1 or 2 protease inhibitors (with the majority resistant to nelfinavir) retained susceptibility to atazanavir despite the presence of key mutations (eg, D30N) associated with protease inhibitor resistance. Of 104 isolates displaying nelfinavir-specific resistance, 84 retained susceptibility to atazanavir. There was a clear trend toward decreased atazanavir susceptibility as isolates exhibited resistance to multiple protease inhibitors. Baseline phenotypic and genotypic analyses of clinical isolates from atazanavir clinical trials of protease inhibitor-experienced subjects showed that isolates cross-resistant to multiple protease inhibitors were also highly cross-resistant (61%-95%) to atazanavir. Greater than 90% of the isolates containing mutations I84V or G48V were resistant to atazanavir. Greater than 60% of isolates

containing L90M, A71V/T, M46I, or a change at V82 were resistant to atazanavir, and 38% of isolates containing a D30N mutation in addition to other changes were resistant to atazanavir. Atazanavir-resistant isolates were highly cross-resistant (51%-100%) to other protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). The I50L and I50V substitutions yielded selective resistance to atazanavir and amprenavir, respectively, and did not appear to confer cross-resistance.

Resistance in vivo: Atazanavir-resistant isolates have been obtained from patients experiencing virologic failure on atazanavir therapy.

Clinical studies of treatment-naïve patients receiving Reyataz 400mg without ritonavir:

There were 23 atazanavir-resistant isolates from studies of treatment-naive patients that showed decreases in susceptibility levels from baseline, and all had evidence of emergence of an I50L substitution on atazanavir therapy (after an average of 50 weeks of therapy) often in combination with an A71V mutation. Phenotypic analysis of the isolates containing the signature mutation I50L showed atazanavir-specific resistance, which coincided with increased susceptibility to other protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir).

Clinical studies of treatment-naïve patients receiving Reyataz 300mg with ritonavir 100mg:

48 weeks of treatment

The Phase III Study AI424138 included 440 patients randomized to atazanavir/ritonavir and 443 patients randomized to lopinavir/ritonavir. Genotypic analysis was undertaken on patients with virologic failure defined as viral rebound ³ 400 copies/mL or failure to achieve viral suppression < 400 copies/mL over 48 weeks of treatment or discontinuation due to insufficient viral load response before 48 weeks. Patients with any major protease inhibitor substitutions at amino acid positions 50, 84 and 88 were determined to have resistance to atazanavir/ritonavir. Patients with any major protease inhibitor substitutions at amino acid positions 32, 48 and 82 were determined to have resistance to lopinavir/ritonavir.

For those patients with virologic failure in the first 48 weeks of the study, baseline genotypic analysis was successful for 25 of 27 atazanavir/ritonavir treated patients and 22 of 26 lopinavir/ritonavir treated patients. Paired baseline and on-study genotypic analysis was successful for 17 of 27 atazanavir/ritonavir treated patients and 15 of 26 lopinavir/ritonavir patients. All patients in both arms of the study had baseline PI substitutions. Major PI substitutions were observed at baseline in two patients; both had phenotypic resistance to both atazanavir/ritonavir and lopinavir/ritonavir and both were randomised to the atazanavir/ritonavir arm of the trial.

While on treatment, one patient with major baseline PI substitutions (I54V, V82A, L90M) developed the atazanavir associated major PI substitution 150L. Another atazanavir/ritonavir treated patient with four baseline atazanavir-associated minor PI substitutions (M36I, I62V, A71A/T and I93L) developed phenotypic resistance to atazanavir along with additional

atazanavir-associated minor substitutions (L10L/F, A71I, G73S). This patient also developed resistance to 3TC/FTC, didanosine nelfinavir, indinavir, ritonavir, saquinavir and fosamprenavir while remaining sensitive to all other NRTIs, LPV/RTV, tipranavir and darunavir. The isolate remained phenotypically sensitive to TDF despite the presence of K65K/R, K70K/E and M184V.

96 weeks of treatment

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 of the virologic failure isolates had a 56-fold decreases 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 MI84I (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, 30% (18 of 60) of atazanavir-resistant isolates from studies of treatment-experienced patients treated with atazanavir (n=13) or atazanavir plus ritonavir (n=5) showed evidence of an I50L substitution. The remaining 70% (n=42) of isolates with emerging resistance on atazanavir therapy and all 40 resistant isolates from patients on atazanavir plus saquinavir showed no evidence of the emergence of the I50L substitution. Instead, these isolates displayed decreased susceptibility to multiple protease inhibitors and contained mutations associated with resistance to multiple protease inhibitors. These mutations included I84V, L90M, A71V/T, N88S/D, and M46I, which conferred atazanavir resistance and reduced the clinical response to atazanavir.

Generally, if multiple protease inhibitor mutations were present in the HIV–1 of the patient at baseline, atazanavir resistance developed through mutations associated with resistance to other protease inhibitors instead of the I50L mutation. These mutations conferred high cross-resistance to other protease inhibitors with >90% of the isolates resistant to nelfinavir, indinavir, ritonavir, and saquinavir, 83% resistant to lopinavir, and 65% resistant to amprenavir.

In highly treatment-experienced patients receiving atazanavir 300 mg once daily and ritonavir 100 mg once daily (together with tenofovir and an NRTI), the presence at baseline of fewer than four of the protease inhibitor resistance-associated substitutions 10, 20, 24, 33, 36, 46, 48, 54, 63, 71, 73, 82, 84, or 90 was associated with a greater treatment response at Week 48 (70% with HIV RNA <400 copies/mL) than the presence of four or more such substitutions (28% with HIV RNA <400 copies/mL). Genotypic and/or phenotypic analysis of baseline virus may aid in determining atazanavir susceptibility before initiation of atazanavir therapy

CLINICAL TRIALS:

Adult Patients without prior antiretroviral therapy

Study AI424138 is a 96 week open-label, randomised, multicenter study of 883 HIV-1 infected treatment-naive patients comparing efficacy and safety of atazanavir/ritonavir (ATV/RTV) 300/100 mg once daily with lopinavir/ritonavir (LPV/RTV) 400/100 mg twice daily each in combination with fixed dose tenofovir/emtricitabine 300/200 once daily. The primary objective of the study was to compare the proportion of patients with HIV RNA < 50 copies/mL at week 48 between ATV/RTV and LPV/RTV. Patient demographic and baseline characteristics were well matched between treatment arms. Overall, patients had a mean age of 36 years (range 19-72), 48% were Caucasian, 18% Black, 9% Asian, 24% Hispanic/ mixed race and 69% were male. The overall median baseline plasma CD4+ cell count was 205 cells/mm^3 (range 2 to 810 cells/mm^3) and the overall mean baseline plasma HIV-1 RNA level was 4.94 $\log_{10}$ copies/mL (range: 2.60 to 5.88 $\log_{10}$ copies/mL). Treatment response and outcomes through Week 48 and Week 96 are presented in Table 7.

Table 7. Outcomes of Randomised Treatment Through Week 48 and Week 96 (Study AI424-138)

Outcome	Reyataz 300mg + ritonavir 100mg (once daily) with tenofovir/emtricitabine (once daily)[a] (n=440)		lopinavir 400mg + ritonavir 100mg (twice daily) with tenofovir/emtricitabine (once daily)[a] (n=443)	
	48 Weeks	96 Weeks	48 Weeks	96 Weeks
Responder[b]	78%[c]	74%[d]	76%[c]	68%[d]
Virologic failure[e]	14%	12%	12%	12%
Never suppressed through Week 48 or Week 96	9%	2%	6%	1%
Rebound	4%	8%	4%	9%
Discontinued due to insufficient viral load response	1%	3%	2%	2%
Death	1%	1%	<1%	<1%
Discontinued due to adverse event	2%	3%	3%	5%
Discontinued for other reasons[f]	5%	9%	7%	13%

[a]As a fixed-dose combination: 300mg tenofovir, 200mg emtricitabine once daily.
[b]Patients achieved confirmed HIV RNA <50 copies/mL at week 48 and Week 96 respectively. Roche Amplicor®, v1.5 ultra-sensitive assay.
[c]Pre-specified ITT analysis using as-randomised cohort: ATV/RTV 78% and LPV/RTV 76% [difference estimate: 1.7 (95% confidence interval: -3.8, 7.1)]
[d]Pre-specifed ITT analysis using as-randomised cohort: ATV/RTV 74% and LPV/RTV 68% [difference estimate: 6.1 (95% confidence interval: 0.3, 12.0)].

[e]Includes viral rebound, discontinued due to insufficient viral load response, 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, non-compliance, protocol violation and other reasons.

The proportion of responders among patients with high viral loads (ie, baseline HIV RNA ≥100,000 copies/mL) was comparable for the Reyataz/ritonavir (74% at both 48 weeks and 96 weeks) and lopinavir/ritonavir arms (72% at 48 weeks and 66% at 96 weeks). The median increase from baseline in CD4+ cell count was 191 (48 weeks) and 261 (96 weeks) cells/mm^3 for the Reyataz/ritonavir arm and 200 (48 weeks) and 273 (96 weeks) cells/mm^3 for the lopinavir/ritonavir arm.

Study 034: Reyataz once daily compared to efavirenz once daily, each in combination with fixed-dose lamivudine + zidovudine twice daily. Study AI424-034 was a randomised double-blind, multicenter trial comparing Reyataz (400 mg once daily) to efavirenz (600 mg once daily), each in combination with a fixed-dose combination of zidovudine (300 mg) and lamivudine (150 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/mm^3 (range: 64 to 1424 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.8 $\log_{10}$ copies /mL (range 2.2 to 5.9 $\log_{10}$ copies/mL). Treatment response and outcomes through week 48 are presented in Table 8.

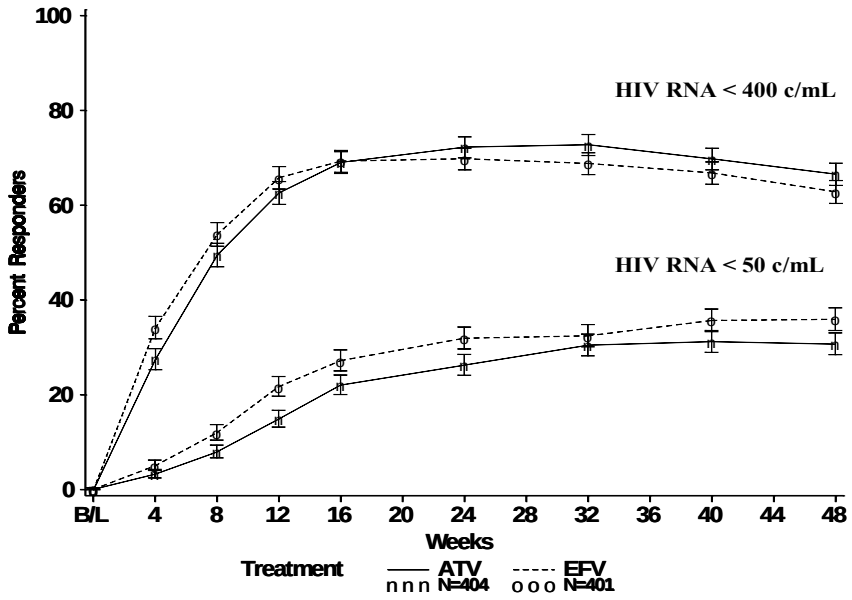
Table 8. Treatment Outcome at Week 48 - Treated Subjects (AI424034)

	Reyataz 400 mg once daily + lamivudine + zidovudine (N = 404)	**Efavirenz 600 mg once daily + lamivudine + zidovudine (N = 401)**
Responder[a]	67% [31%][b]	63% [36%]
Virologic failure[c]	20%	19%
Never suppressed through Week 48	7%	7%
Rebound	13%	11%
Death[d]	0%	<1%
Disease progression	<1%	<1%
Discontinued due to adverse event[e]	6%	9%
Discontinued due to other reason	6%	9%

[a] Responders achieved and maintained to Week 48 2 consecutive HIV RNA < 400 c/mL.
[b] Percentages in brackets represent responders who achieved and maintained to Week 48 at least 2 consecutive HIV RNA < 50 c/mL.
[c] Virologic failure includes rebound (ie, 2 consecutive HIV RNA ³ 400 c/mL or last HIV RNA ³ 400 c/mL) and failing to achieve confirmed HIV RNA < 400 c/mL through Week 48.
[d] All deaths were not considered related to study therapy.
[e] 23 of the 26 subjects on ATV, and 33 of the 36 subjects on EFV who discontinued due to AEs did so for reasons considered related to study drug.

The mean increase from baseline in CD4+ cell count was 176 cells/mm for the Reyataz arm and 160 cells/mm^3 for the efavirenz arm.

Figure 1. Response through 48 weeks for patients treated with Reyataz (ATV) or efavirenz (EFV) in Study 034 (adult patients without prior antiretroviral experience)



Study 008 was a 48-week study of two doses of Reyataz 400 mg once daily (n = 181) or 600 mg once daily (n = 195) compared to nelfinavir 1,250 mg BID (n = 91) in combination with stavudine (40 mg) and lamivudine (150 mg) twice daily. At baseline, mean HIV RNA levels were 4.74 $\log_{10}$ copies/mL and 4.73 $\log_{10}$ copies/mL for the Reyataz 400 mg and nelfinavir groups, respectively. The mean CD4 counts at baseline were 294 cells/mm^3 and 283 cells/mm^3 for the Reyataz 400 mg and nelfinavir groups, respectively. Results from this study are shown in Figure 2 and Table 9.

Figure 2. Observed response through 48 weeks of treatment with Reyataz (ATV) 400 mg or nelfinavir (NFV) in Study 008 (adult patients without prior antiretroviral experience)

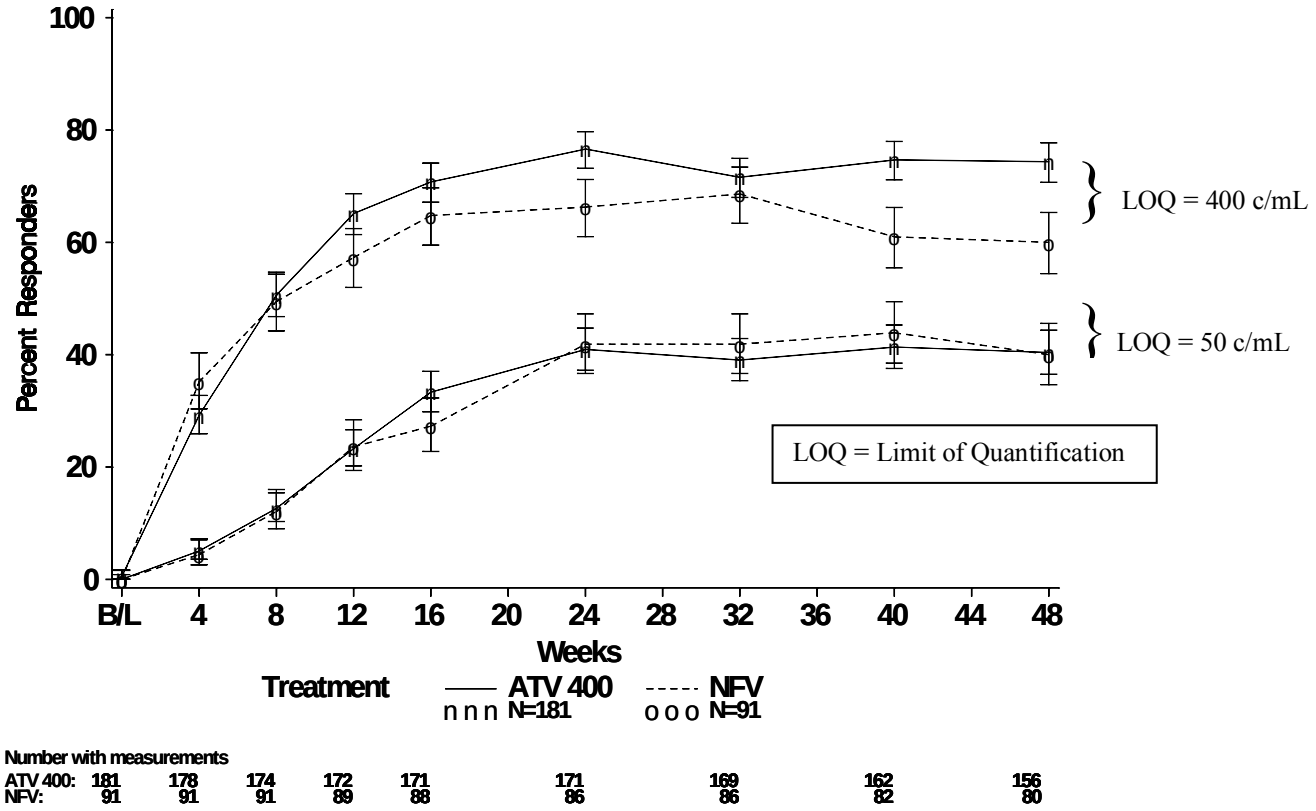


Table 9. Outcomes of Treatment in Study 008 through Week 48 (Adult Patients without Prior Antiretroviral Experience)

	Study 008[a]	
	ATV[b]	**NFV**
Randomised Patients	n = 181	n = 91
Percent with HIV RNA < 400 copies/ml[c]	64%	53%
ATV-Control Treatment Difference (95% CI)	11.0% (-1.1, 23.2)	
Patients Completing 48 Weeks of Treatment	n = 156	n = 80
Percent with HIV RNA < 400 copies/ml[c]	74%	60%
ATV-Control Treatment Difference (95% CI)	13.8% (1.6, 26.1)*	
HIV RNA Mean Change from Baseline (log_{10} copies/mL)[c,d]	-2.51	-2.31
CD4 Mean change from Baseline (cells/mm^3) at Week 48	234	211

*$p < 0.05$
[a] NRTI backbones = 3TC/d4T (study 008)
[b] 400 mg once daily

[c] Roche Ultra Sensitive Amplicor® HIV-1 Monitor assay, version 1.0 or 1.5, as appropriate
[d] Protocol-defined primary outcome measure
ATV – atazanavir, NFV – nelfinavir, CI – 95% confidence intervals

Adult Patients with prior antiretroviral therapy

Study 045 was a randomised, multicenter trial comparing Reyataz (300 mg once daily) with ritonavir (100 mg once daily) to Reyataz (400 mg once daily) with saquinavir soft gelatine capsules (1,200 mg once daily), and to lopinavir + ritonavir (400/100 mg fixed dose combination twice daily, soft gelatine capsules), each in combination with tenofovir and one NRTI, in 347 (of 358 randomised) patients with virologic failure on two or more prior regimens containing at least one PI, NRTI, and NNRTI. For randomised patients, the mean time of prior antiretroviral exposure was 138 weeks for PIs, 280 weeks for NRTIs, and 85 weeks for NNRTIs. The mean baseline CD4 cell count was 336 cells/mm^3 (range: 14 to 1,543 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.4 log_{10} copies/mL (range: 2.6 to 5.9 log_{10} copies/mL).

The primary endpoint for this study is the time-averaged difference in change from baseline in HIV RNA through 24 and 48 weeks.

Through the 48 weeks of treatment, the decreases from baseline in HIV RNA levels (primary endpoint) were 1.93 log_{10} copies/mL for Reyataz + ritonavir and 1.87 log_{10} copies/mL for lopinavir + ritonavir. The primary endpoint was time-averaged difference in HIV RNA levels, Reyataz + ritonavir minus lopinavir + ritonavir (97.5% Confidence Intervals). Reyataz + ritonavir was considered to be non-inferior if the upper 97.5% CI for the TAD was less than 0.5 log_{10} copies/mL.

At 48 weeks, non-inferiority was demonstrated. The time averaged difference in HIV RNA was 0.13 (-0.12; 0.39). The mean decrease from baseline HIV RNA levels for Reyataz + ritonavir was 1.93 log_{10} copies/mL. For lopinavir + ritonavir the decrease was 1.87 log_{10} copies/mL.

At 96 weeks the time-averaged difference in HIV RNA levels was 0.14(-0.13; 0.41). The mean decrease from baseline HIV RNA levels for Reyataz + ritonavir was 2.29 log_{10} copies/mL, and for lopinavir + ritonavir the mean decrease was 2.08 log_{10} copies/mL. Durability of efficacy was demonstrated. Further outcomes of treatment are shown in Table 10.

Table 10. AI424045 Efficacy Endpoints – Adult Randomized Subjects

	Week 48		**Week 96**	
	ATV/RTV N = 120 [a]	**LPV/RTV N = 123**	**ATV/RTV N = 120**	**LPV/RTV N = 123**
HIV RNA < 400 c/mL[b,c]	53%	54%	43%	46%
HIV RNA < 50 c/mL[b,c]	36%	42%	32%	35%
CD4 cell count mean change from baseline (cells/mm^3)	110	121	122	154

Table 10. AI424045 Efficacy Endpoints – Adult Randomized Subjects

	Week 48	Week 96

[a] Reyataz 300 mg with ritonavir 100 mg once daily
[b] Subjects achieved and maintained 2 consecutive HIV RNA < 400 (50) c/mL through the analysis week. Subjects who completed the study were censored in the Week 96 analyses.
[C] Roche Amplicor[O] Ultra Sensitive HIV-1 Monitor Assay; version 1.0 or 1.5 as appropriate.
ATV – atazanavir; LPV – lopinavir; RTV - ritonavir

Response to treatment assessed as HIV RNA change from baseline was analysed by baseline genotypic mutation at 48 weeks. Patients who had four or more of the following mutations 10, 20, 24, 32, 33, 36, 46, 68, 50, 54, 63, 71, 73, 82, 84, 90 were considered. The results significantly favoured the lopinavir + ritonavir arm.

Reyataz plus saquinavir was shown to be inferior to lopinavir plus ritonavir.

Adult patients co-infected with hepatitis B and/or hepatitis C

Analyses have been performed that compare outcomes in study 008 for those patients without baseline evidence of either chronic HBV or HCV infection with those with chronic HBV and/or HCV. Virologic suppression was comparable for the Reyataz 400 mg once daily patients, regardless of chronic hepatitis status. The Week 48 mean change from baseline in HIV RNA for 19 chronic hepatitis positive patients was -2.46 $\log_{10}$ copies/mL, comparable to -2.51 $\log_{10}$ copies/mL for 132 hepatitis negative patients. In study AI424-138, 42 of 61 patients (69%) co-infected with HBV and/or HCV, achieved confirmed HIV RNA <50 copies/mL at week 48. Among hepatitis negative patients, 300 of 378 (79%) achieved confirmed HIV RNA <50 copies/mL at week 48.

Children - PACTG 1020A

Assessment of the pharmacokinetics, safety, tolerability, and efficacy of Reyataz is based on data from the open-label, multicentre clinical trial PACTG 1020A conducted in patients from 3 months to 21 years of age. In this study, 105 patients (43 antiretroviral-naïve and 62 antiretroviral-experienced) received once daily Reyataz, with or without ritonavir, in combination with two NRTIs. Using an ITT analysis, the overall proportions of antiretroviral-naïve and –experienced patients with HIV RNA <400 copies/mL at Week 96 were 51% (22/43) and 34% (21/62), respectively. The overall proportions of antiretroviral-naïve and –experienced patients with HIV RNA <50 copies/mL at Week 96 were 47% (20/43) and 24% (15/62), respectively. The median increase from baseline in absolute CD4 count at 96 weeks of therapy was 335 cells/mm^3 in antiretroviral-naïve patients and 220 cells/mm^3 in antiretroviral-experienced patients.

INDICATIONS

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

This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts from controlled studies (see Clinical Trials).

CONTRAINDICATIONS

Hypersensitivity to atazanavir or to any of the excipients (see list of excipients – page 1).

Patients with severe hepatic insufficiency. Atazanavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment (see DOSAGE and ADMINISTRATION, PRECAUTIONS – for patients with mild to moderate hepatic insufficiency and PHARMACOLOGY - Pharmacokinetics).

Reyataz should not be used in combination with rifampicin.

Reyataz should not be used in combination with simvastatin or lovastatin.

Patients taking Reyataz should not use medicinal products that are substrates of the CYP3A4 isoform of cytochrome P450 and have narrow therapeutic windows. Co-administration may result in competitive inhibition of the metabolism of these medicinal products and create the potential for serious and/or life-threatening adverse events such as cardiac arrhythmia (e.g., cisapride, pimozide), prolonged sedation or respiratory depression (e.g., orally administered midazolam, triazolam), or other events (e.g., ergot derivatives).

Reyataz should not be used in combination with products containing St. John's wort (Hypericum perforatum).

Reyataz should not be used in combination with alfuzosin.

Reyataz should not be used in combination with salmeterol.

Reyataz should not be used with the PDE5 inhibitor sildenafil when used for the treatment of pulmonary arterial hypertension. A safe and effective dose in combination with Reyataz has not been established for sildenafil when used for the treatment of pulmonary arterial hypertension. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, priapism, and syncope). For use of Reyataz with sildenafil (when used for the treatment of erectile dysfunction), please refer to INTERACTIONS WITH OTHER MEDICINES**.**

PRECAUTIONS

Impaired hepatic function

Reyataz should be used with caution in patients with mild to moderate hepatic insufficiency. Atazanavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment (see DOSAGE and ADMINISTRATION, CONTRAINDICATIONS – for patients with severe hepatic insufficiency, and PHARMACOLOGY - Pharmacokinetics). 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.

Hyperbilirubinemia and jaundice

Most patients taking Reyataz experience asymptomatic elevations in indirect (unconjugated) bilirubin, and this may be associated with scleral icterus and jaundice in some patients. This isolated hyperbilirubinemia is reversible upon discontinuation of Reyataz. Hyperbilirubinemia

was related to atazanavir plasma concentrations and not generally associated with elevation of serum transaminases. Preclinical studies suggest that elevation in bilirubin was not associated with haemolysis and was related to inhibition of UDP-glucuronosyl transferase (UGT) by atazanavir. Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies. No long-term safety data are available for patients experiencing persistent elevations in total bilirubin >5 times ULN. Alternative antiretroviral therapy to REYATAZ may be considered if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for patients. Dose reduction of atazanavir is not recommended since long-term efficacy of reduced doses has not been established (see ADVERSE EFFECTS).

Cardiac effects

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

In a pharmacokinetic study between atazanavir 400 mg once daily and diltiazem 180 mg once daily, a CYP3A4 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 electrocardiographic 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 INTERACTIONS WITH OTHER MEDICINES.)

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 (eg, verapamil). (See INTERACTIONS WITH OTHER MEDICINES). 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).

Rash

In controlled clinical trials (n=1597), rash (all grades, regardless of causality) occurred in 21% of patients treated with Reyataz. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of initiating therapy with Reyataz. In most patients, rash resolves within 2 weeks while continuing Reyataz therapy. The discontinuation rate for rash in clinical trials was 0.4%. Reyataz should be discontinued if severe rash develops.

Cases of Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions including drug rash, eosinophilia, and systemic symptoms (DRESS) syndrome have been reported in patients receiving Reyataz. Patients should be advised of the signs and symptoms and monitored closely for skin reactions.

Haemophilia
There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in type A and B haemophiliac patients treated with protease inhibitors. In some patients additional factor VIII was given. In most reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship between protease inhibitor therapy and these events has not been established. Haemophiliac patients should be made aware of the possibility of increased bleeding.

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.

Diabetes mellitus/Hyperglycaemia
New onset diabetes mellitus, hyperglycaemia, and exacerbation of existing diabetes mellitus have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitors. In some of these, the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions, some of which required therapy with agents that have been associated with development of diabetes or hyperglycaemia.

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

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

Lactic acidosis
Cases of lactic acidosis, sometimes fatal, and symptomatic hyperlactatemia have been reported in patients receiving Reyataz in combination with nucleoside analogues, which are known to be associated with increased risk of lactic acidosis. In studies where didanosine and stavudine were administered with atazanavir to patients without prior antiretroviral therapy, lactic acidosis/symptomatic hyperlactatemia was observed in 2.2% of subjects. Female gender and obesity are known risk factors for lactic acidosis. The contribution of Reyataz to the risk of development of lactic acidosis has not been established.

Rare lactose/galactose metabolic conditions
Patients with rare hereditary problems of galactose intolerance, glucose/galactose malabsorption or the Lapp lactase deficiency should not take Reyataz.

Nephrolithiasis and Cholelithiasis
Cases of nephrolithiasis and/or cholelithiasis have been reported during postmarketing surveillance in HIV-infected patients receiving Reyataz therapy. Some patients required hospitalisation for additional management and some had complications. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made. If signs or symptoms of nephrolithiasis and/or cholelithiasis occur, temporary interruption or discontinuation of therapy may be considered.

Carcinogenesis, mutagenesis and impairment of fertility
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 incidences 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 nontumorigenic 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 highest dose are approximately two (males) and six (females) times the exposure in humans given atazanavir 400 mg daily. The increased incidence of benign hepatic adenomas in high-dose female mice was likely the result of increased hepatocellular proliferation secondary to cytotoxic liver changes (single-cell necrosis) and is considered unlikely to have clinical relevance at human therapeutic exposures.

Atazanavir was negative in reverse-mutation assays in bacteria and in *in vivo* micronucleus and *ex vivo* DNA repair tests in rats. In an *in vitro* primary human lymphocyte cytogenetic assay, atazanavir increased the frequency of chromosome aberrations at cytotoxic concentrations in the absence and presence of metabolic activation. However, atazanavir did not induce chromosome aberrations in the absence and presence of metabolic activation at concentrations that were approximately 3 and 22 times the C_{max}, respectively, and 12 and 98 times the average steady-state concentration, respectively, in humans given the recommended dose. In *in vivo* studies in rats, atazanavir did not induce micronuclei in bone

marrow, DNA damage in duodenum (comet assay), or unscheduled DNA repair in liver at plasma and tissue concentrations exceeding those that were clastogenic *in vitro.*

Atazanavir produced no effects on mating, fertility or early embryonic development in rats at doses that provided exposures equivalent to (males) and at least two times (females) exposure in humans given 400mg once daily. Altered oestrus cycles were observed in female rats treated with oral doses resulting in similar estimated systemic drug exposures (AUC).

Use in Pregnancy. Pregnancy Category B2

***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 1800-067-567.

Fetal-Risk Summary

No teratogenic effects were observed in rabbits exposed to a comparable human dose of 400mg daily. No teratogenic effects were observed in rats exposed to the human equivalent of 800mg daily. In the pre- and postnatal development assessment of rats, transient weight loss or suppression of weight gain occurred in the offspring at maternally toxic doses. Offspring were unaffected at a lower dose which produced maternal exposure equivalent to that observed in humans given 400mg twice daily.

Clinical Considerations

Reyataz should be given during pregnancy only after special consideration of the potential benefits and risks (see PRECAUTIONS). In clinical trials, fatal cases of lactic acidosis have occurred in pregnant women receiving Reyataz in combination with nucleoside analogues, which are known to be associated with increased risk of lactic acidosis.

Hyperbilirubinaemia (predominantly unconjugated) occurs frequently during treatment with Reyataz. It is not known whether Reyataz administered to the mother during pregnancy will exacerbate physiological hyperbilirubinaemia and lead to kernicterus in neonates. In the prepartum period, additional monitoring and alternative therapy to Reyataz should be considered.

Human Data

Clinical Trials: In clinical trial AI424-182, Reyataz/ritonavir (300mg/100mg or 400mg/100mg) in combination with zidovudine/lamivudine was administered to 41 pregnant women during the second or third trimester. Among the 39 women who completed the study, 38 women achieved a HIV RNA <50 copies/mL at time of delivery. Six of 20 (30%) women on Reyataz/ritonavir 300mg/100mg and 13 of 21 (62%) women on Reyataz/ritonavir 400mg/100mg experienced Grades 3 to 4 hyperbilirubinemia. There were no cases of lactic acidosis observed in the clinical trial AI424-182.

Forty infants had test results that were negative for HIV-1 DNA at the time of delivery and/or during the first 6 months postpartum. All 40 infants received antiretroviral prophylactic treatment containing zidovudine. Three of 20 infants (15%) born to women treated with Reyataz/ritonavir 300mg/100mg and four of 20 infants (20%) born to women treated with Reyataz/ritonavir 400mg/100mg experienced Grade 3-4 bilirubin. There was no evidence of pathologic jaundice and six of 40 infants in this study received phototherapy for a maximum of 4 days. There were no reported cases of kernicterus in neonates.

Post-Marketing Data: As of December 2009, there were 315 identified cases with prospective first trimester exposure to atazanavir and known outcome in the postmarketing database. There was no association between atazanavir and specific birth defects observed in the postmarketing data.

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

Use in Lactation
It is not known whether atazanavir and/or its metabolites are excreted in human milk. Studies in rats revealed that atazanavir and/or its metabolites are excreted in the milk. Transient reductions in offspring body weights were observed in a pre- and post-natal development study in rats, at a dose that resulted in a systemic drug exposure (AUC) that was approximately 2-fold higher than that expected in humans given the recommended dose.

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.

Use in Children
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 paediatric patients from 3 months to 21 years of age. In this study, 182 paediatric and adolescent patients (83 antiretroviral-naive and 99 antiretroviral-experienced) received once daily REYATAZ, with or without ritonavir, in combination with two NRTIs. Reyataz is recommended for paediatric and adolescent patients from 6 years to 18 years of age (see DOSAGE AND ADMINISTRATION section). There are no dosing recommendations for Reyataz in paediatric patients less than 6 years of age. Reyataz should not be administered to infants below the age of 3 months due to the risk of kernicterus.

Due to potential for inter-patient variability in atazanavir exposures, close monitoring of clinical status for efficacy (HIV RNA viral load and CD4 counts) and signs and symptoms of toxicity is recommended. In clinical trial PACTG 1020A, 50% of patients receiving the recommended capsule dosage regimen required an increase in atazanavir dose to maintain exposure within the target range based on therapeutic drug monitoring. Therefore,

consideration should also be given to using therapeutic drug monitoring when it is available and well-validated.

Asymptomatic PR interval prolongation was more frequent in paediatric patients than in adults. Asymptomatic first-degree (23%) and second-degree (1%) AV block was observed in paediatric patients. Caution should be used with medicinal products known to induce PR prolongations. In paediatric 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. Cardiac monitoring is recommended based on the presence of clinical findings (eg., bradycardia).

INTERACTIONS WITH OTHER MEDICINES

Atazanavir is an inhibitor of CYP3A4 and UGT1A1. Coadministration of Reyataz and drugs primarily metabolized by CYP3A4 (eg, calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants, and phosphodiesterase inhibitors) or UGT1A1 (eg, irinotecan) may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse effects (see Tables 11 and 12). Atazanavir is metabolized in the liver by the cytochrome P450 enzyme system. Coadministration of Reyataz and drugs that induce CYP3A4, such as rifampin, may decrease atazanavir plasma concentrations and reduce its therapeutic effect. Coadministration of Reyataz and drugs that inhibit CYP3A4 may increase atazanavir plasma concentrations.

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 prescribing information for ritonavir should be consulted for information on drug interactions with ritonavir.

Atazanavir solubility decreases as pH increases. The recommended oral dosage of Reyataz depends on the treatment history of the patient and the use of coadministered drugs. Reduced plasma concentrations of atazanavir may occur if antacids, proton-pump inhibitors, buffered medications, and H_2-receptor antagonists, are administrated with atazanavir. Please refer to Table 12 and the DOSAGE AND ADMINISTRATION section for recommendations for use of Reyataz with gastric acid lowering medications.

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

Drugs that are contraindicated or not recommended for coadministration with Reyataz are included in Table 11. 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.

Attachment 1: Product information for AusPAR Reyataz Atazanavir Bristol-Myers Squibb Australian Pty. Ltd. PM-2012-01034-3-2 Final 21 October 2013. This Product Information was approved at the time this AusPAR was published.

Table 11. Drugs That Should Not Be Administered with Reyataz

Drug class: Specific Drugs	Clinical Comment
Alpha 1-adrenoceptor antagonist:alfuzosin	CONTRAINDICATED. Potential for increased alfuzosin concentration which can result in hypotension.
Antimycobacterials: rifampin	CONTRAINDICATED. Decreases plasma concentrations and AUC of most protease inhibitors by about 90%. This may result in loss of therapeutic effect and development of resistance.
Antineoplastics: irinotecan	Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.
Benzodiazepines: orally administered midazolam*, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression (see PRECAUTIONS for parenteral midazolam).
Ergot Derivatives: dihydrorergotamine, ergotamine, ergonovine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin.	CONTRAINDICATED. Potential for serious reactions such as myopathy including rhabdomyolysis. (See also Table 11: Drug Interactions: HMG-CoA Reductase Inhibitors: *atorvastatin.*)
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.
PDE5 inhibitor: sildenafil** for the treatment of pulmonary arterial hypertension.	CONTRAINDICATED. A safe and effective dose in combination with Reyataz has not been established for sildenafil when used for the treatment of pulmonary arterial hypertension. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, priapism, and syncope).
Herbal Products: St. John's wort (*Hypericum perforatum*)	CONTRAINDICATED. Patients taking Reyataz should not use products containing St. John's wort (*Hypericum perforatum*) because coadministration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance.
Inhaled beta agonists: salmeterol	CONTRAINDICATED. Concomitant use of salmeterol and Reyataz may result in increased cardiovascular events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. Coadministration of salmeterol and Reyataz is not recommended

Table 11b. Drugs that should not be administered when Reyataz is administered with ritonavir

The metabolic profile for ritonavir may predominate when used in combination with atazanavir because ritonavir is a more potent CYP3A4 inhibitor than atazanavir. The product information for ritonavir should be consulted when atazanavir is boosted with ritonavir.

Anti arrhythmics: quinidine	Atazanavir/ritonavir: CONTRAINDICATED if atazanavir is coadministrated with ritonavir due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Calcium Channel Blockers: bepridil	Potential for serious and/or life-threatening adverse events. CONTRAINDICATED if atazanavir is coadministered with ritonavir.

*see Table 12, ***Other Agents***: Benzodiazepines.
**see Table 12 for sildenafil dosing recommendations when used to treat erectile dysfunction.

In a clinical study of co-administration to healthy subjects of ritonavir 100 mg twice daily and intranasal fluticasone propionate 50 micrograms four times daily for 7 days, the fluticasone propionate plasma levels increased significantly whereas the intrinsic cortisol levels decreased by approximately 86% (90% CI 82%, 89%). The effect of high fluticasone systemic exposure on ritonavir plasma levels is not yet known.

Systemic corticosteroid effects have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Concomitant use of Reyataz/ritonavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4 (eg budesonide) is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effect (eg Cushing's syndrome and adrenal suppression). Use of corticosteroid that is not metabolised by CYP3A4, (eg beclomethasone), could be considered.

In the case of withdrawal of fluticasone propionate co-administered with ritonavir, progressive dose reduction may have to be performed over a longer period.

Attachment 1: Product information for AusPAR Reyataz Atazanavir Bristol-Myers Squibb Australian Pty. Ltd. PM-2012-01034-3-2 Final 21 October 2013. This Product Information was approved at the time this AusPAR was published.

Table 12. 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 Atazanavir or Concomitant Drug	Clinical Comment
HIV Antiviral Agents		
Nucleoside Reverse Transcriptase Inhibitors (NRTIs): didanosine buffered formulations	↓ atazanavir	Coadministration with Reyataz did not alter exposure to didanosine; however, exposure to atazanavir was markedly decreased by coadministration of Reyataz with didanosine buffered tablets (presumably due to the increase in gastric pH caused by buffers in the didanosine tablets). In addition, it is recommended that didanosine be administered on an empty stomach; therefore, Reyataz should be given (with food) 2 h before or 1 h after didanosine buffered formulations. Because didanosine EC capsules are to be given on an empty stomach and Reyataz is to be given with food, they also should be administered at different times.
Nucleotide Reverse Transcriptase Inhibitors: tenofovir disoproxil fumarate	↓ atazanavir	Tenofovir may decrease the AUC and C_{min} of Reyataz. When coadministered with tenofovir, it is recommended that Reyataz 300 mg be given with ritonavir 100 mg and tenofovir 300 mg (all as a single daily dose with food). Reyataz without ritonavir should not be coadministered with tenofovir. Atazanavir increases tenofovir disoproxil fumarate concentrations. The mechanism of this interaction is unknown. Higher tenofovir disoproxil fumarate concentrations could potentiate tenofovir disoproxil fumarate-associated adverse events, including renal disorders. Patients receiving atazanavir and tenofovir disoproxil fumarate should be monitored for tenofovir disoproxil fumarate-associated adverse events.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs): efavirenz	↓ atazanavir	Efavirenz decreases atazanavir exposure. Co-administration of Reyataz and efavirenz is not recommended for treatment-experienced or treatment-naïve patients due to decreased atazanavir exposure. However, if judged unavoidable in treatment-naïve patients, dose recommendations are included in the DOSAGE AND ADMINISTRATION section.
Non-nucleoside Reverse Transcriptase Inhibitors: nevirapine	↓ atazanavir	Nevirapine substantially decreases atazanavir exposure. There is potential risk for nevirapine associated toxicity due to increased nevirapine exposures. Co-administration of Reyataz with nevirapine is not recommended.
Protease Inhibitors: boceprevir	↓ atazanavir	Exposure to atazanavir was decreased when boceprevir at 800 mg three times daily was coadministered with Reyataz 300 mg and ritonavir 100 mg once daily. Exposure to boceprevir was not significantly altered.

Table 12. 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 Atazanavir or Concomitant Drug	Clinical Comment
Protease Inhibitors: saquinavir (soft gelatin capsules)	- saquinavir	Appropriate dosing recommendations for this combination, with respect to efficacy and safety, have not been established. A total daily dose of saquinavir of 1200 mg once daily coadministered with Reyataz 400 mg once daily has been explored in a clinical study but has not been shown to provide adequate efficacy (see PHARMACOLOGY - Clinical Trials).
Protease Inhibitors: ritonavir	- atazanavir	If Reyataz is coadministered with ritonavir, it is recommended that Reyataz 300 mg once daily be given with ritonavir 100 mg once daily with food. See the complete prescribing information for ritonavir for information on drug interactions with ritonavir
Other protease inhibitors	- protease inhibitor	Although not studied, the coadministration of atazanavir plus ritonavir with other protease inhibitors would be expected to increase exposure to the other protease inhibitor and is not recommended.
Other Agents		
Antacids and buffered medications	¯ atazanavir	Reduced plasma concentrations of atazanavir are expected if antacids, including buffered medications, are administered with Reyataz. Reyataz should be administered 2 h before or 1 h after these medications.
Antiarrhythmics: amiodarone, lidocaine (systemic), quinidine	- amiodarone, lidocaine (systemic), quinidine	Coadministration with Reyataz has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with Reyataz. Quinidine is contraindicated when atazanavir is coadministered with ritonavir.
Anticoagulants: warfarin	- warfarin	Coadministration with Reyataz has the potential to produce serious and/or life-threatening bleeding and has not been studied. It is recommended that INR (International Normalized Ratio) be monitored.
Antidepressants: tricyclic antidepressants	- tricyclic antidepressants	Coadministration with Reyataz has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with Reyataz.
trazodone	- trazodone	Concomitant use of trazodone and atazanavir with or without ritonavir may increase plasma concentrations of trazodone. Adverse event 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 atazanavir, the combination should be used with caution and a lower dose of trazodone should be considered.

Table 12. 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 Atazanavir or Concomitant Drug	Clinical Comment
Antiepileptics:		
Carbamazepine:	¯ atazanavir	Plasma concentrations of atazanavir may be decreased when carbamazepine is administered with Reyataz without ritonavir. Coadministration of carbamazepine and Reyataz without ritonavir is not recommended. Ritonavir may increase plasma levels of carbamazepine. If patients beginning treatment with Reyataz/ritonavir have been titrated to a stable dose of carbamazepine, a dose reduction for carbamazepine may be necessary.
Phenytoin, phenobarbital	¯ atazanavir	Plasma concentrations of atazanavir may be decreased when phenytoin or phenobarbital is administered with Reyataz without ritonavir. Coadministration of phenytoin or phenobarbital and Reyataz without ritonavir is not recommended. Ritonavir may decrease plasma levels of phenytoin and phenobarbital. When Reyataz with ritonavir is coadministered with either phenytoin or phenobarbital, a dose adjustment of phenytoin or phenobarbital may be required
Lamotrigine:	¯ lamotrigine:	Coadministration of lamotrigine and Reyataz ***with*** ritonavir may decrease lamotrigine plasma concentrations. Dose adjustment of lamotrigine may be required when coadministered with Reyataz and ritonavir. Coadministration of lamotrigine and Reyataz ***without*** ritonavir is not expected to decrease lamotrigine plasma concentrations. No dose adjustment of lamotrigine is required when coadministered with Reyataz without ritonavir
Antifungals: ketoconazole, itraconazole,	- atazanavir - ritonavir	Coadministration of ketoconazole has only been studied with atazanavir without ritonavir (negligible increase in atazanavir AUC and Cmax). Plasma levels of both atazanavir and ritonavir may be increased by ketoconazole and itraconazole. High doses of ketoconazole and itraconazole (>200mg/day) should be used cautiously with atazanavir and ritonavir.

Table 12. 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 Atazanavir or Concomitant Drug	Clinical Comment
Antifungal; voriconazole	¯ atazanavir ¯ voriconazole (with at least one functional CYP2C19 allele) - voriconazole (without a functional CYP2C19 allele)	Coadministration of voriconazole (200 mg twice daily) with REYATAZ/ritonavir (300/100 mg once daily) in subjects with at least one functional CYP2C19 allele decreased plasma concentrations of both voriconazole and atazanavir. Coadministration of voriconazole (50 mg twice daily) with REYATAZ/ritonavir (300/100 mg once daily) in subjects *without* a functional CYP2C19 allele increased plasma concentrations of voriconazole and decreased plasma concentrations of atazanavir. Voriconazole should not be administered to patients receiving REYATAZ and ritonavir unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Patients should be carefully monitored for voriconazole-associated adverse events (e.g. liver toxicity, eye disorders) and loss of either voriconazole or atazanavir efficacy during the co-administration of voriconazole and REYATAZ/ritonavir.
Antimycobacterials: rifabutin	- rifabutin	Exposure to rifabutin is increased when it is coadministered with atazanavir. A rifabutin dose reduction of up to 75% (eg, 150 mg every other day or 3 times per week) is recommended. Increased monitoring for adverse reactions is warranted in patients receiving the combination of rifabutin and Reyataz with or without ritonavir. Further dose reduction of rifabutin may be necessary.
Calcium channel blockers: diltiazem	- diltiazem and desacetyl-diltiazem	Caution is warranted. A dose reduction of diltiazem by 50% should be considered. ECG monitoring is recommended.
eg, felodipine, nifedipine, nicardipine, and verapamil	- calcium channel blocker	Caution is warranted. Dose titration of the calcium channel blocker should be considered. ECG monitoring is recommended.
Erectile dysfunction agents: sildenafil tadalafil, vardenafil	- sildenafil - tadalafil - vardenafil	Phosphodiesterase (PDE5) inhibitors (sildenfil, tadalafil, vardenafil): Coadministration of a protease inhibitor with PDE5 inhibitor is expected to substantially increase the PDE5 inhibitor concentration and, may result in an increase in PDE5 inhibitor-associated adverse events including syncope, visual disturbances and priapism. Use with caution and monitor for adverse events. Reduced doses are recommended (Sildenafil, 25mg every 48 hours; tadalafil, 10mg every 72 hours; vardenafil, no more than 2.5mg every 72 hours), and patients should be monitored for adverse events.
HMG-CoA reductase inhibitors: atorvastatin	- atorvastatin	The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including Reyataz, are used in combination with atorvastatin. Caution should be exercised.

Table 12. 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 Atazanavir or Concomitant Drug	Clinical Comment
H_2-Receptor antagonists: Famotidine	¯ atazanavir	Reduced plasma concentrations of atazanavir are expected if H_2-receptor antagonists are administered with Reyataz. This may result in loss of therapeutic effect and development of resistance. *In treatment- naïve patients:* The H_2-receptor antagonist dose should not exceed a 40mg dose equivalent of famotidine twice daily. Reyataz 300mg with ritonavir 100mg 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 H_2-receptor antagonist. *In treatment-experienced patients:* Whenever a H_2-receptor antagonist is given to a patient receiving Reyataz with ritonavir, the H_2-receptor antagonist dose should not exceed a dose equivalent to famotidine 20mg twice daily, and the Reyataz and ritonavir doses should be administered simultaneously with, and/or at least 10 hours after, the dose of the H_2-receptor antagonist. · Reyataz 300mg with ritonavir 100mg once daily (all as a single dose with food) if taken with a H_2-receptor antagonist and without tenofovir. · Reyataz 400mg with ritonavir 100mg once daily (all as a single dose with food) if taken with both tenofovir and a H_2-receptor antagonist.
Immunosuppressants: cyclosporin, sirolimus, tacrolimus	- immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with Reyataz.
Macrolide antibiotics: clarithromycin	- clarithromycin ¯ 14-OH clarithromycin - atazanavir	Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a dose reduction of clarithromycin by 50% should be considered when it is coadministered with Reyataz. In addition, concentrations of the active metabolite 14-OH clarithromycin are significantly reduced; consider alternative therapy for indications other than infections due to *Mycobacterium avium* complex.

Attachment 1: Product information for AusPAR Reyataz Atazanavir Bristol-Myers Squibb Australian Pty. Ltd. PM-2012-01034-3-2 Final 21 October 2013. This Product Information was approved at the time this AusPAR was published.

Table 12. 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 Atazanavir or Concomitant Drug	Clinical Comment
Benzodiazepines: Parenteral midazolam	- benzodiazepine	*Midazolam*: 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 administration. Therefore, Reyataz should not be coadministered with orally administered midazolam, whereas caution should be used with coadministration of Reyataz and parenteral midazolam. No data are available on concomitant use of Reyataz with intravenous midazolam; data from concomitant use of other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels. If Reyataz is coadministered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustments should be assessed.
Oral contraceptives: ethinyl estradiol and norgestimate or norethindrone	– ethinyl estradiol - norgestimate (In combination with atazanavir 300 mg and ritonavir 100 mg once daily).[d]	Mean concentrations of ethinyl estradiol and norethindrone are increased when they are coadministered with Reyataz. Administration of Reyataz/ritonavir with ethinyl estradiol and norgestimate decreases the mean concentration of ethinyl estradiol, and increases the mean concentration of 17-deacetylnorgestimate, the active metabolite of norgestimate.
	- ethinyl estradiol - norethindrone (In combination with atazanavir 400 mg once daily.)	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 25µg of ethinyl estradiol have not been studied; therefore alternative methods of contraception are recommended.

Table 12. 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 Atazanavir or Concomitant Drug	Clinical Comment
Proton Pump Inhibitors: omeprazole	¯ atazanavir	Plasma concentrations of atazanavir were substantially decreased when Reyataz 400mg or Reyataz 300mg/ritonavir 100mg once daily was administered with omeprazole 40mg once daily, which may result in loss of therapeutic effect and development of resistance. *In treatment-naïve patients:* The proton-pump inhibitor dose should not exceed a 20mg dose equivalent of omeprazole and must be taken approximately 12 hours prior to the Reyataz 300mg with ritonavir 100mg dose. Reyataz without ritonavir should not be coadministered with omeprazole *In treatment-experienced patients:* Proton-pump inhibitors should not be used in treatment-experienced patients receiving Reyataz.
Opioids: buprenorphine	- buprenorphine and norbuprenorphine	Concentrations of buprenorphine and norbuprenorphine were increased when buprenorphine was coadministered with Reyataz, with or without ritonavir, due to CYP3A4 and UGT1A1 inhibition. Coadministration of Reyataz plus ritonavir with buprenorphine 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.
colchicine	- colchicine	Exposure to colchicine may be increased when coadministered with Reyataz. Colchicine is a CYP3A4 substrate (see CONTRAINDICATIONS on the use of Reyataz with medications that are substrates for CYP3A4).

Table 12. 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 Atazanavir or Concomitant Drug	Clinical Comment
Endothelin receptor antagonist: bosentan	↓ atazanavir	Bosentan is metabolized by CYP3A4 and is an inducer of CYP3A4. Plasma concentrations of atazanavir may be decreased when bosentan is administered with Reyataz without ritonavir. Coadministration of bosentan and Reyataz without ritonavir is not recommended. Prescribers should consult the complete prescribing information for bosentan when considering using this medicine in combination with Reyataz and ritonavir.

[a] For magnitude of interactions see **CLINICAL PHARMACOLOGY**: Tables 5 and 6.

Based on known metabolic profiles, clinically significant drug interactions are not expected between Reyataz and fluvastatin, pravastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, erythromycin, or itraconazole. There were no clinically significant drug interactions observed when Reyataz was coadministered with fluconazole or paracetamol. Reyataz does not interact with substrates of CYP2D6 (eg, nortriptyline, desipramine, metoprolol).

ADVERSE EFFECTS

Treatment-Emergent Adverse Events in Adult Treatment-Naive Patients

Selected clinical adverse events of moderate or severe intensity reported in treatment-naïve patients receiving combination therapy including Reyataz 300mg with ritonavir 100mg or Reyataz 400 mg (without ritonavir) are presented in Tables 13 and 14 respectively. For other information regarding observed or potentially serious adverse events, see PRECAUTIONS.

Table 13: Selected[a] Treatment-Emergent Adverse Reactions[b] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-naïve Patients[c], Study AI424-138.

	Phase III Study AI424-138	
	96 weeks[d] Reyataz 300mg plus ritonavir 100mg (once daily) and tenofovir plus emtricitabine[e] (n=441)	**96 weeks[d] lopinavir 400mg plus ritonavir 100mg (twice daily) and tenofovir plus emtricitabine[e] (n=437)**
Digestive System		
Nausea	4%	8%
Jaundice/scleral icterus	5 %	*

Diarrhoea	2%	12 %
Skin and Appendages		
Rash	3%	2%

* None reported in this treatment arm.
[a] Only clinical adverse reactions that were not laboratory abnormalities are included in the table. Laboratory abnormalities as measured on study are shown in Table 13.
[b] Includes events of possible, probable, certain, or unknown relationship to treatment regimen
[c] Based on the regimen containing Reyataz.
[d] Median time on therapy.
[e] As a fixed-dose combination: 300mg tenofovir, 200mg emtricitabine once daily.

Table 14. Selected Treatment-Emergent Adverse Events of Moderate or Severe Intensity Reported in ³ 3% of Adult Treatment-Naive Patients[a]

	Phase III Study AI424-034		Phase II Studies AI424-007, -008	
	64 weeks[b] Reyataz 400 mg once daily + lamivudine + zidovudine[d] (n=404)	64 weeks[b] efavirenz 600 mg once daily + lamivudine + zidovudine[d] (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)
Body as a Whole				
Headache	14%	13%	10%	8%
Fever	4%	6%	5%	5%
Pain	3%	2%	1%	2%
Fatigue	2%	2%	3%	2%
Back pain	2%	5%	6%	3%
Digestive System				
Nausea	16%	13%	10%	6%
Jaundice/scleral icterus	7%	<1%	8%	*
Abdominal pain	6%	5%	10%	8%
Vomiting	6%	8%	8%	7%
Diarrhea	6%	7%	8%	25%
Metabolic and Nutritional System				
Lipodystrophy	1%	1%	8%	3%
Musculoskeletal System				
Arthralgia	<1%	2%	4%	4%
Nervous System				
Depression	4%	5%	8%	3%
Insomnia	3%	5%	1%	<1%
Dizziness	3%	8%	1%	*
Peripheral neurologic symptoms	1%	2%	8%	7%
Respiratory System				
Increased cough	3%	4%	5%	1%
Skin and Appendages				
Rash	9%	13%	10%	3%

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

Treatment-Emergent Adverse Events in Treatment-Experienced Patients:

In Phase III clinical trials, Reyataz has been studied in 144 treatment-experienced patients in combination with two NRTIs (Study 043) and in 229 treatment-experienced patients in combination with either ritonavir, tenofovir, and one NRTI or saquinavir, tenofovir, and one NRTI (Study 045).

Treatment-Emergent Adverse Events in All Reyataz-Treated Patients:

Reyataz has been evaluated for safety and tolerability in combination therapy with other antiretroviral medicinal products in controlled clinical trials. There were 1151 patients with 52 weeks median duration of treatment who received Reyataz 400 mg once daily. There were 655 patients with 96 weeks median duration of treatment who received Reyataz 300mg with ritonavir 100mg. Adverse events were consistent between patients who received Reyataz 400mg once daily and patients who received Reyataz 300mg with ritonavir 100mg once daily, except that jaundice and elevated total bilirubin levels were reported more frequently with Reyataz plus ritonavir.

Among patients who received Reyataz 400mg once daily or Reyataz 300mg with ritonavir 100mg once daily, the only adverse events of any severity reported very commonly with at least a possible relationship to regimens containing Reyataz and one or more NRTIs were nausea (20%), diarrhoea (10%) and jaundice (13%). Among patients receiving Reyataz 300mg with ritonavir 100mg, the frequency of jaundice was 19%. In the majority of cases, jaundice was reported with a few days to a few months after the initiation of treatment (see PRECAUTIONS).

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy, and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia (see PRECAUTIONS).

Adult patients

The following adverse events of moderate intensity or greater with at least a possible relationship to regimens containing Reyataz and one or more NRTIs have also been reported. The frequency of adverse reactions listed below is defined using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), or very rare (<1/10,000).

Immune system disorder:	uncommon: hypersensitivity
Metabolism and nutrition	uncommon: anorexia, appetite increased, weight

disorders:	decreased, weight gain
Psychiatric disorders:	uncommon: anxiety, insomnia, depression, disorientation, sleep disorder, abnormal dream
Nervous system disorders:	common: headache; uncommon: peripheral neuropathy, amnesia, dizziness, somnolence, dysgeusia;
Eye disorders:	common: scleral icterus
Cardiac disorders and vascular disorders	uncommon: syncope, hypertension; rare: oedema, palpitation
Respiratory, thoracic and mediastinal disorders:	uncommon: dyspnea
Gastrointestinal disorders:	common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting; uncommon: dry mouth, flatulence, gastritis, pancreatitis, abdominal distension, stomatitis aphthous:
Hepatobiliary disorders:	common: jaundice; uncommon: hepatitis; rare: hepatosplenomegaly
Skin and subcutaneous tissue disorders:	common: rash; uncommon: alopecia, pruritus, urticaria; rare: vasodilatation, vesiculobullous rash, eczema
Musculoskeletal and connective tissue disorders:	uncommon: arthralgia, muscle atrophy, myalgia; rare: myopathy
Renal and urinary disorders:	uncommon: hematuria, nephrolithiasis, frequency of micturition, proteinuria; rare: kidney pain
Reproductive system and breast disorders:	uncommon: gynecomastia
General disorders and administration site conditions:	common: asthenia, lipodystrophy syndrome, fatigue; uncommon: chest pain, fever, malaise, gait disturbances

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

Paediatric and Adolescent Patients

Assessment of the pharmacokinetics, safety, tolerability and efficacy of Reyataz is based on data from the open-label, multicentre clinical trial PACTG 1020A conducted in paediatric patients from 3 months to 21 years of age. The safety profile of Reyataz in paediatric patients (6 to <18 years of age) is presented below.

The most common Grade 2-4 adverse events ≥5%, (regardless of causality) reported in paediatric patients were cough (21%), fever (18%), jaundice/scleral icterus (15%), rash (14%), vomiting (12%), diarrhoea (9%), headache (8%), peripheral oedema (7%), extremity pain (6%), nasal congestion (6%), oropharyngeal pain (6%), wheezing (6%) and rhinorrhoea (6%). Asymptomatic grade 2-4 atrioventricular block was reported in <2% of patients.

The most common Grade 3-4 laboratory abnormalities occurring in paediatric patients were elevation of total bilirubin (≥54.72µmol/L, 58%), neutropenia (9%) and hypoglycaemia (4%). All other Grade 3-4 laboratory abnormalities occurred with a frequency of less than 3%.

Postmarketing experience

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.

Cardiac disorders and vascular disorders: second degree AV block, third-degree AV block, QTc prolongation, Torsades de pointes

Metabolism and nutrition disorders: hyperglycemia, diabetes mellitus

Renal and urinary disorders: nephrolithiasis, interstitial nephritis

Hepatobiliary disorders: cholelithiasis, cholecystitis, cholestasis

Skin and subcutaneous tissue disorders: angioedema

Laboratory Abnormalities: The percentages of adult treatment-naive patients treated with combination therapy including Reyataz 300mg with ritonavir 100mg and Reyataz 400mg (without ritonavir) with Grade 3-4 laboratory abnormalities are presented in Table 15 and 16, respectively.

Table 15. Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-

Naïve Patients[a], Study AI424-138.

		Phase III Study AI424-138	
		96 weeks[b] Reyataz 300mg plus ritonavir 100mg (once daily) and tenofovir plus emtricitabine[d]	96 weeks[b] lopinavir 400mg plus ritonavir 100mg (twice daily) and tenofovir plus emtricitabine[d]
Variable	Limit	(n=441)	(n=437)
Chemistry	High		
SGOT/AST	≥ 5.1 x ULN	3 %	1%
SGPT/ALT	≥ 5.1 x ULN	3%	2%
Total Bilirubin	≥ 2.6 x ULN	44 %	<1%
Lipase	≥ 2.1 x ULN	2%	2%
Creatine Kinase	≥ 5.1 x ULN	8 %	7 %
Total Cholesterol	≥ 240mg/dL (6.216 mmol/L)	11 %	25 %
Haematology	Low		
Neutrophils	< 750 cells/mm^3	5 %	2%

[a] Based on the regimen containing Reyataz
[b] Median time on therapy
[c] ULN = upper limit of normal
[d] As a fixed-dose combination: 300mg tenofovir, 200mg emtricitabine once daily.

Attachment 1: Product information for AusPAR Reyataz Atazanavir Bristol-Myers Squibb Australian Pty. Ltd. PM-2012-01034-3-2 Final 21 October 2013. This Product Information was approved at the time this AusPAR was published.

Table 16. Selected Grade 3-4 Laboratory Abnormalities Reported in ³ 2% of Adult Treatment-Naive Patients[a]

		Phase III Study AI424-034		Phase II Studies AI424-007, -008	
Variable	**Limit**[d]	**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				
SGOT/AST	³ 5.1 x ULN	2%	2%	7%	5%
SGPT/ALT	³ 5.1 x ULN	4%	3%	9%	7%
Total Bilirubin	³ 2.6 x ULN	35%	<1%	47%	3%
Amylase	³ 2.1 x ULN	*	*	14%	10%
Lipase	³ 2.1 x ULN	<1%	1%	4%	5%
Hematology	Low				
Hemoglobin	<8.0 g/dL	5%	3%	<1%	4%
Neutrophils	<750 cells/mm^3	7%	9%	3%	7%

*None reported in this treatment arm. Amylase was not routinely tested in the protocol.

[a]Based on regimen(s) containing Reyataz.

[b]Median time on therapy.

[c]Includes long-term follow-up.

[d]ULN = upper limit of normal; grading system used is the Modified WHO system for grading acute and subacute toxicity effects.

[e]As a fixed-dose combination.

The percentages of adult treatment-experienced patients treated with combination therapy including Reyataz with Grade 3-4 laboratory abnormalities are presented in Table 17.

Table 17. Selected Grade 3-4 Laboratory Abnormalities Reported in ³ 2% of Adult Treatment-Experienced Patients[a]

		Phase III Study AI424-043		Phase III Study AI424-045	
		48 weeks[b] Reyataz 400 mg once daily + 2 NRTIs	48 weeks[b] lopinavir + ritonavir (400/100 mg) BID[e] + 2 NRTIs	96 weeks[c] Reyataz 300 mg once daily + ritonavir 100 mg once daily + tenofovir + NRTI	96 weeks[c] lopinavir + ritonavir (400/100 mg) BID[e] + tenofovir + NRTI
Variable	**Limit[d]**	**(n=144)**	**(n=146)**	**(n=119)**	**(n=118)**
Chemistry	High				
SGOT/AST	³ 5.1 x ULN	3%	3%	3%	4%
SGPT/ALT	³ 5.1 x ULN	7%	3%	5%	3%
Total Bilirubin	³ 2.6 x ULN	25%	<1%	53%	<1%
Lipase	³ 2.1 x ULN	4%	3%	11%	13%
Hematology	Low				
Platelets	<50,000 /mm^3	0	0	5%	5%
Neutrophils	<750 cells/mm^3	6%	5%	8%	10%

[a]Based on regimen(s) containing Reyataz.
[b]Study 043 Median time on therapy.
[c]Median time on therapy for study 045 was 76 weeks.
[d]ULN=upper limit of normal.
[e]As a fixed-dose combination.

The most frequently reported laboratory abnormality in patients receiving regimens containing Reyataz and one or more NRTIs was elevated total bilirubin reported predominantly as elevated indirect [unconjugated] bilirubin (87% Grade 1, 2, 3, or 4). Grade 3 or 4 elevation of total bilirubin was noted 37%, (6% Grade 4). Among experienced patients treated with Reyataz 300mg once daily with 100mg ritonavir once daily for a median duration of 95 weeks, 53% had Grade 3-4 total bilirubin elevations. Among naïve patients treated with Reyataz 300mg once daily with 100mg ritonavir once daily for a median duration of 96 weeks, 48% had Grade 3-4 total bilirubin elevations.

Other marked clinical laboratory abnormalities (Grade 3 or 4) reported in ≥2% of patients receiving regimens containing Reyataz and or more NRTIs included: elevated creatine kinase (7%), elevated alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT)

(5%), low neutrophils (5%), elevated aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) (3%), and elevated lipase (3%).

Two percent of patients treated with Reyataz experienced concurrent Grade 3-4 ALT/AST and Grade 3-4 total bilirubin elevations.

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.

Among 1151 patients receiving atazanavir 400mg daily, 177 patients were co-infected with chronic hepatitis B or C, and among 655 patients receiving atazanavir 300mg daily with ritonavir 100mg once daily, 97 patients were co-infected with chronic hepatitis B or C. Co-infected patients were more likely to have baseline hepatic transaminase elevations than those without chronic viral hepatitis. No differences in frequency of bilirubin elevations were observed between these patients and those without viral hepatitis. The frequency of treatment emergent hepatitis or transaminase evaluations in co-infected patients was comparable between Reyataz and comparator regimens).

In studies 008 and 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.

In study AI424-138, 60 patients treated with Reyataz/ritonavir 300mg/100mg once daily, and 51 patients treated with lopinavir/ritonavir 400mg/100mg 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.

Effects on lipids:

Unlike other protease inhibitors, Reyataz was not associated with clinically important changes from baseline in LDL cholesterol, triglycerides, or total cholesterol mean plasma concentrations. In studies 007, 008, 034, 043, 045, and 138 there were no clinically important changes from baseline in total serum cholesterol, fasting LDL cholesterol, or fasting triglyceride concentrations. Reyataz had significantly lower mean percent change from baseline in treatment-naive and protease inhibitor-experienced patients (see Table 18 and 19).

Lipid changes in treatment-naïve patients receiving combination therapy including Reyataz without ritonavir.

Table 18. Lipid - Mean Percent Changes from Baseline in Reyataz Clinical Trials in Antiretroviral-naive Adult Patients

	Study 034[a] 48 Weeks		Study 008[a] 48 Weeks		Study 007[a] 48 Weeks	
	ATV[c]	**EFV**	**ATV[b]**	**NFV**	**ATV[c]**	**NFV**
Total Cholesterol	+2%**	+21%	+5%**	+25%	+7%**	+28%
LDL Cholesterol[c]	+1%**	+18%	+5%[d, *]	+23%[d]	-7%**	+31%
HDL Cholesterol	+13%**	+24%	+12%[d]	+9%[d]	+20%	+16%
Triglycerides[c]	-9%**	+23%	+7%*	+50%	+2%*	+42%

*p < 0.001, **p < 0.0001;
[a] NRTI backbones = zidovudine/lamivudine (study 034), lamivudine/stavudine (study 008), didanosine/stavudine (study 007)
[b] 400 mg QD
[c] Fasting values
[d] Week 56
Values are excluded after the start of serum-lipid reduction therapy.
ATV – atazanavir, EFV – efavirenz, NFV – nelfinavir, LPV - lopinavir

Lipid changes in treatment-naïve patients receiving combination therapy including Reyataz 300mg with ritonavir 100mg once daily.

Table 19. Lipids - mean Change from baseline, Study AI424-138

	ATV/RTV[a,b] Change[d] (%) (n=372[f])	LPV/RTV[b,c] Change[d] (%) (n=335[f])	ATV/RTV - LPV/RTV Difference Estimate (95% CI)[e]
LDL-Cholesterol[g]			
Week 48	+14%	+19%	-4.5% (-8.4%, -0.4%)
Week 96	+14%	+17%	-1.7% (-5.9%, -2.6%)
HDL-Cholesterol[g]			
Week 48	+29%	+37%	-5.8% (-9.9%, -1.5%)
Week 96	+21%	+29%	-5.5% (-10%, -0.8%)
Total Cholesterol[g]			
Week 48	+13%	+25%	-9.8% (-12.3%, -7.3%)*
Week 96	+13%	+25%	-8.9% (-11.6%, -6.1%)*
Triglycerides[g]			
Week 48	+15%	+52%	-24.6% (-29.6%, -19.4%)*
Week 96	+13%	+50%	-24.5% (-29.9%, -18.8%)*

* $p < 0.0001$

[a] Reyataz 300mg plus ritonavir 100mg once daily with the fixed-dose combination: 300mg tenofovir, 200mg 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 400mg plus ritonavir 100mg twice daily with the fixed-dose combination 300mg tenofovir, 200mg 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] Difference estimates were stratified by qualifying HIV RNA and region.

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

[g] Fasting.

Attachment 1: Product information for AusPAR Reyataz Atazanavir Bristol-Myers Squibb Australian Pty. Ltd. PM-2012-01034-3-2 Final 21 October 2013. This Product Information was approved at the time this AusPAR was published.

Lipid changes in treatment-experienced patients.

The data available on the lipid profile (mean change from baseline) from study 045 are described in the following table (Table 20).

Table 20. AI424045 Lipid Mean Changes from Baseline

	Week 48		Week 96	
	ATV[a]/RTV	**LPV/RTV**	**ATV[a]/RTV**	**LPV/RTV**
Total Cholesterol	-8%	6%	-7%	9%
LDL Cholesterol[b]	-10%	1%	-11%	1%
HDL Cholesterol	-7%	2%	-5%	7%
Triglycerides[b]	-4%	30%	-2%	30%

[a] 300 mg once daily
[b] Fasting values
NRTI backbone: tenofovir disprovil fumarate + NRTI
Values are excluded after the start of serum-lipid reduction therapy.
ATV – atazanavir, RTV - ritonavir, LPV - lopinavir

DOSAGE and ADMINISTRATION

General Dosing Recommendations:

Reyataz capsules must be taken with food.

Reyataz capsules should be taken WHOLE. The recommended doses are to be administered using combinations of registered capsule strengths; eg a dose of 300mg may be administered as one 300mg capsule or two 150mg capsules.

The recommended oral dosage of Reyataz depends on the treatment history of the patient and the use of other coadministered drugs. When coadministered with H_2-receptor antagonists, or proton-pump inhibitors, dose separation may be required (see recommendations below).

When coadministered with didanosine buffered or enteric-coated formulations Reyataz should be given (with food) 2 hours before or 1 hour after didanosine.

Reyataz without ritonavir is not recommended for treatment-experienced patients with prior virologic failure.

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

For further information refer to PHARMACOLOGY – pharmacokinetics including Tables 5 and 6; CONTRAINDICATIONS and PRECAUTIONS.

Dose Recommendations for Therapy-Naïve Adult Patients

Reyataz 400mg once daily

Or

Reyataz 300mg with ritonavir 100mg once daily.

Concomitant therapy:
Reyataz without ritonavir is not recommended when co-administered with the drugs listed below. Reyataz 300mg with ritonavir 100mg should be administered with any of the following:

- Tenofovir
- Efavirenz: Coadministration of REYATAZ with efavirenz is not recommended. If the combination of Reyataz and efavirenz is judged to be unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of Reyataz to 400mg with 100mg of ritonavir both administered as a single dose with food and efavirenz administered on an empty stomach, preferably at bedtime.
- H_2-receptor antagonist: The H_2-receptor antagonist dose should not exceed a 40mg dose equivalent of famotidine twice daily. Reyataz 300mg and ritonavir 100mg should be administered simultaneously with, and/or at least 10 hours after, the dose of the H_2-receptor antagonist.
- Proton-pump inhibitors: The proton-pump inhibitor dose should not exceed a 20mg dose equivalent of omeprazole and must be taken approximately 12 hours prior to the Reyataz 300mg and ritonavir 100mg dose.

Dose Recommendations for Therapy-Experienced Adult Patients

Reyataz 300mg with ritonavir 100mg once daily

Reyataz without ritonavir is not recommended for treatment experienced patients with prior virologic failure.

Concomitant Therapy:

- Whenever a H_2-receptor antagonist is given to a patient receiving Reyataz with ritonavir, the H_2-receptor antagonist dose should not exceed a dose equivalent to famotidine 20mg twice daily, and the Reyataz and ritonavir doses should be

administered simultaneously with, and/or at least 10 hours after, the dose of the H_2-receptor antagonist.

- Reyataz 300mg with ritonavir 100mg once daily if taken with a H_2-receptor antagonist.
- Reyataz 400mg with ritonavir 100mg once daily if taken with both tenofovir and a H_2-receptor antagonist.

Proton-pump inhibitors should not be used in treatment-experienced patients receiving Reyataz.

Efavirenz: In treatment-experienced patients, REYATAZ should not be coadministered with efavirenz.

Paediatric Patients (6 – 18 years of age)

The dosage of Reyataz for treatment naïve and treatment experienced paediatric patients (6 to 18 years of age) is shown in Table 21 and should not exceed the recommended adult dosage.

Reyataz capsules must be taken with food.

For treatment-naïve patients at least 13 years of age and at least 40 kg, who are unable to tolerate ritonavir, the recommended dose is Reyataz 400mg (without ritonavir) once daily with food.

Table 21. Paediatric and Adolescent Dose for Reyataz capsules with ritonavir (6 to 18 years of age)[a,b]

Body Weight[c] (kg)	Reyataz Dose (mg)[d]	Ritonavir dose (mg)	Approximate Corresponding BSA (m^2)
15 to less than 20	150	100[e]	0.65-0.78
20 to less than 40	200	100[e]	0.79-1.26
at least 40	300	100[e]	≥ 1.27

[a]Dosage recommendations in Table 21 were derived from observed data in a clinical study that used atazanavir 205mg/m^2 with ritonavir dosed at 100mg/m^2 up to a maximum dose of 100mg ritonavir.
[b]The Reyataz and ritonavir dose should be taken once daily with food.
[c] There are limited or no data in paediatric patients less than 6 years of age and less than 15 kg.
[d] Doses of Reyataz can be achieved using a combination of commercially available capsule strengths.
[e] Ritonavir capsule or liquid.

Paediatric patients less than 6 years of age:

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

Patients with renal impairment: For patients with renal impairment, including those with severe renal impairment who are not managed by haemodialysis, no dosage adjustment is required for Reyataz. Treatment-naïve patients with end stage renal disease managed with haemodialysis should receive Reyataz 300mg with ritonavir 100mg.

Reyataz should not be administered to HIV-treatment experienced patients with end stage renal disease managed with haemodialysis (see PHARMACOLOGY - Pharmacokinetics).

Patients with hepatic impairment: Reyataz should be used with caution in patients with mild to moderate hepatic insufficiency. A dose reduction to 300 mg once daily should be considered for patients with moderate hepatic insufficiency (Child-Pugh Class B). Reyataz should not be used in patients with severe hepatic insufficiency (Child-Pugh Class C, see CONTRAINDICATIONS, PRECAUTIONS and PHARMACOLOGY - Pharmacokinetics). Reyataz in combination with ritonavir has not been studied in subjects with hepatic impairment and should be used with caution in patients with mild hepatic impairment. Reyataz with ritonavir is not recommended for patients with moderate to severe impairment.

OVERDOSAGE

Human experience of acute overdose with Reyataz is limited. Single doses up to 1,200 mg have been taken by healthy volunteers without symptomatic untoward effects. A single self-administered overdose of 29.2 g of Reyataz in an HIV-infected patient (73 times a 400-mg dose) was associated with asymptomatic bifascicular block and PR interval prolongation. These events resolved spontaneously. At high doses that lead to high drug exposures, jaundice [predominantly due to unconjugated (indirect) hyperbilirubinaemia without associated liver function test changes] or cardiac conduction abnormalities, including PR and/or QT interval prolongations, may be observed (see PRECAUTIONS and ADVERSE EFFECTS).

Treatment of overdose with Reyataz should consist of general supportive measures, including monitoring of vital signs and electrocardiogram and observations of the patient's clinical status. There is no specific antidote for overdose with Reyataz. Since atazanavir is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicine.

In case of overdose, immediately contact the Poisons Information Centre on 13 11 26 for advice.

Attachment 1: Product information for AusPAR Reyataz Atazanavir Bristol-Myers Squibb Australian Pty. Ltd. PM-2012-01034-3-2 Final 21 October 2013. This Product Information was approved at the time this AusPAR was published.

PRESENTATION AND STORAGE CONDITIONS

Capsules:
Reyataz (atazanavir) capsules are available in plastic bottles in the following strengths:

Product Strength and Pack Size	Capsule Shell Colour	Markings on Capsule
100 mg 60's	Blue and white	BMS 100 mg (white) & 3623 (blue)
150 mg 60's	Blue and Powder blue	BMS 150 mg (white) & 3624 (blue)
200 mg 60's	Blue	BMS 200 mg (white) & 3631 (white)
300mg 30's	Red and blue	BMS 300mg (white) & 3622 (white)

Storage Conditions: Store below 25^0C.

POISON SCHEDULE OF THE MEDICINE

S4

NAME AND ADDRESS OF THE SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
4 Nexus Court, Mulgrave,
Victoria 3170, Australia.

AUSTRALIAN REGISTRATION NUMBERS

Capsules
Bottles:
100 mg capsules AUST R 99054
150 mg capsules AUST R 99055
200 mg capsules AUST R 99056
300 mg capsules AUST R 134967

Attachment 1: Product information for AusPAR Reyataz Atazanavir Bristol-Myers Squibb Australian Pty. Ltd. PM-2012-01034-3-2 Final 21 October 2013. This Product Information was approved at the time this AusPAR was published.

DATE OF FIRST INCLUSION IN THE ARTG

21 January 2004

DATE OF MOST RECENT AMENDMENT:

25 July 2013