

Bioequivalence Study Recommendation for Atazanavir Sulfate Capsules by US FDA and a Contrary View

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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 immunodeficiency virus (HIV) and used in combination with other HIV medications.

Atazanavir is the first protease inhibitor approved for once-daily dosing, and also appears to be less likely to cause lipodystrophy and elevated cholesterol as side effects. It may also not be cross-resistant with other protease inhibitor. When boosted with ritonavir it is of equivalent potency to lopinavir for use in *salvage* therapy in patients with a degree of drug resistance; although boosting with ritonavir reduces the metabolic advantages of atazanavir.

The U.S. Food and Drug Administration (FDA) approved atazanavir with three different strengths such as 100 mg, 150 mg and 200 mg, on June 20, 2003. On October 20, 2006, the FDA approved a new formulation of atazanavir (300 mg capsules) to be taken as part of combination drug therapy. This formulation should reduce pill burden, as one 300 mg capsule may replace two 150 mg capsules. Atazanavir is marketed under the trade name Reyataz by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA [1].

Office of Generic Drug (US FDA) Recommendation for Bioequivalence Study

Generic company has to get approval from the US FDA to market the product. To ensure the safety and efficacy US FDA has laid some guidelines and recommendation to generic companies to follow. Similarly, Office of Generic Drug (OGD), US FDA, has recommended the bioequivalence study for the Atazanavir sulfate Capsules. OGD has recommended two (Fasting and Fed) studies with normal healthy male and females, general population. Single-dose, two-way crossover in-vivo study with 300 mg strength has been recommended for the BE studies. Atazanavir has to be measured in the plasma. It has been assumed that the recommendation of US FDA is based on the clinical studies, bioequivalence study, act provided by Innovator company.

Dosage and Administration

The US FDA approved patient information leaflet of Reyataz states general dosing recommendations as follow-

- REYATAZ Capsules must be taken with food.

Therapy –naïve patient

- Reyataz 400 mg (Two 200 mg capsules) once daily taken with food.

Therapy –experienced patient

- Reyataz 300 mg (one 300 mg capsule or two 150 mg capsules) once daily plus Ritonavir 100 mg once a daily taken with food
- 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 100 mg once daily have not been established.

Pharmacokinetics

The pharmacokinetics of Atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients after administration of REYATAZ 400 mg once daily and after administration of REYATAZ 300 mg with Ritonavir 100 mg once daily (Tables 1 and 2).

Absorption

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

Food Effect

Administration of REYATAZ with food enhances bioavailability and reduces pharmacokinetic variability. Administration of a single 400 mg dose of REYATAZ with a light meal (357 kcal, 8.2 g fat, 10.6 g protein) resulted in a 70% increase in AUC and 57% increase in C_{max} relative to the fasting state. Administration of a single 400 mg dose of REYATAZ with a high-fat meal (721 kcal, 37.3 g fat, 29.4 g protein) resulted in a mean increase in AUC of 35% with no change in C_{max} relative to the fasting state. Administration of REYATAZ (Atazanavir sulfate) with either a light meal or high-fat meal decreased the coefficient of variation of AUC and C_{max} by approximately one half compared to the fasting state.

Distribution

Atazanavir is 86% bound to human serum proteins and protein binding is independent of concentration. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively).

Metabolism

Atazanavir is extensively metabolized in humans. The major biotransformation pathways of Atazanavir in humans consisted of monooxygenation and dioxygenation. Other minor biotransformation pathways for Atazanavir or its metabolites consisted of glucuronidation, N-dealkylation, hydrolysis, and oxygenation with dehydrogenation. Two minor metabolites of Atazanavir in plasma have been characterized. Neither metabolite demonstrated *in vitro* antiviral

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Received June 27, 2012; Published October 30, 2012

Citation: Shimpi S (2012) Bioequivalence Study Recommendation for Atazanavir Sulfate Capsules by US FDA and a Contrary View. 1:388. doi:10.4172/scientificreports.388

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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)

^an= 26

^bn= 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 + Ritonavir 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 + Ritonavir 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.

Elimination

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 Contrary View

The BE recommendation for Atazanavir Sulfate Capsules is two way, cross over, *in 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 Identifier: 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 Ritonavir. 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.

Declaration

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, Princeton.