CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 206-353

Supporting document/s:

Supporting Document	Sponsor Submission Date	CDER Received Date
1	4/04/14	4/05/14

Product: Atazanavir/Cobicistat Fixed Dose Combination (ATV-COBI FDC)

Indication: Treatment of HIV infection

Applicant: Bristol-Myers Squibb Co.

Review Division: Division of Antiviral Products

Reviewer(s): Peyton Myers, PhD
Mark Powley, PhD

Supervisor/Team Leader: Hanan Ghantous, Ph.D., DABT

Division Director: Debra B. Birnkrant, M.D.

Project Manager: Sammie Beam, R.Ph.

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1 Executive Summary

1.1 Introduction

Bristol-Myers Squibb Co. (BMS) has submitted an NDA to support the fixed dose combination (FDA) therapy of atazanavir (ATV or BMS-232632; HIV-1 protease inhibitor) and cobicistat (COBI or GS-9350; CYP450 3A enzyme inhibitor) for the treatment of HIV infection. The proposed clinical dose regimen includes 300 mg/day ATV + 150 mg/day COBI.

There are approved NDAs for ATV and ritonavir (also a CYP3A inhibitor). This will be the first FDC for ATV and COBI.

1.2 Brief Discussion of Nonclinical Findings

Only one study (3 months in rats) was submitted for review. All other nonclinical data are in the respective NDAs for the single drug products.

The cobicistat drug substance was within specifications accepted under NDA #203-100. The 3 new degradants were qualified by a 3-month study in rats and (Q)SAR analysis. See Appendix 1 for further discussion of the impurity findings.

1.3 Recommendations

1.3.1 Approvability

There are no nonclinical pharmacology and toxicology issues which would preclude the approval of the FDC of ATV(300 mg/day)+COBI(150 mg/day)

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

The label for the FDC of ATV+COBI is merged from the single drug product NDA labels. The merged label is acceptable.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of EVOTAZ in pregnant women. Because animal reproduction studies are not always predictive of human response, EVOTAZ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Do not give EVOTAZ to treatment-experienced pregnant patients taking an H2-receptor antagonist and/or tenofovir DF during the second or third trimester.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to EVOTAZ, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Risk Summary

Atazanavir with ritonavir has been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate.

Cases of lactic acidosis syndrome, sometimes fatal, and symptomatic hyperlactatemia have occurred in pregnant women using atazanavir in combination with nucleoside analogues. Nucleoside analogues are associated with an increased risk of lactic acidosis syndrome.

Hyperbilirubinemia occurs frequently in patients who take atazanavir, including pregnant women. All infants, including neonates exposed to atazanavir in utero, should be monitored for the development of severe hyperbilirubinemia during the first few days of life.

Animal Data

Atazanavir: In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals at systemic drug exposure levels (AUC) 0.7 (in rabbits) to 1.2 (in rats) times those observed at the human clinical dose (300 mg/day atazanavir (b) (4) with 100 mg/day ritonavir). In pre- and postnatal development studies in the rat, atazanavir caused body weight loss or weight gain suppression in the animal offspring with maternal drug exposure (AUC) 1.3 times the human exposure at this clinical dose. However, maternal toxicity also occurred at this exposure level.

Cobicistat: Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with cobicistat during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 1.4 and 3.3 times higher than the exposure in humans at the recommended daily dose of 150 mg.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Atazanavir: Long-term carcinogenicity studies in mice and rats were carried out with atazanavir for two years. In the mouse study, drug-related increases in hepatocellular adenomas were found in females at 360 mg/kg/day. The systemic drug exposure (AUC) at the NOAEL in females, (120 mg/kg/day) was 2.8 times and in males (80 mg/kg/day) was 2.9 times higher than those in humans at the clinical dose (300 mg/day atazanavir (b) (4) with 100 mg/day ritonavir, nonpregnant patients). In the rat study, no drug-related increases in tumor incidence were observed at doses up to 1200 mg/kg/day, for which AUCs were 1.1 (males) or 3.9 (females) times those measured in humans at the clinical dose.

Cobicistat: In a long-term carcinogenicity study in mice, no drug-related increases in tumor incidence were observed at doses up to 50 and 100 mg/kg/day (males and females, respectively). Cobicistat exposures at these doses were approximately 7 (male) and 16 (females) times, respectively, the human systemic exposure at the therapeutic daily dose. In a long-term carcinogenicity study of cobicistat in rats, an increased incidence of follicular cell adenomas and/or carcinomas in the thyroid gland was observed at doses of 25 and 50 mg/kg/day in males, and at 30 mg/kg/day in females. The follicular cell findings are considered to be rat-specific, secondary to hepatic microsomal enzyme induction and thyroid hormone imbalance, and are not relevant for humans. At the highest doses tested in the rat carcinogenicity study, systemic exposures were approximately 2 times the human systemic exposure at the therapeutic daily dose.

Mutagenesis

Atazanavir: Atazanavir tested positive in an in vitro clastogenicity test using primary human lymphocytes, in the absence and presence of metabolic activation. Atazanavir tested negative in the in vitro Ames reverse-mutation assay, in vivo micronucleus and DNA repair tests in rats, and in vivo DNA damage test in rat duodenum (comet assay).

Cobicistat: Cobicistat was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

Impairment of Fertility

Atazanavir: At the systemic drug exposure levels (AUC) 0.9 (in male rats) or 2.3 (in female rats) times that of the human clinical dose, (300 mg/day atazanavir

(b) (4) with 100 mg/day ritonavir) significant effects on mating, fertility, or early embryonic development were not observed.

Cobicistat: Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) approximately 3-fold higher than human exposures at the recommended 150 mg daily dose. Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately similar human exposures at the recommended 150 mg daily dose.

2 Drug Information

2.1 Drug

Generic Name

Atazanavir (b) (4) /cobicistat 300mg/150mg (ATV/COBI) Fixed-Dose Combination (FDC) tablets

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 203-100 -- COBI FDC
NDA 203-094 -- COBI
NDA 021-567 – ATV

2.3 Drug Formulation

Fixed Dose Tablets

2.4 Comments on Novel Excipients

N/A.

2.5 Comments on Impurities/Degradants of Concern

The cobicistat drug substance was within specifications accepted under NDA 203-100. The 3 new degradants were qualified by a 3-month study in rats and (Q)SAR analysis. See Appendix for further discussion of the impurity findings.

2.6 Proposed Clinical Population and Dosing Regimen

HIV treatment with 300mg/150mg (ATV/COBI) Fixed-Dose Combination (FDC) tablets

2.7 Regulatory Background

ATV and COBI are both approved under their respective NDAs. This is the FDC tablet combination with ATV and COBI. All data for COBI and ATV are in their respective NDAs.

3 Studies Submitted

3.1 Studies Reviewed

3-Month Oral Qualifying Toxicity Study in Rats (Study no DM13009) – reviewed in the Appendix by Dr. Powley.

3.2 Studies Not Reviewed

All nonclinical studies were reviewed.

3.3 Previous Reviews Referenced

None.

12 Appendix/Attachments

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Reviewer:	Mark W. Powley, Ph.D.
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Division Director:	Debra B. Birnkrant, M.D.
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This review focuses on qualification of impurities, degradants, and residual solvents. Regulatory decision making utilizes information presented in ICH guidelines M7 "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" and Q3B(R2) "Impurities in New Drug Products".

All proposed specifications are considered acceptable from a pharmacology/toxicology perspective based on evaluations from previous submissions as well as the results of a general toxicology study and (quantitative) structure-activity relationship [(Q)SAR] predictions of mutagenicity.

2 Qualification of Atazanavir Drug Substance

Specifications for the atazanavir drug substance are within the specifications accepted under ND#21-567 and associated supplements. Specifications for the current submission are summarized below.

Table 1. Atazanavir drug substance specifications

Impurity	Proposed Specification
Organic Impurity	
	(b) (4)
Residual Solvents	
	(b) (4)

3 Qualification of Cobicistat Drug Substance

Specifications for the cobicistat drug substance are within the specifications accepted under NDA#203-100. Specifications for the current submission are summarized below.

Table 2. Cobicistat drug substance specifications

Impurity	Proposed Specification
Organic Impurities	
(b) (4)	
Residual Solvents	
(b) (4)	

4 Qualification of Atazanavir/Cobicistat Fixed Dose Combination Drug Product

Specifications for the atazanavir/cobicistat fixed dose combination drug product are within the qualified levels described in NDA#203-100 or those supported by a general toxicology study. Specifications for the current submission are summarized below.

Table 3. Atazanavir/Cobicistat fixed dose combination drug product specifications

Degradant	Qualified Level	Proposed Specification
(b) (4)		

[a] *qualification described in NDA#203-100*
[b] *qualification described in Section 4.1*

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4.1 Qualification of [redacted]

Degradants are qualified using data from a general toxicology study and (Q)SAR predictions of mutagenicity. Although the proposed specifications for [redacted] *exceed the ICH Q3B(R2) qualification threshold (i.e., typically requires experimental data from the Ames and in vitro chromosomal aberration assays), (Q)SAR was considered adequate evaluation of genotoxic potential due to the indication.*

General Toxicology – [redacted] *are qualified by a 3-month study in Sprague-Dawley rats (Study no. DM13009 – reviewed in Appendix). As results for 30 mg/kg/day cobicistat spiked with degradants are similar to 30 mg/kg/day cobicistat alone, this dose is used to calculate qualified levels. Overall, the qualified levels of degradants summarized below are adequate to support the proposed specifications.*

Table 4. Atazanavir/Cobicistat fixed dose combination drug product general toxicology qualification

Degradant	Toxicology Study Content	Non-Clinical Dose[a]	Qualified Level[b]	Proposed Specification
[redacted]	[redacted]	30 mg/kg/day	[redacted]	[redacted]
		30 mg/kg/day		
		30 mg/kg/day		

[a] 3-month study in rats (Study no. DM13009); no differences in toxicity profile for cobicistat spiked with degradants vs. cobicistat alone

[b] qualified level = [redacted]

Genotoxicity – All 3 degradants are predicted to be negative for bacterial mutagenicity by Derek Nexus (v4.0.5), Leadscope Model Applier (v1.8.3-1), and Case Ultra (v1.4.6.6). Summary data is provided in the Appendix.

Appendix

To: Mark Powley
cc: Hanan Ghantous
From: CDER/OTS/OCP/DARS: The Chemical Informatics Group
Re: NDA 206-653
Date: September 18, 2014

Three degradants of cobicistat have been evaluated by CDER/OTS/OCP/DARS for bacterial mutagenicity using (quantitative) structure-activity relationship [(Q)SAR] models. Three software programs were used: *Derek Nexus* 4.0.5 (*DX*), *Leadscope Model Applier* 1.8.3-1 (*LMA*), and *CASE Ultra* 1.4.6.6 (*CU*). To maximize sensitivity and negative predictivity, a positive prediction from any one software program was used to justify a positive study call.

The (Q)SAR assessment of mutagenic potential for the degradants is consistent with recommendations described in the ICH M7 guideline (e.g., prediction of bacterial mutagenicity using multiple complementary methodologies).

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1. (b) (4)

Bacterial Mutagenicity[1]

(b) (4) Software	*Salmonella* Mutagenicity	*E. coli* Mutagenicity
Derek Nexus	–	–
Leadscope Model Applier	–	–
CASE Ultra	–	–
Overall Software Prediction	–	–
Overall Expert Prediction	–	–

(b) (4) is predicted to be negative for bacterial mutagenicity.

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2. (b) (4)

Bacterial Mutagenicity[1]

(b) (4) Software	*Salmonella* Mutagenicity	*E. coli* Mutagenicity
Derek Nexus	–	–
Leadscope Model Applier	–	–
CASE Ultra	–	–
Overall Software Prediction	–	–
Overall Expert Prediction	–	–

(b) (4) are predicted to be negative for bacterial mutagenicity.

[1] + = positive; – = negative; Eqv = equivocal; NC = test chemical features are not adequately represented in the model training data set, leading to a no call.

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3. (b) (4)

Bacterial Mutagenicity[1]

(b) (4)	Software	*Salmonella* Mutagenicity	*E. coli* Mutagenicity
	Derek Nexus	–	–
	Leadscope Model Applier	–	–
	CASE Ultra	–	–
	Overall Software Prediction	–	–
	Overall Expert Prediction	–	–

(b) (4) is predicted to be negative for bacterial mutagenicity.

This report has been reviewed and approved by CDER/OTS/OCP/DARS.

Title: 3-Month Oral Qualifying Toxicity Study in Rats (Study no DM13009)

Summary – *Mortality, clinical signs/physical examinations, body weights, food consumption, ophthalmic examinations, hematology, coagulation, clinical chemistry, urinalysis, gross pathology, organ weights, histopathology, and toxicokinetics were evaluated in Sprague-Dawley rats after oral administration of 30 mg/kg/day cobicistat spiked with degradants for 3 months. Degradant content included* (b) (4) *For comparison, a group was also administered 30 mg/kg/day of cobicistat alone. The vehicle/control article was 100% (w/v) polyethylene glycol 400. Test-article related effects included red-stained fur and salivation. Numerous changes also occurred in hematology (decreased RBC associated parameters; increased platelets), coagulation (decreased PTT; increased fibrinogen), clinical chemistry (decreased total bilirubin, ALP, AST, total cholesterol, and phosphorus; increased globulin and total protein), and urine chemistry parameters (increased urine total protein concentration and excretion). Effects in liver (increased organ weight correlating with centrilobular hypertrophy) and thyroid (increased organ weight parameters correlating with follicular cell hypertrophy) were consistent with enzyme induction. All effects were considered non-adverse. Toxicokinetic analysis verified exposure to cobicistat.*

Overall, administration of cobicistat spiked with degradants was consistent with effects noted in the concurrent cobicistat alone group. Based on the absence of adverse effects at any dose level, the NOAEL was 30 mg/kg/day of cobicistat spiked with degradants or cobicistat alone.

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/s/

LAINE P MYERS
12/23/2014

HANAN N GHANTOUS
12/24/2014