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Atazanavir is an antiretroviral drug of the protease inhibitor (PI) class. Like other antiretrovirals, it is used to treat infection of human immunode ciency virus (HIV) and used in combination with other

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	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

Table 1: Steady-State Pharmacokinetics of Atazanavir in Healthy Subjects or HIV-Infected Patients in the Fed State.

Arms	Assigned Interventions
A: Active Comparator	Drug: Atazanavir + Ritovir Capsules, Oral, ATV 300mg as 2- 150 mg + RTV 100 mg, single dose, 7 days washout crossed over to Treatment B
B: Active Comparator	Drug: Atazanavir + Ritovir Capsules, Oral, ATV 300mg as single cap + RTV 100 mg, single dose, 7 days washout.

Table 2

activity. *In vitro* studies using human liver microsomes suggested that Atazanavir is metabolized by CYP3A.

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

A C

The BE recommendation for Atazanavir Sulfate Capsules is two way, cross over, *i*n vivo study with 300 mg strength in both fasting and fed condition. A contrary view for this recommendation has been discussed in this section.

Clinical study conducted for Atazanavir shows that most of the study has been conducted either with 400 mg dose and/or 300 mg Atazanavir +100 mg Ritonavir. The pharmacokinetic stated in the approved patient information leaflet is based on the study conducted with Atazanavir 400 mg (two 200 mg capsules) and Atazanavir 300 mg + Ritonavir 100 mg in fed conditions. The summary basis of approval states that as there was very little change in the clinical study formulation and to be marketed formulation, no bioequivalence study was carried out.

To reduce the pill burden FDA has approved the 300 mg formulation to replace the two 150 mg capsules on October 20, 2006. Bioequivalence Study of Atazanavir 300 mg Capsule has been conducted against two 150 mg Atazanavir capsules sponsored by Bristol-Myers Squibb (ClinicalTrials.gov Identifer: NCT00393328). The purpose of this clinical research study is to assess the bioequivalence of atazanavir administered as a single 300 mg capsule relative to two atazanavir 150 mg capsules in healthy subjects. Interestingly this study was also conducted with 100 mg Ritonavir. The detail of study is as follow- The dosage and administration states that Reyataz must be taken with food. Further the recommended dosages are 400 mg Atazanavir daily once or 300 mg Atazanavir with 100 mg Retonavir. The suggested dosage and administration could be based on the metabolism of the Atazanavir in the liver. Atazanavir is assumed to be highly variable drug. The variability is reduced when administered with food. Also Atazanavir shows nonlinear pharmacokinetics. The pharmacokinetic parameters (C_{max} and AUC) for Atazanavir 300 mg + 100 mg Ritonavir are much higher for Atazanavir 400 mg. Compared with Atazanavir 400 mg QD data, administration of Atazanavir /Ritonavir 300/100 mg QD increased the Atazanavir geometric mean values of C_{max}, AUC, and C_{min} by 18%, 103%, and 671%, respectively.

Based on the information the recommendation could be considered for the revision. The possible recommendation could be either one of the following:

1. Only Fed study with 300 mg Atazanavir

   Justification: Dosage recommendation states Atazanavir must be taken with food. Also food enhances bioavailability and reduces pharmacokinetic variability

2. Bioequivalence study with 400 mg Atazanavir (Two 200 mg capsules) with food.

   Justification: Dosage recommendation states Atazanavir 400 mg once daily. Pharmacokinetic is non-linear.

3. Bioequivalence study with 300 mg Atazanavir + 100 mg Ritonavir (Norvir)

   Justification: Dosage recommendation states Atazanavir 300 mg once daily plus Ritonavir 100 mg once daily with food. Both Ritonavir and Atazanavir are metabolized in liver and the pharmacokinetic parameters are significantly higher than 400 mg Atazanavir alone.

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This article represents the personal view of the author and there is no relation of the organization to which author is associated.

Reference

1. FDA-Approved Patient Labeling. REYATAZ (Atazanavir Sulfate) capsules, gelatin coated. E.R. Squib & Sons, L.L.C, Princenton.