CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567

PHARMACOLOGY REVIEW

PHARMACOLOGIST'S REVIEW ON NDA 21-567 (Atazanavir, Revataz®)

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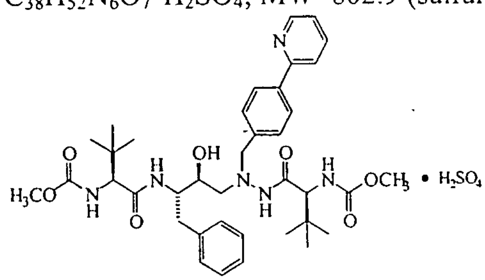
PHARMACOLOGY/TOXICOLOGY REVIEW COVER SHEET

NDA NUMBER:	**21-567**
NUMBER/DATE/TYPE:	000/Dec-20-2002/Original NDA
INFORMATION TO SPONSOR	Yes (x) No ()
SPONSOR	Bristol-Myer-Squibb Pharmaceutical Research Institute, Connecticut, USA
DRUG MANUFACTURER	Same as above
DIVISION NAME:	DAVDP
HFD #:	HFD-530
REVIEW COMPLETION	6/12/03
REVIEWER	**Kuei-Meng Wu**
DRUG TRADE NAME:	Reyataz®
GENERIC NAME	Atazanavir
CODE NAME	BMS-232632-05; CGP-73547
CHEMICAL NAME	[3*S*-(3*R**, 8*R**, 9*R**, 12*R**)]-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 salt
FORMULA/MW	$C_{38}H_{52}N_6O_7 \cdot H_2SO_4$; MW=802.9 (sulfuric acid salt); 704.9 (free base)
STRUCTURE	
RELATED INDs	
DRUG CLASS:	Antiviral
INDICATION:	Treatment of HIV infection
CLINICAL FORMULATION:	200 mg strengths (as free base equivalent) capsules
ROUTE	Oral
PROPOSED USE:	HIV Infection

DISCLAIMER: Tabular and graphical information is from sponsor's submission unless stated otherwise.

I. Introduction and Drug History

Atazanavir (BMS-232632) is a new azapeptide HIV protease inhibitor which has no apparent in vitro ability to inhibit other human aspartyl proteases. The NDA is originated from an ongoing IND — that was initially submitted on 9/3/98. The preclinical program of this NDA consisted of animal toxicity studies conducted in rodents, dogs, and rabbits in support of the intended human uses. Portion of the toxicity studies have been reviewed under IND — (see Pharmacologist's Reviews on original IND and its amendments). This document reviews the up-to-date preclinical pharmacology/toxicology study reports and provides summary and comments on overall nonclinical safety information and the proposed labeling on atazanavir.

II. Summary of Preclinical Safety Information

Animal toxicity studies conducted with atazanavir include

- Single-dose toxicity studies in rats and mice
- Repeat-dose toxicity studies in rats and dogs
- Pre-carcinogenicity rangefinding studies in rats and mice
- Reproductive toxicity studies in rats, and rabbits
- *In vitro* and *in vivo* mutagenicity assays
- Special toxicity studies

For a detailed evaluation on the animal toxicology studies that were not reviewed under IND — please refer to the APPENDIX (I) of this document. Key preclinical safety information is recapitulated and issues discussed below.

III. Executive Summary of Toxicity Profile

Major toxicity findings and key target organ/system of toxicity were identified in a series of repeat-dose toxicity studies conducted in rodents, and dogs, as highlighted below.

1. Hepatotoxicity

The liver toxicity profile of atazanavir in rats, dogs and mice is summarized based on key studies submitted as follows. The toxicological implications, no-adverse-effect level (NOAEL), and the associated systemic drug exposure of each study are provided as follows:

STUDY & DOSE mg/kg/day	Liver Function Test	Liver Pathology	NOAEL/AUC (mg/kg; ug·h/mL)	Toxicological Implications
Rat, Two-Week 300, 600, 1200	ALP↑ (600/1200♀); Bilirubin↑(1200[illegible]♀)	LiverWt↑, Hepatocyte hypertrophy (600/1200♀)	300/22♂-34♀	1. Hepatobiliary dysfunction 2. Enzyme induction
Rat, Six-Month 100, 300, 900	ALT↑, AST↑ (all dose groups ♂♀)	LiverWt ↑, Hepatocyte hypertrophy (♀, all doses); Hepatocellular vacuolation (all dose groups ♂♀);	Failed to find the NOAEL (<100)	1. Hepatocellular damage 2. Enzyme induction
Dog, Two-Week 90, 180, 360	ALP↑, Bilirubin↑ ALT↑, AST↑, GGT↑,	Not reported (Moribund at ≥180)	Failed to find the NOAEL (<90)	1. Hepatocellular damage 2. Hepatobiliary dysfunction

STUDY & DOSE mg/kg/day	Liver Function Test	Liver Pathology	NOAEL/AUC (mg/kg; ug·h/mL)	Toxicological Implications
	urine bilirubin↑ (all dose groups♂♀)		AUC Ranges: 80-210♂ & 136-586♀ ug·h/mL	
Dog, Two-Week 10, 30, 75	Not Remarkable	Not Remarkable	75/12♂-7♀	"Safe" for 2 weeks of treatment up to 75 mg/kg; see remarks above for higher doses.
Dog, Nine-Month 10 (2nd&3rd months→180), 30, 90	Bilirubin↑(≥30♂♀); LiverWt↑ (≥30♀); ALP↑ (≥90♂♀); GGT↑ (≥30♂)	Not Remarkable	10/1♂-3♀	1. Hepatobiliary dysfunction 2. Enzyme induction
Mouse, Three-Month 20, 40, 80(♂) 40, 160, 640(♀)	ALT↑, AST↑, Bilirubin↑ (≥80♂, 160♀)	LiverWt↑, hepatocellular hypertrophy & vacuolation (♀≥160)	20♂-40♀/11♂-34♀	1. Hepatocellular damage 2. Hepatobiliary dysfunction 3. Enzyme induction

1. HEPATOTOXICITY (CONT'D): ROLE OF UDPGT

The role of the bilirubin metabolizing enzyme, UDPGT, and plasma protein binding in the hyperbilirubinemia seen in humans and animals were investigated by the following three in vitro studies:

STUDY	RESULTS	COMMENTS
In Vitro, Inhibitory Effects on Bilirubin Glucuronidation by H-UGT 1A1 or H-LM	Potency: Atazanavir (IC_{50}≈2 uM) > saquinavir, nelfinavir (neither induced hyperbilirubinemia; IC_{50}≈2-8 uM) >> indinavir (caused hyperbilirubinemia; IC_{50}≈70-90 uM)	1. 2 uM=1.4 ug/ml (MW=705) falls within the effective exposure ranges of above toxicity studies (e.g., Cmax=2-3 ug/ml at 100 mg/kg [6-month rat]; Cmax=2-4 ug/ml at 30 mg/kg [9-month dog study]). (2 uM was within the range of clinical exposure [400mg qd Css]) 2. The role of atazanavir metabolites (BMS 421419/551180) on UDPGT is unknown and no in vitro study regarding this topic has been conducted. 3. In summary, increases in bilirubin seen in the above whole animal toxicity studies might partly result from inhibition of UDPGT.
In Vitro, Inhibitory Effects on Rate of Bilirubin Glucuronidation by H-UGT 1A1	Potency: Atazanavir (Ki≈2 uM; 28.7%*) >> indinavir (Ki≈48 uM; 2.5%); *: Estimated % inhibition of bilirubin glucuronidation rate at Css.	
In Vitro, Competitive Effects on Albumin Binding of Bilirubin	No effect, suggesting that hyperbilirubinemia is not due to competitive plasma albumin binding of bilirubin by atazanavir.	

1. HEPATOTOXICITY (CONT'D): CONCLUSIONS

The following remarks can be made in regard to effect of atazanavir in liver:

1. Atazanavir produced significant hepatotoxicity in animals.
2. Atazanavir-induced hepatic effects included at least the following three components: hepatocellular damage (increased in ALT and/or AST), hepatobiliary dysfunction (increased in bilirubin, GGT and/or ALP), and enzyme induction (hepatocellular hypertrophy or increased liver weight).
3. Atazanavir-induced lipid profile benefits, as reported in human trials, were not observed in animal studies. In contrast, opposite effects were reported, for example, cholesterol, and/or triglycerides were increased in a 2-week dog study dosed at 90-360

mg/kg/day), and cholesterol was increased by atazanavir in a 6-month rat study dosed at 100-900 mg/kg/day.

4. Atazanavir-induced hepatotoxicity is a cross-species phenomenon, occurring in rats, dogs and mice.
5. Atazanavir-induced hepatotoxicity occurred in a dose-proportional and treatment duration-proportional manner.
6. The NOAELs of atazanavir-induced hepatotoxicity decreased as treatment duration increased. NOAEL dropped from 300 to <100 mg/kg in rats and from 75 to 10 mg/kg in dogs, as treatment duration prolonged from 2 weeks to 6 months.
7. The exposure at NOAEL in the 6-month dog study (10 mg/kg, 1-3 ug.h/ml) was equivalent to the daily human clinical exposure (1.3-2 ug.h/ml at 400 mg qd). Thus, margin of safety = 1 (i.e., no margin).
8. Hyperbilirubinemia observed in both animals and humans might partly result from atazanavir's interference on bilirubin glucuronidation by UDPGT.
9. The atazanavir-induced hepatic enzyme induction in animals, supported by the lower exposure levels seen after long duration of repeated drug treatment, is different from the enzyme inhibition results reported from the human studies that showed P450 CYP3A4 is inhibited by atazanavir.

2. Cardiovascular Toxicity: QT Prolongation

In a 2-week whole animal (dog) toxicity study, atazanavir produced sinus bradycardia, and PR/QRS/QT prolongation at 90-360 mg/kg. The sponsor indicated that these cardiac electrophysiological effects might be secondary to the poor health and moribund conditions caused by the drug. In humans, certain effects on EKG such as AV blocks and QT prolongation were variously reported. The sponsor conducted the following in vitro electrophysiological studies to attempt to clarify these safety concerns against atazanavir.

Ion Currents or Action Potential	Agent DOSE uM	Effects	Interpretations & Comments (see DISCUSSION below on dose relevancy)
Action Potential, Rabbit Purkinje	Atazanavir 1, 3, 10, 30	APD90↑ (6/10/13% at 3/10/30 uM) [ritonavir: 10/19/19] Vmax↓ (-5/-8/-10 at 3/10/30 uM) [ritonavir: -5/-11/-27]	1. This served the basis of QT↑. 2. Potential to a slow conduction and negative inotropism (Vmax↓). 3. Canine Purkinje model is preferred and more predictable.
IK_r (HERG)	Atazanavir 1, 3, 10, 30	IK_r↓ (15%, 30 uM) Nelfinavir≥saquinavir>> lopinavir ≥ritonavir>> indinavir>atazanavir	This served the basis of APD↑, which may in turn be reflected in QT↑ and various bundle branch blocks and aberrancies seen in patients.
Iks, GP Ventriculocyte	Atazanavir 30	No effect	This indicates that IKs is not involved in the APD↑.
ICa_L, Rat Ventriculocyte	Atazanavir 1, 3, 10, 30	ICa_l↓ (16%, 30 uM) Nelfinavir> atazanavir= saquinavir> indinavir > ritonavir	This served the basis of various types of AV blocks seen in patients. Might also contribute to a potential negative inotropism.
Ina (SCN5A)	Atazanavir 1, 3, 10, 30	INa↓ (16%, 30 uM) Nelfinavir>> lopinavir> saquinavir> ritonavir>> atazanavir=indinavir	This and Vmax↓ pose a potential for slow conduction (and circus movement), and a depressed ejection fraction.

2. CARDIOVASCULAR TOXICITY: QT PROLONGATION (CONT'D)

The effects of atazanavir metabolites, BMS-421419 BMS-551160, on the above in vitro cardio electrophysiological parameters were also investigated (at concentrations of 3, 10, 30 uM), as shown in the following:

Ion Currents or Action Potential	Effects	Interpretations & Comments (see DISCUSSION below on dose relevancy)
Action Potential, Rabbit Purkinje	No effect on APD, but Vmax↓	See related interpretations in table above.
IK_r (HERG)	IK_r↓ (BMS-421419 12%, BMS-551160 15%, 30 uM)	See related interpretations in table above.
IK_s, GP Ventriculocyte	IK_s↓ by BMS-551160 (11%, 30 uM)	See related interpretations in table above.
ICa_L Rat Ventriculocyte	ICa_l↓ (BMS-421419: 21%, BMS-551160: 14%, 30 uM)	See related interpretations in table above.
INa (SCN5A)	INa↓ (BMS-421419: 7%, BMS-551160: 14%, 30 uM)	See related interpretations in table above.

2. CARDIOVASCULAR TOXICITY: QT PROLONGATION (CONT'D) THE ROLE OF PHARMACOKINETIC EXPOSURE PARAMETERS AND CONCLUSIONS

The role of Cmax as one of the key drug exposure parameters for electrophysiological risk assessment is discussed as follows. Clinical daily exposures (Css) of atazanavir are around 2 uM at the 400 mg qd dose. However, Cmax should be taken into consideration for cardiac electrophysiology risk assessment because the transient peak concentration (i.e. Cmax) may endanger a single cardiac impulse and set off arrhythmias leading into sudden cardiac death. Thus, the concentration ranges used in the above in vitro testing should be viewed under two meaningful categories: one that is in the Css range (i.e., 1 and 3 uM) and one that might have occurred as the Cmax (i.e., 10 and 30 uM, which might have not been identified because of time points of measurement).

The following conclusions on cardiac electrophysiological effects of atazanavir can be made based on the data obtained from the in vitro studies:

1. Both atazanavir and its metabolites produced significant cardiac electrophysiological effects in various nonclinical in vitro testings.
2. Atazanavir-induced QT prolongation in patients is supported by the drug's ability to prolong cardiac action potential, which is resulted from the blockade of potassium channels as shown by in vitro studies.
3. Atazanavir-induced bundle branch blocks and aberrancies are related to prolongation of action potential in the Purkinje fiber.
4. Atazanavir-induced AV blocks are related to the blockade of calcium channels and associated slow inward currents.
5. Atazanavir's metabolites may also contribute to the above cardiac electrophysiological effects.
6. Some of the cardiac electrophysiological effects could occur at Css (1-3 uM, APD↑, Vmax↓), whereas others at concentrations beyond the steady state (IK, INa, ICa). The levels of 10-30 uM could be comparable to the peak drug (parent and metabolites combined) concentrations (Cmax) occurring in patients.
7. By using AUC, the in vivo and in vitro NOAELs of atazanavir's cardiac electrophysiology effects were approximately 75 mg/kg (AUC=12♂-7♀ ug.h/ml; dog) and 1 uM (in vitro).

3. OTHER GENERAL ORGAN/SYSTEM TOXICITIES:

Other potential animal toxicities reported in this NDA included

(1) GI Toxicity: emesis, lost of appetite and food consumption (dog; >75 mg/kg/day); decreased food consumption (rat; 1200 mg/kg/day), and
(2) Hematotoxicity: decreases in total leukocyte and absolute lymphocyte counts (rat; 600 - 1200 mg/kg/day)

4. GENOTOXICITY:

Atazanavir increased the frequency of human lymphocytes bearing metaphase chromosome aberrations at the in vitro testing concentration of 30 μg/ml (in the absence or presence of S-9). The drug is thus considered to be clastogenic to the chromosome.

5. TERATOLOGY, MATERNAL, EMBRYONIC AND FETAL TOXICITY

Reproductive toxicology of atazanavir was investigated in rats and rabbits. The key findings are as follows.

Rat.
Atazanavir decreased body weights, body weight gains, and food consumption in males at 1400 mg/kg/day. In females, disturbance of estrous cycle was reported including a prolonged diestrus with abbreviated estrus and metestrus occurring at ≥100 mg/kg. In F_0 generation during gestation and lactation and in F_1 generation

offspring from 4 days of age to early in the growth phase, loss of mean body weight or suppression of weight gain occurred at 1000 mg/kg.

Systemic exposure to atazanavir in males and nongravid females dosed for 3 months at 100, 300, or 900 mg/kg/day ranged from 2 to 2.2 ug/ml, and AUCs ranged from 1.3 to 9.9 ug·hr/ml. In pregnant rats (220 or 1000 mg/kg), Cmax ranged from 4 to 10 ug/ml, and AUC values ranged from 33 to 57 ug·hr/ml, respectively.

Rabbits.
Atazanavir caused maternal toxicity in rabbits at ≥30 mg/kg (decreased body weight gain; reduced food consumption, soft, reduced, and/or absent feces). Lethal gross lesions on the stomach (thinned, pitted, friable, ulcerated, and/or perforated) and intestines (gas-filled and/or pitted) occurred at ≥120 mg. One drug-related abortion at 120 mg/kg/day was reported.

The Cmax and AUC values for atazanavir in pregnant rabbits dosed at 60 mg/kg/day were 5 ug/ml and 29 ug·hr/ml, respectively (*Note*: For comparative purpose, the daily human clinical exposures ranged from 1.3 to 2 ug.h/ml 400 mg qd.)

Conclusions: No significant teratologic findings were reported from studies conducted on atazanavir in pregnant rats or rabbits at the doses tested. There is limited margin of safety in regard to reproductive toxicity for atazanavir, as based upon the exposure data (AUC) listed above.

6. CARCINOGENICITY | Studies are ongoing.

7. INFANT AND NEONATAL TOXICOLOGY: | Not conducted.

8. TOPICAL TOXICITIES | Atazanavir is a strong eye-irritant as shown by the sponsor's bovine corneal opacity and permeability assay. This information should be reflected in the label as a cautionary note in regard to handling of the drug.

IV. EXECUTIVE SUMMARY ON OVERALL PHARM/TOX RISK ASSESSMENT

1. ADEQUACY OF PRECLINICAL TOXICITY STUDIES | The sponsor had employed the conventional species of rats and dogs as their surrogates of atazanavir's toxicity profile exploration. The choice of these two species appeared to be appropriate. The studies showed adequate drug exposures and had identified target organs of toxicity, some of which, were correlative to those seen in humans (hepatic, cardiac, hematological and GI).

One minor remark that can be made here is that drug exposures were not dose-responsively escalated because of the inductive nature of atazanavir on the hepatic P450 enzyme system. This effect has not been supported by any in vitro testing of atazanavir's capability toward P450 enzyme induction, and is in contrast to the human data that show atazanavir predominantly caused hepatic P450 enzyme inhibition on CYP 3A4 as reported by the sponsor in various human pharmacokinetic studies.

While the plasma atazanavir exposures were less dose-responsive, the metabolic profiles between animals and humans and presence of major metabolites in both had been shown to be somewhat similar. Thus, additional utility of the animal toxicity studies may be justified here regarding concerns on the safety profile of these metabolites presented in humans upon which information gained from the animal studies could be considered useful.

2. HYPER-BILIRUBINEMIA

The atazanavir induced-hyperbilirubinemia in patients has triggered significant medical attention paid to concurrent liver enzyme increases during clinical trials and concerns over the drug's potential to produce more severe liver necrosis, and even total liver failure. Safety data from the animal studies appeared to support clinical findings that hepatotoxicity is a cross-species phenomenon that occurred in a dose-proportional and treatment duration-proportional manner in both rats and dogs.

3. UDPGT: MULTIPLICITY, SUBSTRATES, INDUCERS AND INHIBITORS AND INHIBITORS

Hyperbilirubinemia observed in animals might be due to biliary dysfunctions including that resulted from atazanavir's interference on bilirubin glucuronidation by UDPGT. UDPGT is a multi-enzyme system in the liver responsible for the metabolism of various endogenous substances including bilirubin, thyroxin, steroids, etc. Additional information on the substrates, inducers, and inhibitors of UDPGT subtype for bilirubin is provided in the following table.

BILIRUBIN UDPGT SUBTYPE [1A1 (HUG-Br1) (UGT1.1)]	
CHROMOSOME#	2
POLYMORPHISM	Gilberts, Africans 36%, 3% Asians, White 12%
SUBSTRATES	Endogenous: bilirubin, estriol, β-estradiol Drugs: Acetaminophen, ethinylestradiol, troglitazone, buprenorphine Botanicals: anthraquinones, eugenol, naringenin, apigenin, genistein, coumarins
INDUCERS	Clofibrate, dexamethasone, phenobarbital, phenytoin, ritonavir
INHIBITORS (data adapted from this NDA)	Atazanavir (IC50≈2 uM) > saquinavir, nelfinavir (neither induced hyperbilirubinemia; IC50≈2-8 uM) >> indinavir (caused hyperbilirubinemia; IC50≈70-90 uM)
Note: UDPGT Subtypes for AZT and thyroxin are 2B7 and 1A9, respectively.	

V. Overall Conclusions And Recommendations

This NDA in its present form has provided adequate preclinical safety information in support of its approval. The sponsor has employed feasible levels of dosage and number of animals of both sexes in their studies and assay systems. The sponsor has explored the toxicity of the drug and adequately addressed issues regarding the modes and mechanisms of each toxicity uncovered. While the toxicity testing on atazanair is still ongoing (i.e., carcinogenicity studies in both mice and rats), it is concluded that the NDA has provided sufficient preclinical safety information to allow for prediction of potential toxicity in humans with the judicious use of this drug in humans. The following changes in the drug's label are proposed as follows.

VI. Proposed Labeling Changes

1 page(s) of revised draft labeling has been redacted from this portion of the review.

Kuei-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP

Concurrences:
DAVDP/HFD-530/PTL/JFarrelly
Wu/Pharm/6/12/03

Disk: JFarrelly

HFD-530 NDA 21-567 (000)
HFD-530/Division File
HFN-340
HFD-530/CSO
HFD-530/MO
HFD-530/Chem
HFD-530/Micro
HFD-530/Pharm