Summary of Label Changes

CLINICAL PHARMACOLOGY: Drug-Drug Interaction section

The following text was added to this section.

Atazanavir is a metabolism-dependent CYP3A inhibitor, with a K_{inact} value of 0.05 to 0.06 min^{-1} and K_i value of 0.84 to 1.0 µM. Atazanavir is also a direct inhibitor for UGT1A1 (K_i =1.9 µM) and CYP2C8 (K_i =2.1 µM). REYATAZ should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A, UGT1A1, or CYP2C8 (see CONTRAINDICATIONS)."

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

The following information was added to Table 4: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	N	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
				Cmax	AUC	Cmin
ddI (enteric-coated [EC] capsules)[c]	400 mg QD d 8 (fed)	400 mg QD d 2-8	34	1.03 (0.93, 1.14)	0.99 (0.91, 1.08)	0.98 (0.89, 1.08)
	400 mg QD d 19 (fed)	300 mg/ritonavir 100 mg QD d 9-19	31	1.04 (1.01, 1.07)	1.00 (0.96, 1.03)	0.87 (0.82, 0.92)
famotidine	40 mg BID d 7-12	400 mg QD d 1-12 (simultaneous administration)	15	0.53 (0.34, 0.82)	0.59 (0.40, 0.87)	0.58 (0.37, 0.89)
omeprazole	40 mg QD d 7-12[e]	400 mg QD d 1-12	16	0.04 (0.04, 0.05)	0.06 (0.05, 0.07)	0.05 (0.03, 0.07)
rifampin	600 mg QD d 17-26	300 mg QD/ ritonavir 100 mg QD d 7-26	16	0.47 (0.41, 0.53)	0.28 (0.25, 0.32)	0.02 (0.02, 0.03)

[c]400 mg ddI EC and REYATAZ were administered together with food on Days 8 and 19
[e]omeprazole was administered on en empty stomach 2 hours before REYATAZ

The following information was added to Table 5: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of REYATAZ

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	N	Ratio (90% Confidence Interval) of Coadministered Pharmacokinetic Parameters with/without Reyataz; No Effect = 1.00		
				Cmax	AUC	Cmin
ddI (enteric-coated [EC] capsules)[c]	400 mg QD d 1 (fasted), 8 (fed)	400 mg QD, d 2-8	34	0.64 (0.55, 0.74)	0.66 (0.60, 0.74)	1.13 (0.91, 1.41)
methadone	stable maintenance dose, d 1-15	400 mg QD, d 2-15	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)
omeprazole[e]	40 mg single dose d 7 and d 20	400 mg QD d 1-12	16	1.24 (1.04, 1.47)	1.45 (1.20, 1.76)	NA
Tenofovir	300 mg QD d 1-7 (pm) d 25-34 (pm)[i]	300 mg QD/ritonavir 100 mg qd D 25-34 (am)[i]	12	1.34 (1.20, 1.51)	1.37 (1.30, 1.45)	1.29 (1.21, 1.36)

[c]400 mg ddI EC and REYATAZ were administered toether with food on Days 8 and 19
[d] ®-methadone is the active isomer of methadone
[e] omeprazole was used as a metabolic probe for CY2C19. Omperazole was given 2 hours after REYATAZ on Day 7; and was given alone 2 hours after a light meal on Day 20
[i] administration of tenofovir and REYATAZ was temporally separated by 12 hours

PRECAUTIONS: Drug Interactions

Information regarding atazanavir is an inhibitor of CYP2C8 was added. In addition the following text was added.

Reduced plasma concentrations of atazanavir are expected if proton-pump inhibitors (see Table 10), antacids, buffered medications, or H_2-receptor antagonists (see Table 11) are administered with atazanavir.

The following text was added or revised in Table 10 and 11:

Table 10 Drugs That Should Not Be Administered with Reyataz

Antimycobacterials: rifampin	Rifampin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect and development of resistance.
Proton-Pump Inhibitors	Omeprazole substantially decreases plasma concentrations of atazanavir. Concomitant use of proton-pump inhibitors and REYATAZ may result in loss of therapeutic effect and development of resistance.

Table 11: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated):

Nucleoside Reverse Transcriptase Inhibitors (NRTIs): didanosine buffered formulations enteric-coated (EC) capsules	↓ atazanavir ↓ didanosine	Coadministration of REYATAZ with didanosine buffered tablets results in a marked decrease in atazanavir exposure. It is recommended that REYATAZ be given (with food) 2 h before or 1 hr after didanosine buffered formulations. Simultaneous administration of didanosine EC and REYATAZ with food results in a decrease in didanosine exposure. Thus, REYATAZ and didanosine EC should be administered at different times.
Antifungals: voriconazole	Effect is unknown	Coadministration of voriconazole with REYATAZ, with or without ritonavir, has not been studied. Administration of voriconazole with ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%. Voriconazole should not be administered to patients receiving REYATAZ/ritonavir, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Coadministration of voriconazole with REYATAZ (without ritonavir) may increase atazanavir concentrations; however, no data are available.
H2-Receptor antagonists	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when REYATAZ 400 mg once daily was administered simultaneously with famotidine 40 mg twice daily, which may result in loss of therapeutic effect and development of resistance. In treatment-naïve patients taking an H_2-receptor antagonist, either of the following regimens may be used: REYATAZ 400 mg once daily with food at least 2 hours before and at least 10 hours after the H_2-receptor antagonist OR REYATAZ 300 mg with ritonavir 100 mg once daily with food, without the need for separation from the H_2-receptor antagonist. In treatment-experienced patients, the following regimen should be used: REYATAZ 300 mg with ritonavir 100 mg once daily with food at least 2 hours before and at least 10 hours after the H_2-receptor antagonist.

Additionally, the following text was added to the drug interaction secion:

No clinically significant drug interaction was observed when REYATAZ was coadministered with methadone.

DOSAGE AND ADMINISTRATION

The following text was included in this section:

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

H_2-receptor antagonists.

Treatment-naïve patients: REYATAZ 400 mg once daily with food at least 2 hours before and at least 10 hours after the H_2-receptor antagonist OR REYATAZ 300 mg with ritonavir 100 mg once daily with food, without the need for separation from the H_2-receptor antagonist.

Treatment-experienced patients: REYATAZ 300 mg with ritonavir 100 mg once daily with food at least 2 hours before and at least 10 hours after the H_2-receptor antagonist.