CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206353Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 206353 **SDN**: 000 **DATE REVIEWED:** 10/01/2014
Virology Reviewer: Eric F. Donaldson, Ph.D.

Reviewer's Name: Eric F. Donaldson, Ph.D.

Sponsor: Bristol-Myers Squibb Company
5 Research Parkway
Mailstop 2CW-506
Wallingford, CT 06492
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Lisa Percival, Director of Global Regulatory Sciences
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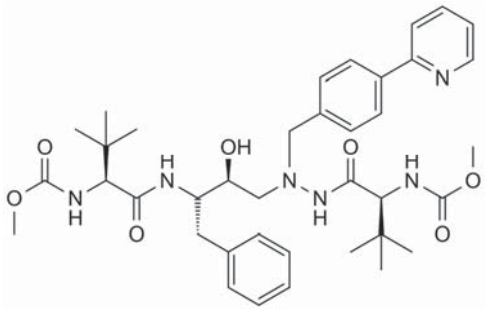
Initial Submission Dates: July 22, 2014
Correspondence Date: July 22, 2014
CDER Receipt Date: July 22, 2014
Assigned Date: July 22, 2014
NDA Review Complete Date: 10/01/2014
PDUFA Date: 2/4/2015

Submission #	Date Received by CDER	Date Assigned
N206353 SDN 000	July 22, 2014	09/26/2014

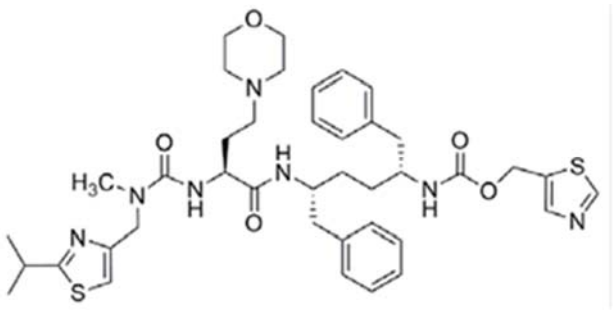
Product Names: Atazanavir sulfate (Reyataz®) and cobicistat

Chemical Name: *Atazanavir sulfate*: (3*S*,8*S*,9*S*,12*S*)-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 (1:1). *Cobicistat*: 1,3-thiazol-5-ylmethyl [(2*R*,5*R*)-5-{[(2*S*)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate.

Structure, physical or biological composition:



Atazanavir sulfate



Cobicistat

Molecular Formula: *Atazanavir sulfate*: $C_{38}H_{52}N_6O_7 \bullet H_2SO_4$; *cobicistat*: $C_{40}H_{53}N_7O_5S_2$

Molecular Weight: *Atazanavir sulfate*: 704.9; *cobicistat*: 776.0

Drug Category: *Atazanavir sulfate*: HIV-1 antiviral; *cobicistat*: a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family

Indication: For the treatment of HIV-1 in combination with other antiretroviral drugs

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Dosage Form/Route of administration: Tablets: 300 mg of atazanavir and 150 mg of cobicistat. Recommended dosage in adults: One tablet once daily, taken orally with food.

Supporting documents: NDA022282, ANDA204806, ANDA200196, ANDA091673, ANDA091611, ANDA078785, sNDA21567, and NDA206352.

Abbreviations: α-1AGP, alpha-1 acidic glycoprotein; APV, amprenavir; ARV, antiretroviral; ATV, atazanavir; CC, cytotoxic concentration; CI, combination index; d4T, stavudine; DC, discontinuation; ddI, didanosine; DNA, deoxyribonucleic acid; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IC, inhibitory concentration; IDV, indinavir; LOQ, Limit of Quantification; LPLV, last patient last visit; LPV, lopinavir; moi, multiplicity of infection; mAb, monoclonal antibody; NFV, nelfinavir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PBMCs, peripheral blood mononuclear cells; PCR, polymerase chain reaction; PI, protease inhibitor; pol, polymerase; PPT, polypropylene tubes; PR, protease; RNA, ribonucleic acid; RT, reverse transcriptase; RTI, reverse transcriptase inhibitor; RTV, ritonavir; TLOVR, Time to Loss of Virologic Response; TP, triphosphate; SQV, saquinavir; WT, wild-type

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NDA: 206353 **SDN**: 000 **DATE REVIEWED:** 10/01/2014
Virology Reviewer: Eric F. Donaldson, Ph.D.

Executive Summary

Atazanavir (Reyataz®; ATV) is a protease inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. This HIV-1 antiviral drug was originally approved by the FDA in 2003 (NDA-21567, approved on June 20, 2003). Atazanavir capsules (150, 200, and 300 mg), in combination with low-dose ritonavir (RTV) as a pharmacokinetic enhancer, has been approved for the treatment of HIV-1-infected adults and pediatric patients ≥6 years of age in the United States (tentative approval on November 18, 2011).

Cobicistat (COBI), an inhibitor of cytochrome P-450 (CYP) 3A enzymes, was developed by Gilead Sciences, Inc. (Gilead) for use as a PK enhancer of antiretroviral (ARV) agents, including the PI, ATV. Cobicistat is a structural analogue of RTV, has no ARV activity, and in biochemical assays, has been shown to be a more specific mechanism-based CYP3A inhibitor than RTV. COBI was approved by the FDA on September 24, 2014.

The ATV/COBI product is an immediate release FDC tablet of ATV and COBI (trade name to be determined). The proposed indication is for the treatment of HIV-1 infection. The current adult dosage form under development for commercialization is an oval (b) (4) film-coated tablet, containing 300 mg ATV (the approved dose in adults) as the free base and 150 mg COBI to be taken orally.

This review focused strictly on the label for TRADENAME™. The sponsor made modifications to the Microbiology (12.4) section of the label to reflect the use of cobicistat in combination with atazanavir. In general, the sponsor deleted information (b) (4)

The sponsor also removed all language from the label regarding (b) (4)

1 Recommendations

We recommend adding information to the label regarding baseline resistance in treatment-experienced subjects. This language was in the previously approved label for ATV/RTV. Recommended changes to **Section 1 Indications and Usage** are shown in red. In addition, we recommend that all references to (b) (4) be changed to *Microbiology (12.4)*.

1 INDICATIONS AND USAGE

TRADENAME™ (atazanavir (b) (4) and cobicistat) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.

Limitations of Use:

- Use of TRADENAME™ in treatment-experienced patients should be guided by the number of baseline primary protease inhibitor resistance substitutions [*see Microbiology (12.4)*].

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 206353 **SDN**: 000 **DATE REVIEWED:** 10/01/2014
Virology Reviewer: Eric F. Donaldson, Ph.D.

2 Administrative Signatures

2.1 Reviewer's Signature

_____
Eric F. Donaldson, Ph.D.
Virology Reviewer, Division of Antiviral Products

2.2 Concurrence

_____
Julian J. O'Rear, Ph.D.
Virology Team Leader, Division of Antiviral Products

OND Virology Review

1 Introduction and Background

Atazanavir (Reyataz®; ATV) is a protease inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. This HIV-1 antiviral drug was originally approved by the FDA in 2003 (NDA-21567, approved on June 20, 2003). Atazanavir capsules (150, 200, and 300 mg), in combination with low-dose ritonavir (RTV) as a pharmacokinetic enhancer, has been approved for the treatment of HIV-1-infected adults and pediatric patients ≥6 years of age in the United States.

Cobicistat (COBI), an inhibitor of cytochrome P-450 (CYP) 3A enzymes, was developed by Gilead Sciences, Inc. (Gilead) for use as a PK enhancer of antiretroviral (ARV) agents, including the PI, ATV. Cobicistat is a structural analogue of RTV, has no ARV activity, and in vitro, has been shown to be a more specific mechanism-based CYP3A inhibitor than RTV.

The ATV/COBI product is an immediate release FDC tablet of ATV and COBI (trade name to be determined). The proposed indication is for the treatment of HIV-1 infection. The current adult dosage form under development for commercialization is an oval (b) (4) film-coated tablet, containing 300 mg ATV (the approved dose in adults) as the free base and 150 mg COBI to be taken orally.

This review focused strictly on the label for TRADENAME™. Previous labels of atazanavir contained specific language (b) (4) This language was removed by the sponsor from this label.

2 Package Insert

Comment (not to be communicated): The sponsor removed all language from the label regarding whether or not the use of TRADENAME™ in (b) (4) In the most recent atazanavir label, there was a bullet point describing this concern in the **1 INDICATIONS AND USAGE section** that referenced the Microbiology (12.4) section. This language should be added back in to the label.

2.1 Proposed Package Insert (with reviewer-recommended changes)

Only sections relevant to Clinical Virology are shown, with recommended changes highlighted in red:

1 INDICATIONS AND USAGE

TRADENAME™ (atazanavir (b) (4) and cobicistat) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.

Limitations of Use:

- Use of TRADENAME™ in treatment-experienced patients should be guided by the number of baseline primary protease inhibitor resistance substitutions [*see Microbiology (12.4)*].

(b) (4)

12.1 Mechanism of Action

TRADENAME is a fixed-dose combination of the (b) (4) drug atazanavir (b) (4) cobicistat. [*See* (b) (4) *Microbiology (12.4)*.]

2.2 Final Approved Package Insert

The final approved Package Insert was not complete at the time this review was completed.

3 Conclusions

- The sponsor made modifications to the Microbiology (12.4) section of the label to reflect the use of cobicistat in combination with atazanavir.
- In general, they removed data from clinical trials that were not associated (b) (4)
- The sponsor removed all language from the label regarding whether or not the (b) (4) .
- Given that ATV is the efficacious drug, there would still be concerns that baseline resistance-associated substitutions could lead to treatment failure with this combination.

4 Recommendations

4.1 Modify section 1 Indications and Usage to address concerns about pre-existing PI resistance-associated substitutions in the HIV-1 protease of treatment-experienced subjects. Specifically add in the following in section **1 INDICATIONS AND USAGE**:

Limitations of Use:

- Use of TRADENAME™ in treatment-experienced patients should be guided by the number of baseline primary protease inhibitor resistance substitutions [*see Microbiology (12.4)*].

4.2 Change all references of [redacted] (b) (4) to Microbiology (12.4).

5 References

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC F DONALDSON
01/05/2015

TAKASHI E KOMATSU
01/05/2015

JULIAN J O REAR
01/05/2015

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 206353 **SDN:** 000 **DATE REVIEWED:** 12/29/14

Clinical Virology Reviewer: Takashi E. Komatsu, Ph.D., RAC

NDA #: 206353 **Supporting Document Numbers:** 000

Applicant Name and Address:

Bristol-Myers Squibb Co.
5 Research Parkway
P.O. Box 500
Wallingford, CT 06492-7660

Reviewer's Name: Takashi E. Komatsu, Ph.D., RAC

Initial Submission Dates:

Correspondence Date: April 4, 2014
CDER Receipt Date: April 4, 2014
Reviewer Receipt Date: April 4, 2014
Review Complete Date: December 29, 2014
PDUFA Date: February 4, 2015

Amendments:

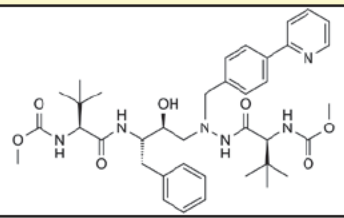
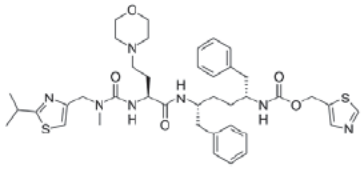
Response to Labeling Comments (SDN 007): July 22, 2014
Response to Labeling Comments (SDN 015): December 11, 2014
Response to Labeling Comments (SDN 018): December 26, 2014

Related/Supporting Documents:

IND 56,897, NDA 21567, NDA 203094, NDA 206353, DMF 25188

Product Name(s):

Proprietary: Evotaz
Non-Proprietary/USAN: atazanavir/cobicistat
Code Name/Number: ATV 300mg/COBI 150mg

Individual Component	ATV	COBI
Structure		
Chemical Name	Dimethyl (3S, 8S, 9S, 12S)-9-benzyl-3,12-di-tert-butyl-8-hydroxy-4,11-dioxo-6-[4-(2-pyridyl)benzyl]-2,5,6,10,13-pentaazaetradecanedioate	1,3-thiazol-5-ylmethyl[(2R,5R)-5-{[(2S)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate

	sulfate (1:1)	
Molecular Formula	$C_{38}H_{52}N_6O_7.H_2SO_4$	$C_{40}H_{53}N_7O_5S_2$
Molecular Mass	704.90	776.02
Drug Class	Protease Inhibitor	Pharmacoenhancer (No anti-HIV-1 activity)
Supporting Document	NDA 21567	NDA 203094

Indication(s): In combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adults.
Dosage Form(s): 300 mg of atazanavir and 150 mg of cobicistat
Route(s) of Administration: Oral
Recommended Dosage: One tablet taken once daily with food
Dispensed: Rx _X_ **OTC** ___ **(Discipline relevant)**

Abbreviations: ADV, adefovir; APV, amprenavir; ARV, antiretroviral; ATR, Atripla; ATV, atazanavir; ATV/r, ritonavir-boosted atazanavir; AZT, zidovudine; bp, base pair; CC_{50}, 50% cytotoxic concentration; COBI, cobicistat; ddI, didanosine; DRV, darunavir; d4T, stavudine; EC_{50}, effective concentration inhibiting viral replication by 50%; EC_{90}, effective concentration inhibiting viral replication by 90%; EFV, efavirenz; ETR, etravirine; ETV, entecavir; FBS, fetal bovine serum; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus (including HIV-1 and -2); HIV-1, human immunodeficiency virus type 1; HIV-2, human immunodeficiency virus type 2; HS, human serum; IDV, indinavir; IL-2, interleukin 2; IN, HIV-1 integrase; INSTI, HIV-1 integrase strand transfer inhibitor; LAM, lamivudine; LPV, lopinavir; L-dT, telbivudine; L-FMAU, clevudine; MDR, multidrug-resistant; MOI, multiplicity of infection; MVC, maraviroc; NDA, new drug application; NFV, nelfinavir; NNRTI, HIV-1 non-nucleoside reverse transcriptase inhibitor; NR, virologic non-response; N(t)RTI, HIV-1 nucleos(t)ide reverse transcriptase inhibitor; NVP, nevirapine; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction; PI, HIV-1 protease inhibitor; PI/r, ritonavir-boosted HIV-1 protease inhibitor; PK, pharmacokinetics; PR, HIV-1 protease; QD, once daily; RAL, raltegravir; RBV, ribavirin; RPV, rilpivirine; RT, HIV-1 reverse transcriptase; RTI, HIV-1 reverse transcriptase inhibitor; RTV, ritonavir; SD, standard deviation; SI, selective index; SQV, saquinavir; SR, suboptimal virologic response; TAM, thymidine analogue mutation; TDF, tenofovir disoproxil fumarate; TFV, tenofovir (active moiety of the diester prodrug TDF); TPV, tipranavir; TVD, Truvada; T-20, enfuvirtide;

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 206353 **SDN:** 000 **DATE REVIEWED:** 12/29/14

Clinical Virology Reviewer: Takashi E. Komatsu, Ph.D., RAC

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DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 206353 **SDN:** 000 **DATE REVIEWED:** 12/29/14

Clinical Virology Reviewer: Takashi E. Komatsu, Ph.D., RAC

EXECUTIVE SUMMARY

This application was submitted in support of a new drug application (NDA) for Evotaz fixed dose combination (FDC) tablets (atazanavir/cobicistat 300mg/150mg) indicated for the treatment of human immunodeficiency virus (HIV-1) infection in combination with other antiretroviral agents in adults. This NDA package includes clinical data from one Phase 1 study (AI424511 – "A Randomized, 5-Period, Crossover Study in Healthy Subjects to Assess the Bioequivalence of Atazanavir when Co-Administered with Cobicistat as a Fixed Dose Combination Relative to the Single Agents Following a Light Meal, the Relative Bioavailability of Atazanavir when Co-Administered with Cobicistat as a Fixed Dose Combination Relative to the Single Agents Under Fasted Conditions, and the Effect of Food on the Bioavailability of Atazanavir in the Fixed Dose Combination.").

Soon after the introduction of protease inhibitors (PI), it was recognized that coadministration of the approved HIV-1 protease inhibitor ritonavir (RTV) with other PIs improves the pharmacokinetics of the approved PI, increasing the serum half life and thereby permitting a more constant exposure to the PI (i.e. reducing C_{max} and increasing C_{min}). RTV was found to be an inhibitor of the CYP3A enzymes involved in the metabolism of PIs. Currently, RTV-boosted HIV-1 PI regimens are a standard of care. However, RTV boosting is limited to PIs in protease inhibitor naïve individuals as absence of a PI could lead to selection of PI resistance-associated substitutions. RTV boosting of PIs has generated a renewed interest in pharmacokinetics (PK) principles and their clinical implications.

COBI is structurally similar to ritonavir and was designed to be a specific inhibitor of CYP3A without HIV-1 protease inhibitory activity. Enzyme inactivation studies have demonstrated that COBI is an efficient inactivator of human hepatic microsomal CYP3A activity, with enzyme kinetic parameters (K_i and k_{inact}) comparable to those of ritonavir.

Atazanavir is an azapeptide HIV-1 protease inhibitor with an EC_{50} value of 2 to 5 nM against a variety of HIV-1 isolates in several cell-types. Atazanavir, in combination with low-dose RTV as a pharmacokinetic enhancer and other approved ARVs, is approved for the treatment of HIV-1 infection. ATV/r is currently indicated for ART-naïve and ART-experienced adults, as well as ART-experienced pediatric patients 6 years of age and older.

The efficacy and safety of COBI in combination with ATV as individual agents have been established in the Phase 3 Study GS-US-216-0114 and the supportive Phase 2 Study GS-US-216-0105 (NDA 203094 SDN 000). Study AI424511 was a bioavailability and bioequivalence studies in healthy subjects.

1. Recommendations

1.1. Recommendation and Conclusion on Approvability:

Approval is recommended with respect to Clinical Virology of this original NDA for Evotaz tablet (atazanavir/cobicistat 300mg/150mg), once daily, as a treatment of human immunodeficiency virus (HIV-1) infection in combination with other antiretroviral agents in adults.

1.2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, If Approvable:

2. Summary of OND Virology Assessments

2.1. Nonclinical Virology

The sponsor did not conduct any new nonclinical virology studies for this submission. All of the nonclinical virology data have been submitted with the Reyataz® submission (NDA 21567, SDN 000) and the Stribild® submission (NDA 203100, SDN 000).

2.2. Clinical Virology

This NDA package includes clinical data from one Phase 1 studies (AI424511 – a phase 1 oral bioavailability study to provide PK and safety data). Study AI424511 was a bioavailability and bioequivalence studies in healthy, uninfected subjects.

3. Administrative

3.1. Reviewer's Signatures

_____

Takashi E. Komatsu, Ph.D., RAC
Clinical Virology Reviewer

3.2. Concurrence

_____

HFD-530/Clin.Virol.TL/J. O'Rear, Ph.D.

CC:
HFD-530/NDA # 206353
HFD-530/Division File
HFD-530/PM/Beam

OND VIROLOGY REVIEW

1. Introduction and Background

1.1. Important milestones in product development

Cobicistat (COBI, TYBOST) is a pharmacokinetic enhancer of the HIV-1 protease inhibitors (PIs) atazanavir and darunavir. Cobicistat is structurally similar to ritonavir and was designed to be a specific inhibitor of CYP3A without HIV-1 protease inhibitory activity. Ritonavir boosting is limited to PIs in treatment-naïve individuals as absence of a PI could lead to selection of PI resistance-associated substitutions. Atazanavir (ATV, Reyataz®), in combination with low-dose ritonavir (RTV) as a pharmacokinetic enhancer and other approved antiretrovirals (ARVs), is approved for the treatment of HIV-1 infection. A fixed dose combination (FDC) tablet atazanavir/cobicistat (300mg/150mg) is proposed in this NDA. This NDA package includes clinical data from one Phase 1 studies (AI424511 – "A Randomized, 5-Period, Crossover Study in Healthy Subjects to Assess the Bioequivalence of Atazanavir when Co-Administered with Cobicistat as a Fixed Dose Combination Relative to the Single Agents Following a Light Meal, the Relative Bioavailability of Atazanavir when Co-Administered with Cobicistat as a Fixed Dose Combination Relative to the Single Agents Under Fasted Conditions, and the Effect of Food on the Bioavailability of Atazanavir in the Fixed Dose Combination."). A pre-NDA meeting with the sponsor was held on 12/9/13.

1.2. Overview of HIV-1

Approximately 33.3 million people worldwide are estimated to be living with human immunodeficiency virus type 1 (HIV-1) infection worldwide (UNAIDS Global Report, 2010). The infection, if left untreated or suboptimally treated, leads to the development of Acquired Immune Deficiency Syndrome (AIDS), characterized by deterioration in immune function, the subsequent occurrence of opportunistic infections, and malignancies, ultimately resulting in death. Standard-of-care for the treatment of HIV-1 infection involves the use of a combination of antiretroviral drugs to suppress viral replication to below quantifiable limits (<50 copies/mL), increase $CD4^+$ T cell counts, and delay disease progression. Current treatment guidelines (DHHS, updated in March, 2012) for treatment-naïve HIV-1 infected patients suggest that initial therapy generally consists of two nucleoside or nucleos(t)ide analog reverse transcriptase inhibitors (N(t)RTIs) in combination with a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI, preferably "boosted" with ritonavir [RTV]), an integrase stand transfer inhibitor (INSTI), or a CCR5 co-receptor antagonist (namely maraviroc [MVC]). For treatment-experienced HIV-1 infected patients, a new regimen contains at least two, preferably three, fully active ARVs to combine with an optimized background antiretroviral regimen, based on the patient's treatment history, and past and current resistance test results.

The use of antiretroviral combination therapy, introduced in the early 1990s, greatly reduced the morbidity and mortality associated with AIDS. However, combination therapy increased adherence challenges for patients due to the regimen-associated factors such as frequent dosing, differential dosing frequency for regimen components, increased pill burden, dietary restrictions, and safety concerns. Poor adherence increases the risk of incomplete viral suppression, development of drug-resistance virus, and disease progression (Chesney, 2000; Chesney et al., 2000). Clinical studies have demonstrated high levels of adherence and treatment success with simple, once-daily, highly active antiretroviral therapy (HAART) regimens, resulting in persistent suppression of HIV-1 viral load (Arribas et al., 2004; Felizarta et al., 2004; Maggiolo et al., 2001). Recently, a meta-analysis of 11 randomized, controlled

trials involving 3,029 subjects also demonstrated that the adherence rate was better with once-daily regimens (+2.9%; 95% confidence interval, 1.0-4.8%) than with twice-daily regimens (Jean-Jacques et al., 2009). Additionally, with some combinations patients may take an incomplete regimen, leading to increased risk of resistance development. This risk can be reduced if a complete treatment regimen (i.e., 2 N(t)RTIs plus one ARV from another class) is available in a once-daily, single pill, fixed-dose combination tablet (FDC), reducing pill burden. To date, three complete regimens in a single-pill have been approved. Two are NNRTI-based with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) as a preferred N(t)RTI backbone, for once-daily administration in the treatment of HIV-1 infection: Atripla® (ATR; 600 mg EFV/200 mg FTC/300 mg TDF; approved on July 12, 2006; NDA 21937, reviewed by Virology Reviewer Narayana Battula, Ph.D.) and Complera® (27.5 mg rilpivirine [RPV]/200 mg FTC/300 mg TDF; approved on August 10, 2011; NDA 202123, reviewed by Virology Reviewer Lisa Naeger, Ph.D.). The third is an INSTI-based FDC with FTC/TDF as a preferred N(t)RTI backbone: Stribild® (150 mg EVG/150 mg COBI/200 mg FTC/300 mg TDF; approved on August 27, 2012; NDA 203100, reviewed by Virology Reviewer Sung Rhee, Ph.D. and Virology Reviewer Takashi Komatsu, Ph.D.).

Soon after the introduction of PIs, it was recognized that coadministration of the approved HIV-1 protease inhibitor ritonavir (RTV) with other PIs improves the pharmacokinetics of the approved PI (Kempf et al., 1997; NDA 20659), increasing the serum half-life and thereby permitting a more constant exposure to the PI (i.e. reducing C_{max} and increasing C_{min}). RTV was found to also be an inhibitor of the CYP3A enzymes involved in the metabolism of PIs. Currently, RTV-boosted HIV-1 PI regimens are a standard of care. However, RTV boosting is limited to PIs in protease inhibitor naïve individuals as absence of a PI could lead to selection of PI resistance-associated substitutions. RTV boosting of PIs has generated a renewed interest in PK principles and their clinical implications. The PK rationales for the combination of PIs and ritonavir (RTV) have been reviewed in various articles and include reduction in dose and dosing frequency, achieving additive or synergistic antiretroviral effects, overcoming established low-level reduced sensitivity through increased drug exposure, and creating a higher genetic barrier to resistance (Heeswijk et al., 2001; Rathbun and Rossi, 2002).

COBI is structurally similar to ritonavir and was designed to be a specific inhibitor of CYP3A without HIV-1 protease inhibitory activity (Figure 1). Enzyme inactivation studies have demonstrated that COBI is an efficient inactivator of human hepatic microsomal CYP3A activity, with enzyme kinetic parameters (K_i and k_{inact}) comparable to those of ritonavir. CYP3A-mediated oxidative metabolism is the major biotransformation pathway for COBI, as it is for ritonavir; however, unlike ritonavir, COBI is a more specific CYP enzyme inhibitor. It is a weak inhibitor of CYP2D6 and does not inhibit CYP1A2, CYP2C9, or CYP2C19. In addition, COBI displays low liability for induction through activation of xenobiotic receptors, including the aryl hydrocarbon receptor, pregnane X receptor, and the constitutive androstane receptor, in human hepatocytes. In contrast, ritonavir, a known potent pregnane X receptor activator, produces significant induction of phase I enzymes, including CYP3A, as well as phase II uridine 5'-diphospho-glucuronosyltransferase enzymes and drug transporters, including P-gp, that lead to clinically significant drug–drug interactions. Other favorable characteristics of COBI are reduced perturbation of the normal adipocyte functions of lipid accumulation and/or response to insulin (please refer to the Clinical Pharmacology reviews by Dr. Vikram Arya, Ph.D. and Dr. Stanley Au, Ph.D., for NDAs 203100 and 203094, respectively).

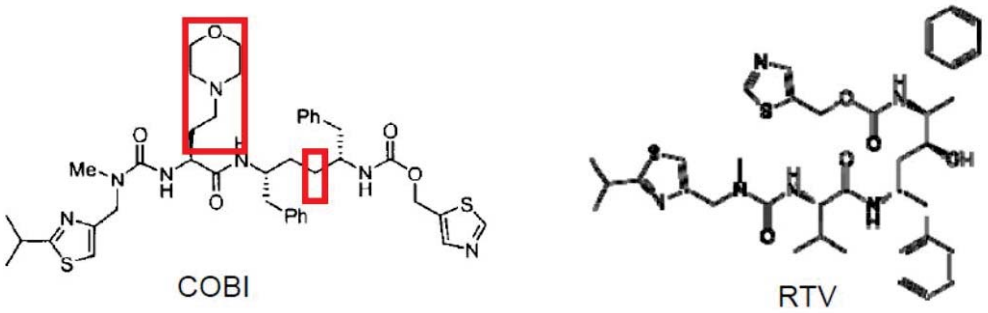

Figure 1: Structures of COBI and RTV.

Atazanavir is an azapeptide HIV-1 protease inhibitor with an EC_{50} value of 2 to 5 nM against a variety of HIV-1 isolates in several cell-types. Atazanavir, in combination with low-dose RTV as a pharmacokinetic enhancer and other approved ARVs, is approved for the treatment of HIV-1 infection (please see the original NDA review of Dr. Lisa Naeger, Ph.D. for NDA 21567 approved on 6/20/03). ATV/r is currently indicated for ART-naïve and ART-experienced adults, as well as ART-experienced pediatric patients 6 years of age and older. The oral dose of atazanavir 300 mg q.d. taken with RTV 100 mg q.d. and with food is recommended in treatment-naïve adult patients as well as in treatment-experienced adult patients with no ATV resistance-associated substitutions (L10I, V11I, V32I, L33F/V/I, E35D/G, M46I/L, I50L, F53L/V, I54V, A71V/T/I, G73S/T/C, V82A/T/L, I85V, L89V/Q/M/T, and L90M).

2. Nonclinical Virology

The sponsor did not conduct any new nonclinical virology studies for this submission. All of the nonclinical virology data have been submitted and reviewed with the Reyataz® (NDA 21567, SDN 000) and Stribild® submissions (NDA 203100, SDN 000). Please see the Clinical Virology reviews of NDA 21567 SDN 000 and NDA 203100 SDN 000 for a detailed analysis of the mechanism of action, antiviral activity in cell culture, cytotoxicity, combination antiviral activity relationships with approved antiretroviral drugs as well as the methods that were used for the analyses for ATV and COBI.

3. Clinical Virology

In a Phase 1 clinical study in healthy volunteers (Study GS-US-216-0110), ATV 300 mg once daily exposures (AUC_{tau}, C_{max}, and C_{trough}) were bioequivalent when boosted by COBI 150 mg once daily or RTV 100 mg once daily (please see the review of Dr. Stanley Au, Ph.D. for NDA 203094). The efficacy and safety of COBI have been established in the Phase 3 Study GS-US-216-0114 and the supportive Phase 2 Study GS-US-216-0105 (please see the Clinical Virology review of NDA 203094 SDN 000). Both of these studies are double-blind and active-controlled studies with combination ARV regimens in ARV-treatment-naive subjects with HIV-1 infection, and both studies were designed to compare COBI 150mg-boosted atazanavir (ATV/co) with RTV 100 mg-boosted atazanavir (ATV/r) in combination with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF). A phase 1 pharmacokinetic study (AI424511) in healthy subjects was conducted to evaluate the bioequivalence of the fixed-dose combination tablet of ATV 300 mg and COBI 150 mg as compared to the separate ATV 300 mg capsule and COBI 150 mg tablet administered concurrently. Study AI424511 was a bioavailability and bioequivalence studies in

healthy subjects so will not be covered in this review. Please see the review of Dr. Vikram Arya, Ph.D., Clinical Pharmacology reviewer, for more details.

4. Conclusion
This original NDA for Evotaz tablets is approvable with respect to Clinical Virology. The proposed indication for the Evotaz tablet is treatment of human immunodeficiency virus (HIV-1) infection in combination with other antiretroviral agents in adults.

Microbiology Package Insert
The words with strikethroughs are the text the sponsor is requested to delete and words highlighted in blue are recommended insertions.

12.1 Mechanism of Action
EVOTAZ is a fixed-dose combination of the anti-retroviral drug, atazanavir (b) (4) and the CYP3A inhibitor (b) (4) cobicistat. [See Microbiology (b) (4) (12.4).]

12.4 Microbiology
Mechanism of Action
EVOTAZ is a fixed-dose combination of atazanavir (ATV) (b) (4) cobicistat. ATV is an azapeptide HIV-1 protease inhibitor (PI) that selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions. Cobicistat is a mechanism-based inhibitor of cytochrome P450 3A (CYP3A). Inhibition of CYP3A-mediated metabolism by cobicistat increases the systemic exposure of CYP3A substrate (b) (4) atazanavir.

Antiviral Activity in Cell Culture
Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC_{50}) value in the absence of human serum of 2 to 5 nM against a variety of laboratory and clinical HIV-1 isolates grown in peripheral blood mononuclear cells, macrophages, CEM-SS cells, and MT 2 cells. ATV has activity against HIV-1 Group M subtype viruses A, B, C, D, AE, AG, F, G, and J isolates in cell culture. ATV has variable activity against HIV-2 isolates (1.9 to 32 nM), with EC_{50} values above the EC_{50} values of failure isolates. Two-drug combination antiviral activity studies with ATV showed no antagonism in cell culture with NNRTIs (delavirdine, efavirenz, and nevirapine), PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine), the HIV-1 fusion inhibitor enfuvirtide, and two compounds used in the treatment of viral hepatitis, adefovir and ribavirin, without enhanced cytotoxicity.

Cobicistat does not inhibit recombinant HIV-1 protease in a biochemical assay and has no detectable antiviral activity in cell culture against HIV-1, HBV, or HCV. The antiviral activity in cell culture of selected HIV-1 antiretroviral drugs was not antagonized by cobicistat.

Resistance
In Cell Culture: HIV-1 isolates with a decreased susceptibility to ATV have been selected in cell culture and obtained from patients treated with ATV or atazanavir (b) (4) ritonavir (b) (4). HIV-1 isolates with 93- to 183-fold reduced susceptibility to ATV from three different viral strains were selected in cell culture by 5 months. The substitutions in these HIV-1 viruses that

contributed to ATV resistance include I50L, N88S, I84V, A71V, and M46I. Changes were also observed at the protease cleavage sites following drug selection. Recombinant viruses containing the I50L substitution without other major PI substitutions were growth impaired and displayed increased susceptibility in cell culture to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). The I50L and I50V substitutions yielded selective resistance to ATV and amprenavir, respectively, and did not appear to be cross-resistant.

Clinical Studies: Resistance to EVOTAZ is driven by atazanavir as cobicistat lacks antiviral activity. For the complete atazanavir resistance-associated substitutions, refer to the atazanavir full prescribing information.

Clinical Studies of Treatment-Naive Patients Receiving Atazanavir 300 mg with Cobicistat 150 mg: In an analysis of treatment-failure subjects who received atazanavir coadministered with cobicistat in Study 114 through Week 48, evaluable genotypic data from paired baseline and treatment-failure isolates were available for 11 of the 12 virologic failures in this group (3%, 11/344). Among the 11 subjects, 2 developed the emtricitabine-associated resistance substitution M184V. No subject developed the tenofovir-associated resistance substitution K65R or any primary resistance substitution associated with protease inhibitors. In the ritonavir group, evaluable genotypic data was available for all 12 virologic failures (3%, 12/348) and no subject had emergent resistance to any component of the regimen.

(b) (4)

(b) (4)

Cross-Resistance
Cross-resistance among PIs has been observed. Baseline phenotypic and genotypic analyses of clinical isolates from ATV clinical trials of PI-experienced patients showed that isolates cross-resistant to multiple PIs were cross-resistant to ATV. Greater than 90% of the isolates with substitutions that included I84V or G48V were resistant to ATV. Greater than 60% of isolates containing L90M, G73S/T/C, A71V/T, I54V, M46I/L, or a change at V82 were resistant to ATV, and 38% of isolates containing a D30N substitution in addition to other changes were resistant to ATV. Isolates resistant to ATV were also cross-resistant to other PIs with >90% of the isolates resistant to indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir, and 80% resistant to amprenavir. In treatment-experienced patients, PI-resistant viral isolates that developed the I50L substitution in addition to other PI resistance-associated substitution were also cross-resistant to other PIs.

International AIDS Society (IAS)-defined (b) (4) PI resistance substitutions, depending on the number and type, may confer a reduced virologic response to atazanavir. Please refer to the "Baseline Genotype/Phenotype and Virologic Outcome Analyses" section in the atazanavir full prescribing information.

Additional changes
- (b) (4) to 'substitution' throughout the label where appropriate.
- Add the 'Baseline Genotype/Phenotype and Virologic Outcome Analyses' section from the REYATAZ label.

(b) (4)

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Clean Version
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/s/

TAKASHI E KOMATSU
12/29/2014

JULIAN J O REAR
12/30/2014

M E M O R A N D U M

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

DATE: 13 May 2014

TO: NDA 206353

FROM: Bryan S. Riley, Ph.D.
Team Leader (Acting)
OPS/New Drug Microbiology Staff

THROUGH: John W. Metcalfe, Ph.D.
Senior Review Microbiologist
OPS/New Drug Microbiology Staff

cc: Sammie G. Beam, RPh
Regulatory Project Manager
OND/DAVP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for EVOTAZ (atazanavir (b) (4) /cobicistat tablet) [Submission Date: 4 April 2014]

The Microbial Limits specification for EVOTAZ is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

EVOTAZ is a Film-Coated Tablet for oral administration.

The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).

M E M O R A N D U M

Table 1 – Microbial Limits Specifications

Test	Acceptance Criteria
Total Aerobic Microbial Count (USP <61>)	NMT (b) (4)
Total Yeast and Mold Count (USP <61>)	NMT (b) (4)
E. coli (USP <62>)	Absent in (b) (4)

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

The drug product stability protocol does not include Microbial Limits testing. However, (b) (4) was monitored for stability batches of the drug product and the results to date have been less than (b) (4).

ADEQUATE

Reviewer Comments – The microbiological quality of the drug product is controlled via a suitable testing protocol at release. Microbial quality of the drug product on stability is assured by the (b) (4) of the drug product (b) (4)

END

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/s/

BRYAN S RILEY
05/16/2014

JOHN W METCALFE
05/16/2014
I concur.