

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203094Orig1s000

203094Orig2s000

Trade Name: Tybost tablet, 150 mg.

Generic Name: cobicistat

Sponsor: Gilead Sciences, Inc.

Approval Date: September 24, 2014

Indication: Tybost (dobicistat) Tablet for the following indications which for administrative purposes, we have designated as follows:

- Original 1: provides for the use as a CYP3A inhibitor indicated to increase systemic exposures of atazanavir in combination with other antiretroviral agents in the treatment of HIV-1 infection.
- Original 2: provides for the use as a CYP3A inhibitor indicated to increase systemic exposures of darunavir in combination with other antiretroviral agents in the treatment of HIV-1 infection.

CENTER FOR DRUG EVALUATION AND RESEARCH

203094Orig1s000

203094Orig2s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	X
Labeling	X
REMS	
Summary Review	X
Officer/Employee List	X
Office Director Memo	
Cross Discipline Team Leader Review	X
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	X
Statistical Review(s)	X
Microbiology / Virology Review(s)	X
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	X
Proprietary Name Review(s)	X
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203094Orig1s000

203094Orig2s000

APPROVAL LETTER



NDA 203094 Original 1

NDA APPROVAL

Gilead Sciences, Inc.
Attention: Christophe Beraud, PhD
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

Please refer to your New Drug Application (NDA) dated June 27, 2012, received June 28, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tybost (cobicistat) tablet, 150 mg.

We acknowledge receipt of your amendments dated.

June 28, 2012	February 11, 2013 (2)	March 6, 2014
July 9, 2012	February 22, 2013	March 28, 2014
August 21, 2012	February 25, 2013	March 31, 2014
September 7, 2012	March 4, 2013	April 3, 2014
September 10, 2012	March 8, 2013	April 7, 2014
September 11, 2012	March 21, 2013	April 9, 2014
October 2, 2012	April 9, 2013	April 24, 2014
October 5, 2012	April 16, 2013	April 25, 2014
October 19, 2012	April 17, 2013	May 9, 2014
October 26, 2012	April 23, 2013	May 12, 2014
November 27, 2012	May 22, 2013	May 15, 2014
December 4, 2012	August 13, 2013	July 1, 2014
December 19, 2012	August 14, 2013	July 25, 2014
December 20, 2012	September 17, 2013	August 7, 2014
January 21, 2013	September 30, 2013 (2)	August 12, 2014
January 22, 2013	October 10, 2013	September 12, 2014
January 29, 2013	December 13, 2013 (2)	September 15, 2014
January 31, 2013	January 29, 2014	September 19, 2014

We also acknowledge receipt of the information related to Tybost (cobicistat) 150 mg tablet for the Gilead Access Program that was reviewed as part of this application.

The March 28, 2014, submission constituted a complete response to our April 26, 2013, action letter.

NDA 203094 provides for the use of Tybost (cobicistat) tablet for the following indications which, for administrative purposes, we have designated as follows:

- NDA 203094/Original 1 – provides for the use of Tybost (cobicistat) as a CYP3A inhibitor indicated to increase systemic exposures of atazanavir in combination with other antiretroviral agents in the treatment of HIV-1 infection.
- NDA 203094/Original 2 – provides for the use of Tybost (cobicistat) as a CYP3A inhibitor indicated to increase systemic exposures of darunavir in combination with other antiretroviral agents in the treatment of HIV-1 infection.

The subject of this action letter is NDA 203094/Original 1. A separate action letter will be issued for NDA 203094/Original 2.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

IMMEDIATE CONTAINER LABELS

Submit final printed immediate container labels that are identical to the enclosed immediate container label, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications*

and Related Submissions Using the eCTD Specifications (June 2008). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Container Labels for approved NDA 203094.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to less than three months because necessary studies are impossible or highly impracticable. This is because Tybost (cobicistat) is indicated as a CYP3A inhibitor to increase systemic exposures of atazanavir (ATV) and the pediatric study requirements have been waived for ages birth to less than three months for ATV.

We are deferring submission of your pediatric study for ages 3 months to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

2757-1: Conduct a trial to evaluate pediatric pharmacokinetics (PK), safety and antiviral activity of once daily atazanavir and cobicistat (ATV/COBI) combined with a background regimen in HIV-1 infected pediatric subjects. Subjects receiving ATV/COBI should be from 3 months to less than 18 years of age. Initial evaluation of ATV/COBI exposure must be performed in an initial PK study or substudy to allow dose selection. Using doses selected based on the PK study/substudy, and agreed upon with the FDA, conduct a longer-term pediatric safety and antiviral activity assessment of ATV/COBI combined with a background regimen, assessing activity on the basis of continued HIV-1 RNA virology response and safety monitoring over as least 24 weeks of dosing.

Trial Completion: 10/31/2018
Final Report Submission: 1/31/2019

Submit the protocol to your IND 101283, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signals of a serious risk of drug interactions with certain important medications for the intended patient population, specifically :

- a signal of a serious risk of drug interactions and the associated potential effects of Tybost (cobicistat) combined with atazanavir on estrogen or progestin. There is the possibility that increased or decreased estrogen or progestin exposures resulting from such interactions could result in serious adverse effects such as venous thrombosis or oral contraceptive failure, respectively.
- a signal of a serious risk of predicted potential CYP3A and transporter inhibition effects with Tybost (cobicistat) combined with atazanavir with the possibility that increased statin exposures could result in adverse effects such as myopathy, including rhabdomyolysis.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2757-2 A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of atorvastatin.

The timetable you submitted on July 25, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 6/30/2015
Trial Completion: 4/30/2016
Final Report Submission: 12/31/2016

- 2757-3. A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of rosuvastatin.

The timetable you submitted on July 25, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 6/30/2015
Trial Completion: 4/30/2016
Final Report Submission: 12/31/2016

- 2757-4. A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of the estrogen and progestin components of a combined oral contraceptive.

The timetable you submitted on August 7, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 8/31/2015
Trial Completion: 6/30/2016
Final Report Submission: 2/28/2017

Submit the protocols to your IND 101283, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Karen Winestock, Chief, Project Management Staff, at (301) 301-796-0834 or 301-796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Container Label

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

/s/

DEBRA B BIRNKRANT
09/24/2014



NDA 203094 Original 2

NDA APPROVAL

Gilead Sciences, Inc.
Attention: Christophe Beraud, PhD
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

Please refer to your New Drug Application (NDA) dated June 27, 2012, received June 28, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tybost (cobicistat) tablet, 150 mg.

We acknowledge receipt of your amendments dated:

June 28, 2012	February 11, 2013 (2)	March 6, 2014
July 9, 2012	February 22, 2013	March 26, 2014
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January 29, 2013	December 13, 2013 (2)	September 15, 2014
January 31, 2013	January 29, 2014	September 19, 2014

We also acknowledge receipt of the information related to Tybost (cobicistat) 150 mg tablet for the Gilead Access Program that was reviewed as part of this application.

One of the April 3, 2014, submissions constituted a complete response to our April 26, 2013, action letter.

NDA 203094 provides for the use of Tybost (cobicistat) tablet for the following indications which, for administrative purposes, we have designated as follows:

- NDA 203094/Original 1 – provides for the use of Tybost (cobicistat) as a CYP3A inhibitor indicated to increase systemic exposures of atazanavir in combination with other antiretroviral agents in the treatment of HIV-1 infection.
- NDA 203094/Original 2 – provides for the use of Tybost (cobicistat) as a CYP3A inhibitor indicated to increase systemic exposures of darunavir in combination with other antiretroviral agents in the treatment of HIV-1 infection.

The subject of this action letter is NDA 203094/Original 2. A separate action letter will be issued for NDA 203094/Original 1.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

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and Related Submissions Using the eCTD Specifications (June 2008). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Container Labels for approved NDA 203094.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the products with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to less than three years because evidence strongly suggests that the drug product would be unsafe in this pediatric group. Significant toxicities were observed in a juvenile animal study conducted with darunavir.

We are deferring submission of your pediatric study for ages 3 years to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

2758-1: Conduct a study to evaluate pediatric pharmacokinetics (PK), safety and antiviral activity of once daily darunavir and cobicistat (DRV/COBI) combined with a background regimen in HIV-1 infected pediatric subjects. Subjects receiving DRV/COBI should be from 3 years to less than 18 years of age. Initial evaluation of DRV/COBI exposure must be performed in an initial PK study or substudy to allow dose selection. Using doses selected based on the PK study or substudy, and agreed upon with the FDA, conduct a longer-term pediatric safety and antiviral activity assessment of DRV/COBI combined with a background regimen, assessing activity on the basis of continued HIV-1 RNA virology response and safety monitoring over as least 24 weeks of dosing.

Trial Completion: 10/31/2018
Final Report Submission: 1/31/2019

Submit the protocol to your IND 101283, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signals of a serious risk of drug interactions with certain important medications for the intended patient population, specifically :

- a signal of a serious risk of drug interactions and the associated potential effects of Tybost (cobicistat) combined with darunavir on estrogen or progestin. There is the possibility that increased or decreased estrogen or progestin exposures resulting from such interactions could result in serious adverse effects such as venous thrombosis or oral contraceptive failure, respectively.
- a signal of a serious risk of predicted potential CYP3A and transporter inhibition effects with Tybost (cobicistat) combined with darunavir with the possibility that increased statin exposures could result in adverse effects such as myopathy, including rhabdomyolysis.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2758-2 A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of atorvastatin.

The timetable you submitted on July 25, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 6/30/2015
Trial Completion: 4/30/2016
Final Report Submission: 12/31/2016

- 2758-3. A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of rosuvastatin.

The timetable you submitted on July 25, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 6/30/2015
Trial Completion: 4/30/2016
Final Report Submission: 12/31/2016

- 2758-4. A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of the estrogen and progestin components of a combined oral contraceptive.

The timetable you submitted on August 7, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 8/31/2015
Trial Completion: 6/30/2016
Final Report Submission: 2/28/2017

Submit the protocol(s) to your IND 101283, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Karen Winestock, Chief, Project Management Staff, at (301) 796-0834 or 301-796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Container Label

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

/s/

DEBRA B BIRNKRANT
09/24/2014