

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205551Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW - ADDENDUM			
Office of New Drug Quality Assessment			
Application No.:	NDA 205551	Biopharmaceutics Reviewer: Elsbeth Chikhale, PhD	
Submission Date:	October 22, 2013		
Division:	Division of Antiviral Products	Biopharmaceutics Team Leader: Angelica Dorantes, PhD	
Applicant:	ViiV Healthcare Co.	Acting Supervisor: Richard Lostritto, PhD	
Trade Name:	Triumeq	Date Assigned:	October 23, 2013
Generic Name:	Abacavir, Dolutegravir and Lamivudine	Date of Review:	August 15, 2014
Indication:	Treatment of HIV	Type of Submission: 505(b)(1) Original New Drug Application	
Dosage form/ strengths	Tablets/ 600 mg abacavir / 50 mg dolutegravir / 300 mg lamivudine per tablet		
Route of Administration	Oral		

SUMMARY:

Submission:

This is a 505(b)(1) for a fixed dose combination (FDC) film coated purple oval tablet containing 50 mg (b)(4) dolutegravir (DTG), 600 mg abacavir and 300 mg lamivudine per tablet.

Review:

ONDQA-Biopharmaceutics reviewed the original NDA 205551 submitted 10/22/2013, and a Biopharmaceutics review authored by Dr. Elsbeth Chikhale was placed in DARRTS on 7/7/2014. The review concluded the following:

“At this time of the review process the consult report from the Office of Scientific Investigations is pending. Therefore, from the Biopharmaceutics perspective the information needed to support the approval of this NDA is incomplete and the Biopharmaceutics recommendation for NDA 205551 for Triumeq (abacavir, dolutegravir, and lamivudine) FDC Tablets (600 mg/50 mg/300 mg) is currently PENDING.”

The consult reports from the Office of Scientific Investigations (OSI) were completed and signed in DARRTS on August 15, 2014. This Addendum to the Original Biopharmaceutics review is focused on the evaluation of the information provided by the Office of Scientific Investigations (OSI) in their inspection report for BE study No. ING114580, entitled “An Evaluation of the

Bioequivalence of a Combined Formulated Tablet (50mg/600mg/300mg dolutegravir/abacavir/lamivudine) Compared to One Dolutegravir 50mg Tablet and One EPZICOM (600mg/300mg abacavir/lamivudine) Tablet Administered Concurrently and the Effect of Food on Bioavailability of the Combined Formulation in Healthy Adult Subjects”.

The inspection report (dated 8/15/14 in DARRTS) from the Office of Scientific Investigations (OSI) for the BE study ING114580, included the following conclusion and recommendation:

- The clinical and analytical data from the audited study were found to be reliable. Therefore, this DBGLPC reviewer recommends the data be accepted for the Agency review.

Reviewer’s Assessment of the OSI Inspection Report: SATISFACTORY

This Reviewer concurs with the overall recommendation provided in the OSI’s Inspection Report and therefore, the clinical and analytical data for BE study ING114580 are reliable and the study is acceptable.

In conclusion, the overall results from study ING114580 demonstrate that the proposed FDC drug product is bioequivalent to the separate tablet formulations of DTG 50 mg plus EPZICOM (ABC 600 mg/3TC 300 mg) under fasted conditions.

RECOMMENDATION:

- From a Biopharmaceutics perspective NDA 205551 for Triumeq (abacavir, dolutegravir, and lamivudine) FDC Tablets (600 mg/50 mg/300 mg) is recommended for **APPROVAL**.

Elsbeth Chikhale, Ph.D.

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.

Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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

/s/

ELSBETH G CHIKHALE
08/15/2014

ANGELICA DORANTES
08/15/2014

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 205551	Original Submission Date: October 22, 2013
Brand Name	Triumeq
Generic Name	Abacavir/dolutegravir/lamivudine
Reviewer	Stanley Au, Pharm.D., BCPS
Clinical Pharmacology Team Leader	Shirley Seo, Ph.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products (DAVP)
Applicant	ViiV Healthcare
Formulation; strength(s)	Fixed dose combination tablet: Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg
Indication	Treatment of HIV-1 infection
Review Type	505 (b)(1) New Drug Application, standard review

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1 Executive Summary

The applicant, ViiV Healthcare, submitted a New Drug Application (NDA) that included the ING114580 trial, which evaluated the relative bioavailability of a fixed dose combination tablet consisting of abacavir 600 mg dolutegravir 50 mg, and lamivudine 300 mg compared to a fixed dose combination tablet consisting of abacavir 600 mg and lamivudine 300 mg coadministered with dolutegravir 50 mg. The food effect of the abacavir, dolutegravir and lamivudine fixed dose combination tablets was also evaluated.

For the Clinical Pharmacology review for NDA 205551, only the food effect data from the pivotal relative bioavailability trial (ING114580) was reviewed. The other pertinent review issues for the ING114580 trial that includes evaluating the relative bioavailability data and reviewing the inspection findings from the Office of Scientific Investigations, as well as the relevant bioanalytical information, will be assessed by the biopharmaceutics reviewers within the Office of New Drug Quality Assessment.

1.1 Recommendation

The clinical pharmacology information submitted in the NDA supports the approval of the application.

1.2 Postmarketing Commitments or Requirements

There are no postmarketing commitments or requirements for this NDA.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

A food effect was observed for dolutegravir when administered as a fixed dose combination tablet in combination with abacavir and lamivudine. The single entity dolutegravir label states that dolutegravir may be administered with or without food. The observed increase in dolutegravir exposure when dolutegravir is administered as part of a fixed dose combination tablet with abacavir and lamivudine is within the magnitude of the increase in C_{\max} and $AUC_{(0-\infty)}$ for dolutegravir when administered as a single entity tablet. Therefore, the applicant's recommendation to administer the fixed dose combination tablet with or without food with respect to dolutegravir is acceptable.

A food effect was also observed for abacavir when administered as a fixed dose combination tablet in combination with dolutegravir and lamivudine based on the changes in C_{\max} . The single entity abacavir label states that abacavir may be administered with or without food. The observed decrease in C_{\max} when abacavir is administered as part of a fixed dose combination tablet with lamivudine and dolutegravir is within the magnitude of the decrease in C_{\max} for abacavir when administered as a single entity tablet. Therefore, the applicant's recommendation to administer the fixed dose combination tablet with or without food with respect to abacavir is acceptable.

A food effect was not observed for lamivudine when administered as part of a fixed dose combination tablet with abacavir and dolutegravir. Therefore, the applicant's recommendation to administer the fixed dose combination tablet with or without food when administered with respect to lamivudine is acceptable.

2 Labeling Recommendations

The applicant's proposed revisions and the clinical pharmacology reviewer's proposed modifications for the abacavir, dolutegravir, and lamivudine fixed dose combination tablets U.S. prescribing information are displayed below (highlighted in yellow where applicable).

Highlights

Applicant proposed language	Proposed reviewer changes
<p data-bbox="81 657 428 690">Dosage and administration</p> <div data-bbox="71 706 1035 917" style="background-color: #cccccc; height: 130px; width: 100%;"><p data-bbox="989 706 1035 722" style="text-align: right;">(b) (4)</p></div>	<p data-bbox="1064 657 2007 803"><i>Clinical pharmacology reviewer comment: For abacavir, a dosage adjustment is required in patients with mild hepatic impairment (200 mg twice daily), and abacavir is contraindicated in patients with moderate or severe hepatic impairment.</i></p> <p data-bbox="1064 836 1407 868">Dosage and administration</p> <ul data-bbox="1064 876 2007 982" style="list-style-type: none"><li data-bbox="1064 876 2007 982">• Patients with renal or hepatic impairment: TRIUMEQ should not be administered to patients with creatinine clearance less than 50 mL/min, or with hepatic impairment. (2.2)

Applicant proposed language	Proposed reviewer changes
<p data-bbox="79 354 428 386">Dosage and administration</p> <p data-bbox="79 427 155 459">None</p>	<p data-bbox="1058 354 1407 386">Dosage and administration</p> <ul data-bbox="1058 427 2007 602" style="list-style-type: none"> <li data-bbox="1058 427 2007 602">• Dosing with certain concomitant medications: If efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin are coadministered, then the recommended dolutegravir dosage regimen is 50 mg twice daily. An additional 50 mg dose of dolutegravir, separated by 12 hours from TRIUMEQ, should be taken.

Applicant proposed language	Proposed reviewer changes
<p data-bbox="79 727 312 760">Contraindications</p> <p data-bbox="79 800 155 833">None</p>	<p data-bbox="1058 727 1291 760">Contraindications</p> <ul data-bbox="1058 800 1713 833" style="list-style-type: none"> <li data-bbox="1058 800 1713 833">• Moderate or severe hepatic impairment. (2, 4, 8)

Applicant proposed language	Proposed reviewer changes
<p data-bbox="79 329 310 362">Drug Interactions</p> <div data-bbox="58 370 1047 693" style="background-color: #cccccc; height: 199px; width: 100%; position: relative;"> (b) (4) </div>	<p data-bbox="1060 318 1289 350">Drug Interactions</p> <ul data-bbox="1060 394 2030 537" style="list-style-type: none"> • Co-administration of TRIUMEQ with other drugs can alter the concentration of other drugs and other drugs may alter the concentrations of TRIUMEQ. The potential drug-drug interactions must be considered prior to and during therapy (4, 7, 12.3).

Section 2-Dosage and administration

Applicant proposed changes	Proposed reviewer changes
<div data-bbox="58 863 1047 1135" style="background-color: #cccccc; height: 167px; width: 100%; position: relative;"> (b) (4) </div>	<p data-bbox="1060 885 1764 917">Section 2.2 Patients with Renal or Hepatic Impairment</p> <p data-bbox="1060 961 1906 1065">TRIUMEQ should not be administered to patients with creatinine clearance less than 50 mL/min or any hepatic impairment [<i>see Contraindications (4) and Use in Specific Populations (8.7)</i>]</p>

Applicant proposed changes	Proposed reviewer changes				
None	<p data-bbox="1058 321 2028 496">2.3 Dosing recommendation with certain concomitant medications Because the dolutegravir dosage regimen (50 mg once daily) in TRIUMEQ is insufficient when co-administered with certain medications that may decrease dolutegravir concentrations, the following dolutegravir dosage regimen is recommended.</p> <table border="1" data-bbox="1062 548 1934 894"> <thead> <tr> <th data-bbox="1068 553 1583 597">Co-administered drug</th> <th data-bbox="1589 553 1927 597">Dosing recommendation</th> </tr> </thead> <tbody> <tr> <td data-bbox="1068 602 1583 672">Efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin</td> <td data-bbox="1589 602 1927 889">The recommended dolutegravir dosage regimen is 50 mg twice daily. An additional dolutegravir 50 mg tablet, separated by 12 hours from TRIUMEQ, should be taken.</td> </tr> </tbody> </table>	Co-administered drug	Dosing recommendation	Efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	The recommended dolutegravir dosage regimen is 50 mg twice daily. An additional dolutegravir 50 mg tablet, separated by 12 hours from TRIUMEQ, should be taken.
Co-administered drug	Dosing recommendation				
Efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	The recommended dolutegravir dosage regimen is 50 mg twice daily. An additional dolutegravir 50 mg tablet, separated by 12 hours from TRIUMEQ, should be taken.				

Section 4-Contraindications

Applicant proposed language	Proposed reviewer changes
<ul style="list-style-type: none">receiving dofetilide, due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events [see <i>Drug Interactions (7)</i>].	<ul style="list-style-type: none">receiving dofetilide, due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events with concomitant use of dolutegravir [see <i>Drug Interactions (7)</i>].
Applicant proposed language	Proposed reviewer changes
None	<ul style="list-style-type: none">with moderate or severe hepatic impairment [see <i>Use in Specific Populations (8.7)</i>].

Section 7-Drug Interactions

Applicant proposed language	Proposed reviewer changes
<p>7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents</p> <p>None</p>	<p><i>Reviewer comment: The text below contains information from a dolutegravir NDA supplement (NDA204790, S-1) that was approved while the NDA 205551 review was ongoing.</i></p> <p>7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents</p> <p>In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC₅₀ = 1.93µM) and multidrug and toxin extrusion transporter (MATE) 1 (IC₅₀ = 6.34 µM). In vivo, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide and metformin, Table 5) [see <i>Contraindications (4), Drug Interactions (7.3)</i>].</p> <p>In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC₅₀ = 2.12 µM) and OAT3 (IC₅₀ = 1.97 µM). However, in vivo, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.</p> <p>In vitro, dolutegravir did not inhibit (IC₅₀ >50 µM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1, UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, or multidrug resistance protein (MRP)2, or MRP4. In vitro, dolutegravir did not induce CYP1A2, CYP2B6, CYP3A4. Based on these data and the</p>

results of drug interaction trials, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

In drug interaction trials, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following drugs: tenofovir, methadone, midazolam, rilpivirine, and oral contraceptives containing norgestimate and ethinyl estradiol. Using cross-study comparisons to historical pharmacokinetic data for each interacting drug, dolutegravir did not appear to affect the pharmacokinetics of the following drugs: atazanavir, darunavir, efavirenz, etravirine, fosamprenavir, lopinavir, ritonavir, and telaprevir

Applicant proposed language	Proposed reviewer changes
<p data-bbox="79 329 953 362">7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir</p> <p data-bbox="79 402 155 435">None</p>	<p data-bbox="1062 329 1934 362">7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir</p> <p data-bbox="1062 402 1955 581">Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp in vitro. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentrations and reduce the therapeutic effect of dolutegravir.</p> <p data-bbox="1062 621 1913 686">Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentrations.</p> <p data-bbox="1062 727 1990 906">Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir. (Table 5) [<i>see Drug Interactions (7.3), Clinical Pharmacology (12.3)</i>].</p> <p data-bbox="1062 946 1934 1052">Darunavir/ritonavir, lopinavir/ritonavir, rilpivirine, tenofovir, boceprevir, telaprevir, prednisone, rifabutin, and omeprazole had no clinically significant effect on the pharmacokinetics of dolutegravir.</p>

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Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
<p data-bbox="79 326 940 363">7.3 Established and Other Potentially Significant Drug Interactions</p> <div data-bbox="71 381 1047 852" style="background-color: #cccccc; height: 290px; width: 100%;"></div> <p data-bbox="1003 381 1047 402">(b) (4)</p>	<p data-bbox="1058 326 1919 363">7.3 Established and Other Potentially Significant Drug Interactions</p> <p data-bbox="1058 402 1976 472">There were no drug-drug interaction trials conducted with the abacavir, dolutegravir, and lamivudine fixed-dose combination tablets.</p> <p data-bbox="1058 508 2018 688">Information regarding potential drug interactions with dolutegravir (Table 4) and abacavir are provided below. These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy. [see <i>Clinical Pharmacology</i> (12.3).]</p>

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
Table (b) (4) Established and Other Potentially Significant Drug Interactions: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions	Table (b) (4) Established and Other Potentially Significant Drug Interactions For Dolutegravir : Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Applicant proposed language	Proposed reviewer changes						
<p>Table (b) (4) Established and Other Potentially Significant Drug Interactions: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions</p> <table border="1" data-bbox="100 461 1020 867"> <thead> <tr> <th data-bbox="100 461 359 573">Concomitant Drug Class: Drug Name</th> <th data-bbox="359 461 611 573">Effect on Concentration</th> <th data-bbox="611 461 1020 573">Clinical Comment</th> </tr> </thead> <tbody> <tr> <td data-bbox="100 573 359 867">(b) (4)</td> <td data-bbox="359 573 611 867">(b) (4)</td> <td data-bbox="611 573 1020 867">(b) (4)</td> </tr> </tbody> </table>	Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment	(b) (4)	(b) (4)	(b) (4)	<p><i>Clinical pharmacology reviewer comment: Information regarding the (b) (4) is not currently included in the corresponding table in the dolutegravir U.S. prescribing information and does not need to be included in Table 4 for the abacavir, dolutegravir, and lamivudine fixed-dose combination tablets U.S. prescribing information. The information should be deleted.</i></p>
Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment					
(b) (4)	(b) (4)	(b) (4)					

Applicant proposed language

Table (b) (4) Established and Other Potentially Significant Drug Interactions: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Non-nucleoside reverse transcriptase inhibitor: Efavirenz ^a	↓Dolutegravir (b) (4)	(b) (4)

^a See Clinical Pharmacology (12.3) Table (b) (4) or magnitude of

(b) (4)

Proposed reviewer changes

Table (b) (4) Established and Other Potentially Significant Drug Interactions: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Non-nucleoside reverse transcriptase inhibitor: Efavirenz ^a	↓Dolutegravir	The dolutegravir dosage regimen should be adjusted to 50 mg twice daily. An additional 50 mg dose of dolutegravir, should be taken, separated by 12 hours from TRIUMEQ.

^a See Clinical Pharmacology (12.3) Table (b) (4) or magnitude of interaction.

Applicant proposed language	Proposed reviewer changes												
<p>Table (b) (4) Established and Other Potentially Significant Drug Interactions: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions</p> <table border="1" data-bbox="100 461 1001 756"> <thead> <tr> <th data-bbox="100 461 357 573">Concomitant Drug Class: Drug Name</th> <th data-bbox="357 461 600 573">Effect on Concentration</th> <th data-bbox="600 461 1001 573">Clinical Comment</th> </tr> </thead> <tbody> <tr> <td data-bbox="100 573 357 756">Non-nucleoside reverse transcriptase inhibitor: Nevirapine</td> <td data-bbox="357 573 600 756">↓Dolutegravir</td> <td data-bbox="600 573 1001 756">(b) (4)</td> </tr> </tbody> </table>	Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment	Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	(b) (4)	<p>Table (b) (4) Established and Other Potentially Significant Drug Interactions: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions</p> <table border="1" data-bbox="1075 461 1997 829"> <thead> <tr> <th data-bbox="1075 461 1335 573">Concomitant Drug Class: Drug Name</th> <th data-bbox="1335 461 1587 573">Effect on Concentration</th> <th data-bbox="1587 461 1997 573">Clinical Comment</th> </tr> </thead> <tbody> <tr> <td data-bbox="1075 573 1335 829">Non-nucleoside reverse transcriptase inhibitor: Nevirapine</td> <td data-bbox="1335 573 1587 829">↓Dolutegravir</td> <td data-bbox="1587 573 1997 829">(b) (4) should be avoided because there are insufficient data to make dosing recommendations.</td> </tr> </tbody> </table>	Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment	Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	(b) (4) should be avoided because there are insufficient data to make dosing recommendations.
Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment											
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	(b) (4)											
Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment											
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Applicant proposed language

Table (b) (4) Established and Other Potentially Significant Drug Interactions: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Protease inhibitor: Fosamprenavir/ritonavir ^a Tipranavir/ritonavir ^a	↓Dolutegravir (b) (4)	(b) (4)

^a See Clinical Pharmacology (12.3) Table (b) (4) for magnitude of interaction

(b) (4)

Proposed reviewer changes

Table (b) (4) Established and Other Potentially Significant Drug Interactions: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Protease inhibitor: Fosamprenavir/ritonavir ^a Tipranavir/ritonavir ^a	↓Dolutegravir	The dolutegravir dosage regimen should be adjusted to 50 mg twice daily. An additional dolutegravir 50 mg dose should be taken, separated by 12 hours from TRIUMEQ.

^a See Clinical Pharmacology (12.3) Table (b) (4) for magnitude of interaction.

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)												
<p>Table (b) (4) Established and Other Potentially Significant Drug Interactions: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions</p> <table border="1"> <thead> <tr> <th data-bbox="100 461 359 574">Concomitant Drug Class: Drug Name</th> <th data-bbox="359 461 611 574">Effect on Concentration</th> <th data-bbox="611 461 1020 574">Clinical Comment</th> </tr> </thead> <tbody> <tr> <td data-bbox="100 574 359 834">Oxcarbazepine Phenytoin Phenobarbital Carbamazepine St. John's wort (<i>Hypericum perforatum</i>)</td> <td data-bbox="359 574 611 834">↓Dolutegravir</td> <td data-bbox="611 574 1020 834">(b) (4)</td> </tr> </tbody> </table>	Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment	Oxcarbazepine Phenytoin Phenobarbital Carbamazepine St. John's wort (<i>Hypericum perforatum</i>)	↓Dolutegravir	(b) (4)	<p>Table (b) (4) Established and Other Potentially Significant Drug Interactions: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions</p> <table border="1"> <thead> <tr> <th data-bbox="1079 461 1337 574">Concomitant Drug Class: Drug Name</th> <th data-bbox="1337 461 1589 574">Effect on Concentration</th> <th data-bbox="1589 461 1999 574">Clinical Comment</th> </tr> </thead> <tbody> <tr> <td data-bbox="1079 574 1337 834">Oxcarbazepine Phenytoin Phenobarbital Carbamazepine St. John's wort (<i>Hypericum perforatum</i>)</td> <td data-bbox="1337 574 1589 834">↓Dolutegravir</td> <td data-bbox="1589 574 1999 834">(b) (4) because there are insufficient data to make dosing recommendations.</td> </tr> </tbody> </table>	Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment	Oxcarbazepine Phenytoin Phenobarbital Carbamazepine St. John's wort (<i>Hypericum perforatum</i>)	↓Dolutegravir	(b) (4) because there are insufficient data to make dosing recommendations.
Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment											
Oxcarbazepine Phenytoin Phenobarbital Carbamazepine St. John's wort (<i>Hypericum perforatum</i>)	↓Dolutegravir	(b) (4)											
Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment											
Oxcarbazepine Phenytoin Phenobarbital Carbamazepine St. John's wort (<i>Hypericum perforatum</i>)	↓Dolutegravir	(b) (4) because there are insufficient data to make dosing recommendations.											

Applicant proposed language

Table (b) (4) Established and Other Potentially Significant Drug Interactions: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Rifampin ^a	↓Dolutegravir	(b) (4)

^a See Clinical Pharmacology (12.3) Table (b) (4) or magnitude of interaction.

Proposed reviewer changes

Table (b) (4) Established and Other Potentially Significant Drug Interactions: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Rifampin ^a	↓Dolutegravir	The dolutegravir dosage regimen should be adjusted to 50 mg twice daily. An additional 50 mg dose of dolutegravir should be taken, separated by 12 hours from TRIUMEQ.

^a See Clinical Pharmacology (12.3) Table (b) (4) for magnitude of interaction.

Applicant proposed language	Proposed reviewer changes
<p data-bbox="79 318 940 350">7.3 Established and Other Potentially Significant Drug Interactions</p> <p data-bbox="79 391 155 423">None</p>	<p data-bbox="1062 284 2003 496"><i>Clinical pharmacology reviewer comment: Drug-drug interaction information related to abacavir should be included to provide more comprehensive drug-drug interaction information relevant to the prescribing information for the abacavir and dolutegravir components of the fixed-dose combination tablets. Drug-drug interaction information related to lamivudine does not need to be added to section 7.</i></p> <p data-bbox="1062 537 1919 570">7.3 Established and Other Potentially Significant Drug Interactions</p> <p data-bbox="1062 610 1163 643"><u>Ethanol</u></p> <p data-bbox="1062 651 2018 756">Abacavir: Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure [see <i>Clinical Pharmacology (12.3)</i>].</p> <p data-bbox="1062 797 1209 829"><u>Methadone</u></p> <p data-bbox="1062 837 2028 1154">Abacavir: The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy with 600 mg of abacavir twice daily (twice the currently recommended dose), oral methadone clearance increased [see <i>Clinical Pharmacology (12.3)</i>]. This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients. The addition of methadone had no clinically significant effect on the pharmacokinetic properties of abacavir.</p>

Section 8-Use in Specific Populations

Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)
<p>8.5 Geriatric Use</p> <p>Clinical trials of ██████████^{(b) (4)} did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of TRIUMEQ in elderly patient reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [<i>see Clinical Pharmacology (12.3)</i>].</p>	<p>8.5 Geriatric Use</p> <p>Clinical trials of abacavir, dolutegravir or lamivudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of TRIUMEQ in elderly patient reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [<i>see Clinical Pharmacology (12.3)</i>].</p>

Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)
<p>8.6 Patients With Impaired Renal Function</p> <p>TRIUMEQ is not recommended for patients with impaired renal function (creatinine clearance \geq 50 mL/min) because TRIUMEQ is a fixed-dose combination and the dosage of the individual components cannot be adjusted [<i>see Clinical Pharmacology (12.3)</i>].</p>	<p>8.6 Patients With Impaired Renal Function</p> <p>TRIUMEQ is not recommended for patients with impaired renal function (creatinine clearance <50 mL/min) because TRIUMEQ is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of TRIUMEQ, is required for patients with creatinine clearance <50 mL/min, then the individual components should be used [<i>see Clinical Pharmacology (12.3)</i>].</p>

Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)
<p>8.7 Patients With Impaired Hepatic Function</p> <p>(b) (4)</p> <p>If a dose reduction of abacavir, a component of TRIUMEQ, is required for patients with mild hepatic impairment (Child-Pugh Score A), then the individual components should be used [see <i>Clinical Pharmacology (12.3)</i>].</p>	<p>8.7 Patients With Impaired Hepatic Function</p> <p>TRIUMEQ is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of abacavir, a component of TRIUMEQ, is required for patients with mild hepatic impairment (Child-Pugh Score A), then the individual components should be used. The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate (Child-Pugh Score B) or severe (Child-Pugh Score C) hepatic impairment; therefore, TRIUMEQ is contraindicated in these patients.</p>

Section 10-Overdosage

Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)
<p><u>Abacavir</u>: It is not known whether abacavir can be removed by dialysis.</p>	<p><u>Abacavir</u>: It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.</p>

Section 12-Clinical Pharmacology

Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)
<p>Section 12.2-Pharmacodynamics</p> <p><u>Effects on Electrocardiogram:</u> In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single-dose oral administrations of placebo, dolutegravir 250-mg suspension (exposures approximately 3-fold of the 50-mg once-daily dose at steady state), and moxifloxacin 400 mg (active control) in random sequence. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) for dolutegravir was 2.4 msec (1-sided 95% upper CI: 4.9 msec). Dolutegravir did not prolong the QTc interval over 24 hours postdose.</p> <p> (b) (4)</p>	<p>Section 12.3-Pharmacodynamics</p> <p><u>Effects on Electrocardiogram:</u> A thorough QT trial has been conducted for dolutegravir. Neither the effects of abacavir or lamivudine as single entities or the combination of abacavir, dolutegravir, and lamivudine on the QT interval have been evaluated.</p> <p>In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single-dose oral administrations of placebo, dolutegravir 250-mg suspension (exposures approximately 3-fold of the 50-mg once-daily dose at steady state), and moxifloxacin 400 mg (active control) in random sequence. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) for dolutegravir was 2.4 msec (1-sided 95% upper CI: 4.9 msec). Dolutegravir did not prolong the QTc interval over 24 hours postdose.</p>
<p>Section 12.3-Pharmacokinetics</p> <p>One TRIUMEQ Tablet was bioequivalent to one TIVICAY Tablet (50 mg) plus one EPZICOM Tablet under fasted conditions in healthy subjects (n = 62).</p>	<p>Section 12.3-Pharmacokinetics</p> <p><u>Pharmacokinetics in Adults:</u> One TRIUMEQ Tablet was bioequivalent to one dolutegravir (TIVICAY) tablet (50 mg) plus one abacavir and lamivudine fixed dose combination tablet (EPZICOM) under fasted conditions in healthy subjects (n = 62).</p>

Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)
<p>Section 12.3-Pharmacokinetics</p> <p><i>Dolutegravir:</i> Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours postdose. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and C_{24 h} ranging from 1.2 to 1.5. The absolute bioavailability of dolutegravir has not been established. Dolutegravir is highly bound (98.9%) to human plasma proteins. Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A. Fifty-three percent of total oral dose is excreted unchanged in the feces. Thirty-one percent of the total oral dose is excreted in the urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was (b) (4) 1% of the dose). Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L/h based on population pharmacokinetic analyses.</p>	<p>Section 12.3-Pharmacokinetics</p> <p><i>Dolutegravir:</i> Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours postdose. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and C_{24 h} ranging from 1.2 to 1.5. Dolutegravir is a P-glycoprotein substrate in vitro. The absolute bioavailability of dolutegravir has not been established. Dolutegravir is highly bound (≥98.9%) to human plasma proteins based on in vivo data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50-mg once-daily administration is estimated at 17.4 L based on a population pharmacokinetic analysis.</p> <p>Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A. After a single oral dose of [14C] dolutegravir, 53% of the total oral dose is excreted unchanged in the feces. 31% of the total oral dose is excreted in the urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was <1% of the dose. Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L/h based on population pharmacokinetic analyses.</p>

Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)								
<p data-bbox="79 354 485 383">Section 12.3-Pharmacokinetics</p> <p data-bbox="79 423 1039 570">The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1–infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1–infected subjects. (b) (4)</p> <p data-bbox="79 574 1039 716">(b) (4)</p>	<p data-bbox="1060 354 1461 383">Section 12.3-Pharmacokinetics</p> <p data-bbox="1060 418 1990 565">The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1–infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1–infected subjects.</p> <p data-bbox="1060 602 1776 672">Table 5. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV-1– Infected Adults</p> <table border="1" data-bbox="1157 716 1934 932"> <thead> <tr> <th data-bbox="1163 721 1478 805">Parameter</th> <th data-bbox="1484 721 1927 805">50 mg Once Daily Geometric Mean (%CV)</th> </tr> </thead> <tbody> <tr> <td data-bbox="1163 810 1478 846">AUC₍₀₋₂₄₎ (mcg.h/mL)</td> <td data-bbox="1484 810 1927 846">53.6 (27)</td> </tr> <tr> <td data-bbox="1163 850 1478 886">C_{max} (mcg/mL)</td> <td data-bbox="1484 850 1927 886">3.67 (20)</td> </tr> <tr> <td data-bbox="1163 891 1478 927">C_{min} (mcg/mL)</td> <td data-bbox="1484 891 1927 927">1.11 (46)</td> </tr> </tbody> </table>	Parameter	50 mg Once Daily Geometric Mean (%CV)	AUC ₍₀₋₂₄₎ (mcg.h/mL)	53.6 (27)	C _{max} (mcg/mL)	3.67 (20)	C _{min} (mcg/mL)	1.11 (46)
Parameter	50 mg Once Daily Geometric Mean (%CV)								
AUC ₍₀₋₂₄₎ (mcg.h/mL)	53.6 (27)								
C _{max} (mcg/mL)	3.67 (20)								
C _{min} (mcg/mL)	1.11 (46)								

Applicant proposed changes	Proposed reviewer changes
<p>Section 12.3-Pharmacokinetics</p> <p><i>Cerebrospinal Fluid (CSF):</i> In (b) (4) treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was (b) (4) 2 to 6 hours postdose after (b) (4)</p>	<p>Section 12.3-Pharmacokinetics</p> <p><u>Final action</u></p> <p>The information below from the dolutegravir U.S. prescribing information will be included.</p> <p><i>Cerebrospinal Fluid (CSF):</i> In 11 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 18 ng/mL (range: 4 ng/mL to 23.2 ng/mL) 2 to 6 hours postdose after 2 weeks of treatment. The clinical relevance of this finding has not been established.</p> <p><u>Initial reviewer recommendation</u></p> <p><i>Clinical pharmacology reviewer comment:</i> The information presented for (b) (4) in the abacavir, dolutegravir, and lamivudine fixed dose combination tablets U.S. prescribing information differs from the (b) (4) presented in the dolutegravir U.S. prescribing information. Additionally it is not essential to include (b) (4) in the abacavir, dolutegravir, and lamivudine fixed dose combination tablets U.S. prescribing information and the information should be deleted.</p>

Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)
<p data-bbox="71 354 485 386">Section 12.3-Pharmacokinetics</p> <p data-bbox="71 427 1031 792"><i>Abacavir:</i> Following oral administration, abacavir is rapidly absorbed and extensively distributed. After oral administration of a single dose of 600 mg of abacavir in 20 subjects, C_{max} was 4.26 ± 1.19 mcg/mL (mean \pm SD) and AUC_{∞} was 11.95 ± 2.51 mcg•h/mL. Binding of abacavir to human plasma proteins is approximately 50% and was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase to form the 5'-carboxylic acid and glucuronyl transferase to form the 5'-glucuronide.</p> <div data-bbox="71 797 1024 987" style="background-color: #cccccc; height: 117px; width: 454px; margin-top: 10px;"> (b) (4) </div>	<p data-bbox="1052 354 1461 386">Section 12.3-Pharmacokinetics</p> <p data-bbox="1052 427 2018 565"><i>Clinical pharmacology reviewer comment: The information has been modified to be more consistent with the information presently included in the abacavir U.S. prescribing information or to remove information that is presently not included.</i></p> <p data-bbox="1052 605 2018 1084"><i>Abacavir:</i> Following oral administration, abacavir is rapidly absorbed and extensively distributed. After oral administration of a single dose of 600 mg of abacavir in 20 subjects, C_{max} was 4.26 ± 1.19 mcg/mL (mean \pm SD) and AUC_{∞} was 11.95 ± 2.51 mcg•h/mL. Binding of abacavir to human plasma proteins is approximately 50% and was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase to form the 5'-carboxylic acid and glucuronyl transferase to form the 5'-glucuronide. In single-dose trials, the observed elimination half-life ($t_{1/2}$) was 1.54 ± 0.63 hours. After intravenous administration, total clearance was 0.80 ± 0.24 L/hr/kg (mean \pm SD).</p>

Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)
<p data-bbox="79 358 485 391">Section 12.3-Pharmacokinetics</p> <p data-bbox="79 435 1035 803"><i>Lamivudine:</i> Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy subjects, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 mcg/mL (mean \pm SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg•h/mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours). (b) (4)</p> <div data-bbox="79 803 1008 958" style="background-color: #cccccc; height: 95px; width: 100%;"></div>	<p data-bbox="1062 350 1461 383">Section 12.3-Pharmacokinetics</p> <p data-bbox="1062 427 2018 570"><i>Clinical pharmacology reviewer comment:</i> The information has been modified to be more consistent with the information presently included in the lamivudine U.S. prescribing information or to remove information that is presently not included.</p> <p data-bbox="1062 610 2028 1130"><i>Lamivudine:</i> Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy subjects, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 mcg/mL (mean \pm SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg•h/mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours). In most single-dose studies in HIV-1-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours. In HIV-1-infected patients, total clearance was 398.5 ± 69.1 mL/min (mean \pm SD).</p>

Applicant proposed changes	Proposed reviewer changes
<p>Section 12.3-Pharmacokinetics</p> <p><u>Effect of Food on Oral Absorption:</u> TRIUMEQ may be (b) (4) with (b) (4) or without food. (b) (4)</p>	<p>Section 12.3-Pharmacokinetics</p> <p><u>Effect of Food on Oral Absorption:</u> TRIUMEQ may be taken with or without food.</p> <p>Overall, when compared to fasted conditions, administration of TRIUMEQ to healthy adult subjects with a high fat meal (53% fat, 869 calories) resulted in decreased C_{max} for abacavir and increased C_{max} and AUC for dolutegravir. Lamivudine exposures were not affected by food. With a high fat meal, the C_{max} of abacavir decreased 23% and the C_{max} and AUC of dolutegravir increased 37% and 48%, respectively.</p>

Applicant proposed changes	Proposed reviewer changes
<p>Section 12.3-Pharmacokinetics</p> <p>Special Populations: <i>Renal Impairment:</i> [REDACTED] (b) (4)</p> <p>[REDACTED]</p> <p><i>Hepatic Impairment:</i> [REDACTED] (b) (4)</p> <p>[REDACTED]</p>	<p><i>Clinical pharmacology reviewer comment: In section 12.3, for renal or hepatic impairment, the information has been revised to include relevant pharmacokinetic data instead of [REDACTED] (b) (4)</i></p> <p>[REDACTED]</p> <p>Section 12.3-Pharmacokinetics</p> <p>Special Populations</p> <p><i>Renal Impairment:</i></p> <p>The effect of renal impairment on the combination of abacavir, dolutegravir, and lamivudine has not been evaluated</p> <p><i>Abacavir:</i> The pharmacokinetic properties of abacavir have not been determined in patients with impaired renal function.</p> <p><i>Dolutegravir:</i> In a trial comparing 8 subjects with severe renal impairment (CrCl <30 mL/min) with 8 matched healthy controls, AUC, C_{max}, and C₂₄ of dolutegravir were decreased by 40%, 23%, and 43%, respectively, compared with those in matched healthy subjects. The cause of this decrease is unknown. Population pharmacokinetic analysis indicated that mild and moderate renal impairment had no clinically relevant effect on the exposure of dolutegravir.</p> <p><i>Lamivudine:</i> The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-1-infected adults with impaired renal function (Table 6).</p>

Table 6. Pharmacokinetic Parameters (Mean ± SD) After a Single 300-mg Oral Dose of Lamivudine in 3 Groups of Adults With Varying Degrees of Renal Function

Parameter	Creatinine Clearance Criterion (Number of Subjects)		
	>60 mL/min (n = 6)	10-30 mL/min (n = 4)	<10 mL/min (n = 6)
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C _{max} (mcg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC _∞ (mcg•hr/mL)	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

Applicant proposed changes	Proposed reviewer changes
<p>Section 12.3-Pharmacokinetics</p> <p><i>Hepatic Impairment:</i> [REDACTED] (b) (4)</p>	<p>Section 12.3-Pharmacokinetics</p> <p><i>Hepatic Impairment:</i> The effect of hepatic impairment on the combination of abacavir, dolutegravir, and lamivudine has not been evaluated.</p> <p><i>Abacavir:</i> The pharmacokinetics of abacavir have been studied in subjects with mild hepatic impairment (Child-Pugh score 5 to 6). Results showed that there was a mean increase of 89% in the abacavir AUC and an increase of 58% in the half-life of abacavir after a single dose of 600 mg of abacavir. The AUCs of the metabolites were not modified by mild liver disease; however, the rates of formation and elimination of the metabolites were decreased. The safety, efficacy, and pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment.</p> <p><i>Dolutegravir:</i> In a trial comparing 8 subjects with moderate hepatic impairment (Child- Pugh Score B) with 8 matched healthy controls, exposure of dolutegravir from a single 50-mg dose was similar between the 2 groups. The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied.</p> <p><i>Lamivudine:</i> The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.</p>

Applicant proposed changes	Proposed reviewer changes
<p data-bbox="65 316 483 349">Section 12.3-Pharmacokinetics</p> <div data-bbox="65 373 1047 828" style="background-color: #cccccc; height: 280px; width: 100%;"><p data-bbox="997 373 1047 397">(b) (4)</p></div>	<p data-bbox="1047 316 1459 349">Section 12.3-Pharmacokinetics</p> <p data-bbox="1047 381 2005 462"><i>Clinical pharmacology reviewer comment: The information for (b) (4) can be deleted from section 12.3.</i></p>

Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)
<p>Section 12.3-Pharmacokinetics</p> <p>Pediatric Patients: The pharmacokinetics of (b) (4) in pediatric subjects have not been established. (b) (4)</p>	<p>Section 12.3-Pharmacokinetics</p> <p><i>Clinical pharmacology reviewer comment: The section was revised to clarify that the combination of abacavir, dolutegravir, and lamivudine in pediatric subjects has not been evaluated and the information (b) (4) was removed (b) (4)</i></p> <p><i>Pediatric Patients: The pharmacokinetics of the combination of abacavir, dolutegravir, and lamivudine in pediatric subjects have not been established.</i></p>

Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)
<p>Section 12.3-Pharmacokinetics</p> <p><i>Geriatric Patients: Population (b) (4) analyses using pooled pharmacokinetic data from adult trials indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir. The pharmacokinetics of abacavir and lamivudine have not been studied in subjects over 65 years of age.</i></p>	<p>Section 12.3-Pharmacokinetics</p> <p><i>Final wording</i> <i>Geriatric Patients: Population analyses using pooled pharmacokinetic data from adult trials indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir. The pharmacokinetics of abacavir or lamivudine have not been studied in subjects older than 65 years.</i></p> <p><i>Initial wording to applicant</i> <i>Geriatric Patients: Population analyses using pooled pharmacokinetic data from adult trials indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir. Neither the pharmacokinetics of abacavir or lamivudine have not been studied in subjects over 65 years of age.</i></p>

Applicant proposed changes	Proposed reviewer changes
<p data-bbox="79 318 485 350">Section 12.3-Pharmacokinetics</p> <p data-bbox="79 386 1031 488"><i>Gender:</i> There are no significant gender differences in the pharmacokinetics of the individual components, dolutegravir, abacavir, or lamivudine.</p>	<p data-bbox="1058 318 1463 350">Section 12.3-Pharmacokinetics</p> <p data-bbox="1058 386 1997 534"><i>Gender:</i> There are no significant or clinically relevant gender differences in the pharmacokinetics of the individual components, dolutegravir, abacavir, or lamivudine based on the available information that was analyzed for each of the individual components.</p>

Applicant proposed changes	Proposed reviewer changes
<p data-bbox="79 685 485 717">Section 12.3-Pharmacokinetics</p> <p data-bbox="79 753 1003 824"><i>Race:</i> There are no significant racial differences in pharmacokinetics of the individual components, dolutegravir, abacavir, or lamivudine.</p>	<p data-bbox="1058 685 1463 717">Section 12.3-Pharmacokinetics</p> <p data-bbox="1058 753 1997 901"><i>Race:</i> There are no significant or clinically relevant racial differences in pharmacokinetics of the individual components, dolutegravir, abacavir, or lamivudine based on the available information that was analyzed for each of the individual components.</p>

Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)
<p>Section 12.3-Pharmacokinetics</p> <p><u>Drug Interactions:</u> The drug interaction trials described were conducted with dolutegravir, abacavir, and/or lamivudine; no drug interaction trials have been conducted using (b) (4), no clinically significant drug interactions are expected between dolutegravir, abacavir, and lamivudine.</p> <p>Dosing recommendations as a result of established and other potentially significant drug-drug interactions with (b) (4) are provided in (b) (4) [see Drug Interactions (b) (4)].</p>	<p>Section 12.3-Pharmacokinetics</p> <p><u>Drug Interactions:</u> The drug interaction trials described were conducted with dolutegravir, abacavir, and/or lamivudine as single entities; no drug interaction trials have been conducted using the combination of abacavir, dolutegravir, and lamivudine. No clinically significant drug interactions are expected between dolutegravir, abacavir, and lamivudine.</p> <p>Dosing recommendations as a result of established and other potentially significant drug-drug interactions with doletegravir or abacavir are provided in section 7.3 [see Drug Interactions (7.3)].</p>

Applicant proposed changes	Proposed reviewer changes																																													
<p>Section 12.3-Pharmacokinetics</p> <p>None</p>	<p>Section 12.3-Pharmacokinetics</p> <p><i>Clinical pharmacology reviewer comment: All relevant drug-drug interaction information should be presented in section 12.3.</i></p> <p>Table 7. Summary of Effect of Dolutegravir on the Pharmacokinetics of Coadministered Drugs</p> <table border="1" data-bbox="1052 573 2024 1370"> <thead> <tr> <th rowspan="2">Coadministered Drug(s) and Dose(s)</th> <th rowspan="2">Dose of dolutegravir</th> <th rowspan="2">n</th> <th colspan="3">Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug With/Without Dolutegravir No Effect = 1.00</th> </tr> <tr> <th>C_{max}</th> <th>AUC</th> <th>C_T or C₂₄</th> </tr> </thead> <tbody> <tr> <td>Ethinyl estradiol 0.035 mg</td> <td>50 mg twice daily</td> <td>15</td> <td>0.99 (0.91 to 1.08)</td> <td>1.03 (0.96 to 1.11)</td> <td>1.02 (0.93 to 1.11)</td> </tr> <tr> <td>Methadone 16 to 150 mg</td> <td>50 mg twice daily</td> <td>11</td> <td>1.00 (0.94 to 1.06)</td> <td>0.98 (0.91 to 1.06)</td> <td>0.99 (0.91 to 1.07)</td> </tr> <tr> <td>Midazolam 3 mg</td> <td>25 mg once daily</td> <td>10</td> <td>–</td> <td>0.95 (0.79 to 1.15)</td> <td>–</td> </tr> <tr> <td>Norgestromin 0.25 mg</td> <td>50 mg twice daily</td> <td>15</td> <td>0.89 (0.82 to 0.97)</td> <td>0.98 (0.91 to 1.04)</td> <td>0.93 (0.85 to 1.03)</td> </tr> <tr> <td>Rilpivirine 25 mg once daily</td> <td>50 mg once daily</td> <td>16</td> <td>1.10 (0.99 to 1.22)</td> <td>1.06 (0.98 to 1.16)</td> <td>1.21 (1.07 to 1.38)</td> </tr> <tr> <td>Tenofovir disoproxil fumarate 300 mg once daily</td> <td>50 mg once daily</td> <td>15</td> <td>1.09 (0.97 to 1.23)</td> <td>1.12 (1.01 to 1.24)</td> <td>1.19 (1.04 to 1.35)</td> </tr> </tbody> </table>	Coadministered Drug(s) and Dose(s)	Dose of dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug With/Without Dolutegravir No Effect = 1.00			C _{max}	AUC	C _T or C ₂₄	Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)	Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0.94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)	Midazolam 3 mg	25 mg once daily	10	–	0.95 (0.79 to 1.15)	–	Norgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)	Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)	Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)
Coadministered Drug(s) and Dose(s)	Dose of dolutegravir				n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug With/Without Dolutegravir No Effect = 1.00																																								
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Applicant proposed changes						Proposed reviewer changes (modifications are highlighted)					
Section 12.3-Pharmacokinetics						Section 12.3-Pharmacokinetics					
Table (b) (4) Summary of Effect of (b) (4) on the Pharmacokinetics of (b) (4)						Table (b) (4) Summary of Effect of (b) (4) on the Pharmacokinetics of (b) (4)					
Coadministered Drug(s) and Dose(s)	Dose of (b) (4)	n	Geometric Mean Ratio (90% CI) of (b) (4) Coadministered Drugs No Effect = 1.00								
			C _{max}	AUC	C _τ or C ₂₄						
Coadministered Drug(s) and Dose(s)	Dose of dolutegravir	n	Geometric Mean Ratio (90% CI) of (b) (4) Coadministered Drugs No Effect = 1.00								
			C _{max}	AUC	C _τ or C ₂₄						

Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)
<p>Section 12.3-Pharmacokinetics</p> <p><i>Abacavir and Lamivudine:</i> The drug interactions described are based on trials conducted (b) (4)</p> <p><i>Methadone:</i> In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of (b) (4) twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6% to 42%). (b) (4)</p> <p><i>Ribavirin:</i> In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and</p>	<p>Section 12.3-Pharmacokinetics</p> <p><i>Abacavir or Lamivudine:</i> The drug interactions described are based on trials conducted with abacavir or lamivudine as single entities.</p> <p><i>Interferon Alfa:</i> There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a study of 19 healthy male subjects.</p> <p><i>Methadone:</i> In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of abacavir twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6% to 42%) [see Drug Interactions (7.3)].</p> <p><i>Ribavirin:</i> In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects [see Warnings and Precautions (5.4)].</p> <p><i>Abacavir, Lamivudine, Zidovudine:</i> Fifteen HIV-1-infected subjects were enrolled in a crossover-designed drug interaction trial evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.</p> <p><i>Lamivudine and zidovudine:</i> No clinically significant alterations in</p>

lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects [see *Warnings and Precautions* (5.4)]. The effects of other coadministered drugs on abacavir or lamivudine are provided in Table ^(b)₍₄₎

lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr). The effects of other coadministered drugs on abacavir or lamivudine are provided in Table 9.

Applicant proposed changes						Proposed reviewer changes					
Section 12.3-Pharmacokinetics						Section 12.3-Pharmacokinetics					
Table 8. Effect of Coadministered Drugs on Abacavir or Lamivudine ^{(b) (4)}						Table 9. Effect of Coadministered Drugs on Abacavir or Lamivudine					
Coadministered Drug and Dose	Drug and Dose	n	Concentrations of Abacavir or Lamivudine		Concentration of Coadministered Drug	Coadministered Drug and Dose	Drug and Dose	n	Concentrations of Abacavir or Lamivudine		Concentration of Coadministered Drug
			AUC	Variability					AUC	Variability	
Ethanol 0.7 g/kg	Abacavir 600 mg Single	24	↑41%	90% CI: 35% to 48%	↔	Ethanol 0.7 g/kg	Abacavir Single 600 mg	24	↑41%	90% CI: 35% to 48%	↔*
Nelfinavir 750 mg q 8 h x 7 to 10 days	Lamivudine 150 mg Single	11	↑10%	95% CI: 1% to 20%	↔	Nelfinavir 750 mg q 8 h x 7 to 10 days	Lamivudine Single 150 mg	11	↑10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	Lamivudine 300 mg Single	14	↑43%	90% CI: 32% to 55%	↔	Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	Lamivudine Single 300 mg	14	↑43%	90% CI: 32% to 55%	↔
↑ = Increase; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.						↑ = Increase; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval					
						*In males-the drug-drug interaction was not evaluated in females					

Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)
<p>Section 17-Patient Counseling Information</p> <p><u>Drug Interactions:</u> (b) (4) with (b) (4) dofelilide (TIKOSYN) because (b) (4) can result in potentially life-threatening adverse events [see <i>Contraindications (4)</i>].</p>	<p>Section 17-Patient Counseling Information</p> <p><u>Drug Interactions:</u> (b) (4) with dofelilide (TIKOSYN®) because the interaction between dofelilide and dolutegravir can result in potentially life-threatening adverse events [see <i>Contraindications (4)</i>]. Patients should be advised to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products.</p>

Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)
<p>Medication guide</p> <p>What should I tell my healthcare provider before taking TRIUMEQ? Before you take TRIUMEQ, tell your healthcare provider if you:</p> <ul style="list-style-type: none"> are breastfeeding or plan to breastfeed. Do not breastfeed. It is not known if (b) (4) passes into your breast milk. 	<p>Medication guide</p> <p>What should I tell my healthcare provider before taking TRIUMEQ? Before you take TRIUMEQ, tell your healthcare provider if you:</p> <ul style="list-style-type: none"> are breastfeeding or plan to breastfeed. Do not breastfeed. It is not known if dolutegravir or abacavir passes into your breast milk. Lamivudine has been found in breast milk.

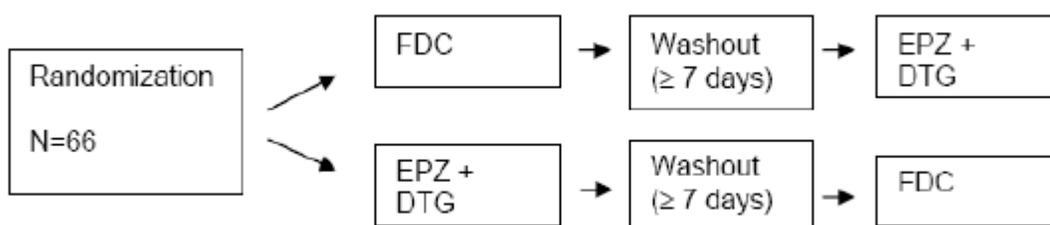
Applicant proposed changes	Proposed reviewer changes (modifications are highlighted)
<p>Medication guide</p> <p>(b) (4) tell your healthcare provider if you take:</p> <ul style="list-style-type: none"> • antacids (b) (4) that contain aluminum, magnesium, sucralfate (CARAFATE), or buffered medicines. TRIUMEQ should be taken at least 2 hours before or 6 hours after you take these medicines. 	<p>Medication guide</p> <p>(b) (4) tell your healthcare provider if you take:</p> <ul style="list-style-type: none"> • Antacids, laxatives or other medicines that contain aluminum, magnesium, sucralfate (CARAFATE[®]), or buffered medicines. TRIUMEQ should be taken at least 2 hours before or 6 hours after you take these medicines.

3 Individual Trial Reviews

ING114580

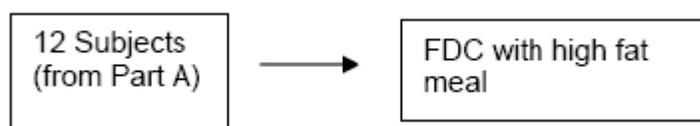
ING114580 was an open label clinical trial that enrolled healthy male and female subjects 18 to 55 years old. The relative bioavailability of two formulations was determined in Part A as outlined in Figure 1 below. Part A will not be discussed as part of the Clinical Pharmacology review; please see the biopharmaceutics review for further information regarding Part A.

Figure 1-ING114580 Part A trial design (FDC=treatment A, EPZ+DTG=treatment B)



Part B evaluated the effect of a high fat meal on the single dose pharmacokinetics of a fixed dose combination (FDC) tablet consisting of abacavir 600 mg, dolutegravir 50 mg, and lamivudine 300 mg that was designated as treatment C. The effect of food on the single dose pharmacokinetics of a fixed dose combination tablet consisting of abacavir 600 mg, dolutegravir 50 mg, and lamivudine 300 mg was evaluated by comparing the exposure data for all three analytes from treatment C under high fat conditions to treatment A under fasted conditions. The trial design for Part B is displayed in Figure 2 below.

Figure 2-ING114580 Part B trial design (treatment C)



In Part B, a high fat meal was administered that consisted of 53% fat and 869 calories. In response to an information request, the specific breakdown of the number of calories for the high fat meal was 32.1 grams or 128 calories from protein, 70.2 grams or 281 calories from carbohydrate, and 51.1 grams or 460 calories from fat. Subjects were fasted overnight for a minimum of ten hours and were administered trial medication 30 minutes (\pm 5 minutes) after the initiation of a high fat meal.

The fixed dose combination formulation that was administered in evaluating effect of food on the single dose pharmacokinetics of a fixed dose combination tablet consisting of abacavir 600 mg, dolutegravir 50 mg, and lamivudine 300 mg was labeled as product

code AF. The differences for the proposed U.S. commercially marketed formulation compared to the formulation administered in the ING114580 trial include the lack of a score mark. Based on a review of the dissolution profiles by the biopharmaceutics reviewer, the differences for the fixed dose combination tablet between the one used in the ING114580 trial and the proposed US commercial formulation are not anticipated to affect either the bioavailability or the food effect results.

The trial permitted the use of acetaminophen up to 2 grams per day. In general, prescription, nonprescription medications, and dietary or herbal supplements were not permitted within 7 days (or 14 days for potential enzyme inducing medications) or five half lives (whichever was longer) before the first dose of trial medication until the follow up visit. There were similar restrictions regarding the use of antacids, vitamins and iron supplements. During the trial, concomitant medications were used by five subjects, and only acetaminophen was used in more than one subject (2 subjects total). The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

Table 1 below displays the results of the food effect assessment on the exposure of abacavir, dolutegravir, and lamivudine when administered as a fixed dose combination tablet.

Table 1-Statistical analyses for abacavir, dolutegravir, and lamivudine with single doses of a FDC tablet containing abacavir 600 mg, dolutegravir 50 mg, and lamivudine 300 mg under fed and fasted conditions

PK Parameter	GLS Mean		Ratio of GLS Means [90% CI]
	FDC Fasted (n = 12)	FDC Fed (n = 12)	FDC Fed vs FDC Fasted
DTG PK Parameters			
AUC(0-∞) (µg.h/mL)	40.54	60.11	1.48 [1.36, 1.62]
AUC(0-t) (µg.h/mL)	37.38	54.85	1.47 [1.35, 1.60]
Cmax (µg/mL)	2.25	3.08	1.37 [1.26, 1.48]
ABC PK Parameters			
AUC(0-∞) (µg.h/mL)	12.96	12.00	0.926 [0.899, 0.953]
AUC(0-t) (µg.h/mL)	12.94	11.96	0.924 [0.898, 0.952]
Cmax (µg/mL)	3.84	2.97	0.774 [0.662, 0.905]
3TC PK Parameters			
AUC(0-∞) (µg.h/mL)	12.08	12.61	1.04 [0.971, 1.12]
AUC(0-t) (µg.h/mL)	11.61	12.18	1.05 [0.963, 1.14]
Cmax (µg/mL)	1.95	1.87	0.960 [0.879, 1.05]

A food effect was observed for dolutegravir when administered as a fixed dose combination tablet in combination with abacavir and lamivudine. Based on the information provided in the original Clinical Pharmacology NDA review (see NDA 204790), when single entity dolutegravir was administered with high fat meals, the dolutegravir C_{max} and AUC_(0-∞) were increased by 67% (90% confidence interval: ↑53%

to ↑83%) and 66% (90% confidence interval: ↑52% to ↑82%), respectively. According to an information request, the high fat meal provided 59.6% fat and 916 calories and the specific breakdown of the number of calories for the high fat meal was 116 calories from protein, 254 calories from carbohydrates, and 547 calories from fat. However, the dolutegravir U.S prescribing information states that dolutegravir may be administered with or without food. The observed increase in dolutegravir exposure when dolutegravir is administered as part of a fixed dose combination tablet with abacavir and lamivudine is within the magnitude of the increase in C_{\max} and $AUC_{(0-\infty)}$ for dolutegravir when administered as a single entity tablet. Therefore, the applicant's recommendation to administer the fixed dose combination tablet with or without food with respect to dolutegravir is acceptable.

A food effect was also observed for abacavir when administered as a fixed dose combination tablet in combination with dolutegravir and lamivudine based on the changes in C_{\max} . Based on the information in the original Clinical Pharmacology NDA review (see NDA 20977), when single entity abacavir was administered with high fat meals, the abacavir C_{\max} and $AUC_{(0-\infty)}$ were decreased by 26% (90% confidence interval: ↓35% to ↓16%) and 3% (90% confidence interval: ↓10% to ↑4%), respectively. According to an information request, the high fat meal provided 62% fat and 967 calories and the specific breakdown of the number of calories for the high fat meal was 132 kilocalories from protein, 232 kilocalories from carbohydrates, and 603 kilocalories from fat. However, the abacavir label states that abacavir may be administered with or without food. The observed decrease in C_{\max} when abacavir is administered as part of a fixed dose combination tablet with lamivudine and dolutegravir is within the magnitude of the decrease in C_{\max} for abacavir when administered as a single entity tablet. Therefore, the applicant's recommendation to administer the fixed dose combination tablet with or without food with respect to abacavir is acceptable.

A food effect was not observed for lamivudine when administered as part of a fixed dose combination tablet with abacavir and dolutegravir. Therefore, the applicant's recommendation to administer the fixed dose combination tablet with or without food when administered with respect to lamivudine is acceptable.

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/s/

STANLEY AU
07/15/2014

SHIRLEY K SEO
07/16/2014

BIOPHARMACEUTICS REVIEW			
Office of New Drug Quality Assessment			
Application No.:	NDA 205551	Biopharmaceutics Reviewer: Elsbeth Chikhale, PhD	
Submission Date:	October 22, 2013		
Division:	Division of Antiviral Products	Biopharmaceutics Team Leader: Angelica Dorantes, PhD	
Applicant:	ViiV Healthcare Co.	Acting Supervisor: Richard Lostritto, PhD	
Trade Name:	Triumeq	Date Assigned:	October 23, 2013
Generic Name:	Abacavir, Dolutegravir and Lamivudine	Date of Review:	July 7, 2014
Indication:	Treatment of HIV	Type of Submission: 505(b)(1) Original New Drug Application	
Dosage form/ strengths	Tablets/ 600 mg abacavir / 50 mg dolutegravir / 300 mg lamivudine per tablet		
Route of Administration	Oral		

SUMMARY

Submission: This is a 505(b)(1) for a fixed dose combination (FDC) film coated purple oval tablet containing 50 mg (b)(4) dolutegravir (DTG), 600 mg abacavir and 300 mg lamivudine per tablet. The proposed once-daily FDC single tablet regimen (STR) that combines the integrase inhibitor (INI) DTG with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir sulfate (abacavir, ABC) and lamivudine (3TC) is being developed for use in the treatment of human immunodeficiency virus (HIV) infection. The Applicant has performed numerous clinical safety and efficacy studies as well as a bioequivalence (BE) study (study ING114580) in healthy volunteers under fasted conditions to compare the bioavailability of the proposed FDC drug product vs. co-administration of the separate tablet formulations of DTG 50 mg and EPZICOM (ABC 600 mg/3TC 300 mg). Dissolution is considered a critical quality attribute for the proposed drug product and will be tested as part of the drug product release and stability testing.

Review: The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of:

- 1) the proposed dissolution methodology and dissolution acceptance criteria for the active drugs
- 2) the bridging of the formulations
- 3) the BE study under fasted conditions
- 4) the bio-analytical method and method validation
- 5) the audit/inspection reports of the BE study

CONCLUSIONS:

ONDQA-Biopharmaceutics had evaluated the information provided in NDA 205551 and concludes the following:

1) Dissolution method:

The following proposed single dissolution method for all three active drugs is acceptable:
USP Apparatus 2 (paddle) at 85 rpm,
Medium: 900 mL of 0.01 M phosphate buffer with 0.5% SDS, pH 6.8 at 37°C

2) Dissolution acceptance criteria:

The following dissolution acceptance criteria are acceptable:

Dolutegravir: Q = (b) / (4) % at 35 minutes

Abacavir and lamivudine: Q = (b) / (4) % at 30 minutes

3) Bioequivalence studies:

Based on the provided data, the proposed FDC drug product is shown to be bioequivalent to the separate tablet formulations of DTG 50 mg plus EPZICOM (ABC 600 mg/3TC 300 mg) under fasting conditions.

4) Bridging of the formulations:

The image change (debossing and scoring) between the tablets used in pivotal BE study (ING114580) and the proposed commercial tablets was supported by comparative dissolution profile data indicating that this image change did not have a significant effect on the dissolution rates of the three active drugs.

5) Bio-analytical method:

The bio-analytical methods used to measure concentrations of DTG, ABC and 3TC in human plasma were sensitive, selective, accurate and reproducible. The proposed bio-analytical methods are suitable and validated. The stability of each of the 3 actives was demonstrated during sample processing and long-term storage.

6) Inspection of BE Studies:

The OSI inspection report for the BE study ING 114580 is currently pending.

RECOMMENDATION:

At this time of the review process the consult report from the Office of Scientific Investigations is pending. Therefore, from the Biopharmaceutics perspective the information needed to support the approval of this NDA is incomplete and the Biopharmaceutics recommendation for NDA 205551 for Triumeq (abacavir, dolutegravir, and lamivudine) FDC Tablets (600 mg/50 mg/300 mg) is currently PENDING.

Elsbeth Chikhale, Ph.D.

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.

Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

BIOPHARMACEUTICS EVALUATION – REVIEWER NOTES

SUBMISSION:

This is a 505(b)(1) for a fixed dose combination (FDC) film coated purple oval tablet containing 50 mg [REDACTED]^{(b) (4)} dolutegravir (DTG), 600 mg abacavir and 300 mg lamivudine per tablet. The Applicant has performed numerous clinical safety and efficacy studies as well as a bioequivalence (BE) study (ING114580) in healthy volunteers under fasted conditions to compare the bioavailability of the proposed FDC drug product vs. co-administration of the separate tablet products of DTG 50 mg and EPZICOM (ABC 600 mg/3TC 300 mg).

Dissolution is considered a critical quality attribute for the proposed drug product and will be tested as part of the drug product release and stability testing.

REVIEW:

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of:

- 1) the proposed dissolution methodology and dissolution acceptance criteria for the active drugs
- 2) the bridging of the formulations
- 3) the BE study under fasted conditions
- 4) the bio-analytical method and method validation
- 5) the audit/inspection reports of the BE study

BIOPHARMACEUTICS INFORMATION:

PROPOSED FORMULATION:

The qualitative and quantitative composition of the proposed tablet is shown in the table below:

Component	Quantity (% w/w)	Function
(b) (4)		

Component	Quantity (mg/tablet)	Function
Dolutegravir (b) (4) ³	(b) (4)	Active (b) (4)
Abacavir Sulfate ⁴	(b) (4)	Active
Lamivudine ¹	300.0	Active
Microcrystalline Cellulose	(b) (4)	(b) (4)
Sodium Starch Glycolate		
Magnesium Stearate		
Film Coating		
Opadry II Purple 85F90057 ⁵	(b) (4)	Film coat (b) (4)
(b) (4)	(b) (4)	(b) (4)
Total Coated Tablet Weight	(b) (4)	(b) (4)

(b) (4)

PROPOSED DISSOLUTION METHODS:

(b) (4)

Reviewer's assessment:

Based on additional dissolution data provided and discussed above as part of the dissolution method (submissions dated 4/18/14 and 6/2/14)(see Table 3 on page 19 of this review), the following dissolution acceptance criteria are agreed upon with the Applicant and are acceptable:

For dolutegravir: $Q = \begin{matrix} (b) \\ (4) \end{matrix} \% \text{ at } 35 \text{ minutes}$

For abacavir and lamivudine: $Q = \begin{matrix} (b) \\ (4) \end{matrix} \% \text{ at } 30 \text{ minutes}$

BRIDGING OF THE FORMULATIONS:

The following formulations have been used during the development of the proposed FDC tablet:

(b) (4)

The pivotal Phase 3 studies were performed using 50 mg DTG tablets in combination with Epzicom (600 mg abacavir and 300 mg lamivudine) tablets. However, the proposed drug product is a FDC with all 3 active ingredients. Therefore, a BE study between these products was conducted. The FDC tablets used in the BE study and the commercial FDC tablets differ only in the debossing and scoring (image change). In order to bridge these two tablet images, the Applicant was asked to submit comparative dissolution profile data.

IR request sent on 5/22/14:

To support the image change (score, shape and debossing/color), provide the comparative dissolution data (raw data, mean, SD, full profiles/figures, f₂ calculation) using the currently proposed dissolution method for the FDC drug product before the image change (used in trial ING114580), and after the image change (commercial to-be-marketed product).

Applicant's Response dated 6/2/14:

The DTG/ABC/3TC Tablets used in pivotal BE study (ING114580) were purple, oval, biconvex tablets with a break-line, debossed with 'TRI 572' on one side and '572 TRI' on the other side (stability image). The proposed commercial tablets are purple, oval, biconvex tablets debossed with '572 Tri' on one side (commercial image). Both of these tablets are manufactured using the same manufacturing process, scale and controls.

The following dissolution data and f₂ similarity factors were generated:

Table 11 Dissolution Data for DTG/ABC/3TC Tablet Batches R572977 (Stability Image and Pivotal Bioequivalence Batch) and R609209 (Commercial Image)

(b) (4)

Reviewer's assessment of response:

The BE study that bridges the drug products used in the Phase 3 trials to the FDC proposed drug product are discussed and evaluated in a separate section below of this review (see below). The image change (debossing and scoring) between the tablets used in pivotal BE study (ING114580) and the proposed commercial tablets was supported by comparative dissolution profile data indicating that this image change did not have a significant effect on the drug dissolution profiles.

BIOEQUIVALENCE STUDY:

To support the approval of the proposed FDC product, the Applicant conducted a bioequivalence study (ING 14580) in healthy volunteers under fasted conditions to compare the bioavailability of the proposed FDC drug product vs. co-administration of the separate tablet formulations of DTG 50 mg and EPZICOM (ABC 600 mg/3TC 300 mg). Attachment 1 includes the Applicant's synopsis for the submitted BE study ING 14580.

Study Number: ING114580

Study Title: "An Evaluation of the Bioequivalence of a Combined Formulated Tablet (50mg/600mg/300mg dolutegravir/abacavir/lamivudine) Compared to One Dolutegravir 50mg Tablet and One EPZICOM (600mg/300mg abacavir/lamivudine) Tablet Administered Concurrently and the Effect of Food on Bioavailability of the Combined Formulation in Healthy Adult Subjects".

Study Objectives:

The primary objective was:

- To evaluate the bioequivalence between a single fixed dose combination (FDC) tablet formulation of dolutegravir (DTG) 50 mg, abacavir (ZIAGEN; ABC) 600 mg, and lamivudine (EPIVIR; 3TC) 300 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus EPZICOM (EPZ) (ABC 600 mg / 3TC 300 mg), with each dose given in the fasted state.

The secondary objectives were:

- To evaluate the effect of food on the bioavailability of the FDC tablet formulation of DTG 50 mg / ABC 600 mg / 3TC 300 mg.
- To assess the safety and tolerability of single dose administration of the combination of DTG, ABC, and 3TC in healthy volunteers either fasted or with food.

This review is only evaluating the BE study, not the food effect study. The food effect study is being reviewed by the Office of Clinical Pharmacology (OCP).

Study Design: This was a single center, randomized, two-part, open-label, crossover study in 66 healthy adult subjects to evaluate the bioequivalence (BE) of a single combined formulated tablet of DTG 50 mg, abacavir 600 mg and lamivudine 300 mg compared to co-administration of the separate tablet formulations of DTG 50 mg and EPZ in the fasted state, and to evaluate the effect of food on the bioavailability of the combined formulation. The study consisted of screening, treatment and follow-up phases. The treatment phase was divided into two parts (Part A and Part B). Part A consisted of 2 single dose treatment sequences (AB, BA) in a randomized, two-period, crossover design with a 7 day washout between doses. Twelve subjects who completed Part A participated in Part B and received a single dose of the combined formulated tablet administered with a high fat meal (Treatment C). There was a 7 day washout between the second dose in Part A and the dose in Part B. The follow-up phase was scheduled 7 to 14 days after the last dose of study drug.

Treatment A	DTG 50 mg/ABC 600 mg/3TC 300 mg FDC tablet, fasted
Treatment B	DTG 50 mg tablet plus a single EPZ tablet, fasted
Treatment C	DTG 50 mg/ABC 600 mg/3TC 300 mg FDC tablet with a high fat meal

Number of subjects: A total of 66 subjects were planned to be enrolled such that approximately 60 subjects would complete dosing.

Summary of Subject Disposition in Study ING114580:

Number of Subjects	FDC Fasted	DTG + EPZ Fasted	Overall
Number of subjects planned, N:	66	66	66
Number of subjects randomized, N:	65	65	66
Number of subjects included in Safety Population, n (%):	65 (100%)	65 (100%)	66 (100%) ²
Number of subjects included in PK Concentration Population, n (%):	64 (98%)	65 (100%)	65 (98%)
Number of subjects included in PK Bioequivalence Summary Population, n (%):	62 (95%)	62 (95%)	62 (94%)
Number of subjects included in PK Food Effect Summary Population, n (%):	12 (18%)	NA	12 (18%)
Number of subjects completed as planned, n (%):	63 (97%)	62 (95%)	62 (95%) ³
Number of subjects withdrawn (any reason), n (%):	2 (3%)	3 (5%)	5 (8%)
Number of subjects withdrawn for AE, n (%):	1 (2%)	0	1 (2%)
Reasons for subject withdrawal, n (%)			
Lost to follow-up	0	1 (2%)	1 (2%)
Adverse events	1 (2%)	0	1 (2%)
Investigator discretion	1 (2%)	2 (3%)	3 (5%)

Criteria for BE Evaluation: The 90 % confidence intervals for the difference of log transformed C_{max} and AUC_{0-t} and AUC_{0-inf} should be within the range of 80-125%.

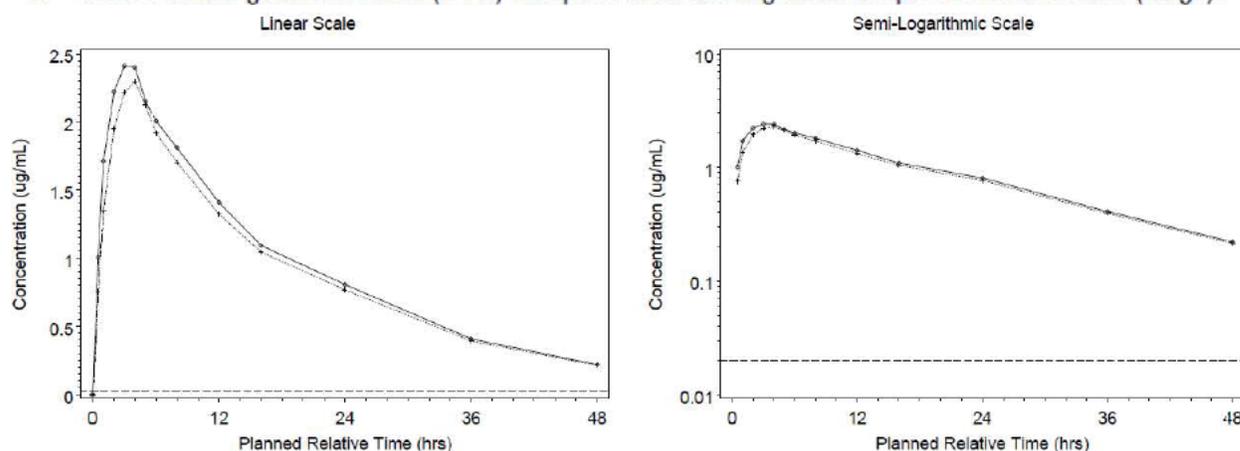
Following \log_e -transformation, the pharmacokinetic (PK) parameters C_{max} , $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $t_{1/2}$, CL/F , and Vz/F for DTG, ABC and 3TC were separately analyzed using a mixed effects analysis of variance (ANOVA) model with fixed effect terms for Sequence, Period and Treatment and with Subject treated as a random effect. Point estimates and their associated 90% confidence intervals (CIs) were constructed for the differences, test treatment (A) – reference treatment (B), for bioequivalence assessment. The point estimates and their associated 90% CIs were then back-transformed to provide point estimates and 90% CIs for the ratios of test/reference on the original scale.

Study Results:

The following PK results were reported for each of the 3 actives:

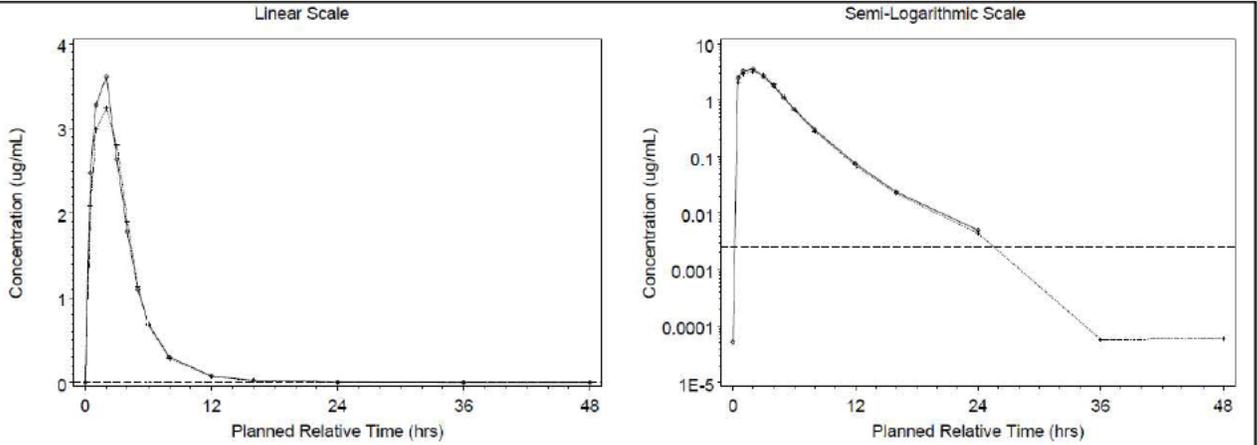
Summary of Plasma DTG Pharmacokinetic Parameters ¹		
DTG PK Parameter	Treatment	
	FDC fasted (n=62)	DTG + EPZ fasted (n=62)
AUC(0-∞) (μg.h/mL)	44.8 (33)	47.4 (34)
AUC(0-t) (μg.h/mL)	40.9 (31)	43.4 (32)
C _{max} (μg/mL)	2.44 (28)	2.54 (29)
C ₂₄ (μg/mL)	0.73 (35)	0.76 (38)
CL/F (L/hr)	1.12 (33)	1.05 (34)
t _{1/2} (h)	12.8 (20)	12.9 (18)
t _{lag} (h)	0.00 (0.0, 0.5)	0.00 (0.0, 0.5)
t _{max} (h)	3.00 (1.0, 8.0)	3.00 (0.5, 8.0)
V _z /F (L)	20.5 (28)	19.6 (32)

1. Values denote geometric mean (CV%) except for t_{max} and t_{lag} which are presented as median (range).



Summary of Plasma ABC Pharmacokinetic Parameters ¹		
ABC PK Parameter	Treatment	
	FDC fasted (n=62)	DTG + EPZ fasted (n=62)
AUC(0-∞) (μg.h/mL)	13.9 (26)	14.5 (24)
AUC(0-t) (μg.h/mL)	13.9 (26)	14.5 (24)
C _{max} (μg/mL)	4.02 (24)	4.37 (26)
CL/F (L/hr)	43.1 (26)	41.4 (24)
t _{1/2} (h)	2.56 (32)	2.54 (27)
t _{lag} (h)	0.00 (0.0, 0.0)	0.00 (0.0, 0.5)
t _{max} (h)	2.00 (0.5, 3.0)	2.00 (0.5, 5.0)
V _z /F (L)	159 (36)	151 (34)

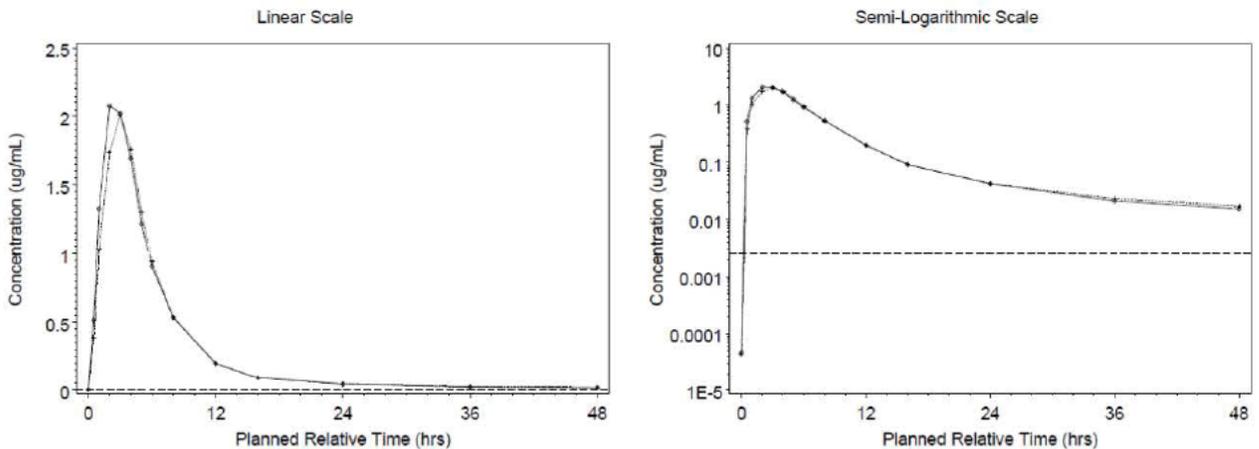
1. Values denote geometric mean (CV%) except for t_{max} and t_{lag} which are presented as median (range).



Summary of Plasma 3TC Pharmacokinetic Parameters¹

3TC PK Parameter	Treatment	
	FDC fasted (n=62)	DTG + EPZ fasted (n=62)
AUC(0-∞) (µg.h/mL)	12.8 (25)	13.1 (21)
AUC(0-t) (µg.h/mL)	12.3 (26)	12.8 (21)
Cmax (µg/mL)	2.11 (29)	2.28 (26)
CL/F (L/hr)	23.5 (25)	22.9 (21)
t1/2 (h)	14.5 (53)	12.7 (41)
tlag (h)	0.00 (0.0, 0.0)	0.00 (0.0, 0.0)
tmax (h)	3.00 (1.0, 5.0)	2.00 (1.0, 4.0)
Vz/F (L)	492 (64)	420 (44)

1. Values denote geometric mean (CV%) except for tmax and tlag which are presented as median (range).



Statistical Comparison of Selected Plasma PK Parameters for Bioequivalence Assessment:

	Ratio of GLS Means [90% CI] FDC Fasted vs DTG + EPZ Fasted
DTG PK Parameters	
AUC(0-∞)	0.945 [0.889, 1.00]
AUC(0-t)	0.943 [0.888, 1.00]
C _{max}	0.961 [0.906, 1.02]
ABC PK Parameters	
AUC(0-∞)	0.960 [0.939, 0.980]
AUC(0-t)	0.960 [0.939, 0.980]
C _{max}	0.920 [0.867, 0.977]
3TC PK Parameters	
AUC(0-∞)	0.972 [0.940, 1.01]
AUC(0-t)	0.960 [0.928, 0.994]
C _{max}	0.926 [0.885, 0.968]

GLS=Geometric least squares

The FDC tablet formulation of DTG 50 mg, ABC 600 mg and 3TC 300 mg was bioequivalent to the separate tablet formulations of DTG 50 mg plus EPZICOM (ABC 600 mg/3TC 300 mg). For each of DTG, ABC, and 3TC, the 90% CIs for the GLS mean ratios for each of the bioequivalence parameters are within the BE criteria range of 0.8 to 1.25.

Reviewer's assessment of the Bioequivalence study under fasting conditions: ACCEPTABLE

This Reviewer confirmed the BE results provided by the Applicant. To confirm the reported results, phoenix software was used to reanalyze the raw data. The following results were obtained:

DTG	90% confidence interval
C _{max}	97.26-109.15
AUC _{0-t}	87.75-111.82
AUC _{0-inf}	99.92-112.06

ABC	90% confidence interval
C _{max}	100.41-114.81
AUC _{0-t}	92.09-108.36
AUC _{0-inf}	102.47-106.72

3TC	90% confidence interval
C _{max}	100.28-111.69
AUC _{0-t}	88.71-109.26
AUC _{0-inf}	100.07-106.67

The overall results demonstrate that the proposed FDC drug product is bioequivalent to the separate tablet formulations of DTG 50 mg plus EPZICOM (ABC 600 mg/3TC 300 mg) under fasting conditions.

BIO-ANALYTICAL METHOD:

The bio-analytical method for the measurement of dolutegravir (DTG) in plasma was based on extraction by protein precipitation using acetonitrile containing an isotopically labeled internal standard ($[^2\text{H}_7\ ^{15}\text{N}]$ -DTG) followed by HPLC-MS/MS analysis with a (b) (4) and multiple reaction monitoring. The method was validated over the concentration range of 20 to 20,000 ng/mL and was used to support the pivotal bioequivalence study (ING114580).

The bio-analytical methods for measuring abacavir and lamivudine in plasma were conducted using validated proprietary methods. These methods were based on extraction by protein precipitation followed by HPLC-MS/MS analysis using a (b) (4) with multiple reaction monitoring. The laboratory used a combination assay to simultaneously measure abacavir (2.5 to 2500 ng/mL) and lamivudine (2.5 to 2500 ng/mL) utilizing the stable isotopically labeled internal standards ($[^2\text{H}_4]$ -abacavir) and ($[^{13}\text{C}^{15}\text{N}_2]$ -lamivudine). The methods were validated and used to support the pivotal bioequivalence study (ING114580).

IR dated 1/23/14: *Provide a summary table for the bio-analytical method validation (used for study ING 114580) for each drug substance.*

Applicant's Response dated 2/26/14:

A summary of the bio-analytical methods and the method validation parameters was provided and is included in Attachment 1.

Reviewer's assessment of the bio-analytical method and method validation: **ACCEPTABLE**

The bio-analytical methods used to measure concentrations of DTG, ABC and 3TC in human plasma were sensitive, selective, accurate and reproducible. The proposed bio-analytical methods are suitable and validated. The stability of each of the 3 actives was demonstrated during sample processing and long-term storage.

REVIEWER'S OVERALL CONCLUSIONS:

1) Dissolution methods:

The following proposed dissolution method (one method for all three inactive ingredients) is acceptable:

Equipment: USP Apparatus 2 (paddle) at 85 rpm,

Medium: 900 mL of 0.01 M phosphate buffer with 0.5% SDS, pH 6.8 at 37°C

2) Dissolution acceptance criteria:

The following dissolution acceptance criteria are acceptable:

Dolutegravir: $Q = \frac{(b)}{(4)}\%$ at 35 minutes

Abacavir and lamivudine: $Q = \frac{(b)}{(4)}\%$ at 30 minutes

3) Bioequivalence studies:

Based on the provided data, the proposed FDC drug product is shown to be bioequivalent to the separate tablet formulations of DTG 50 mg plus EPZICOM (ABC 600 mg/3TC 300 mg) under fasting conditions.

4) Bridging of the formulations:

The image change (debossing and scoring) between the tablets used in pivotal BE study (ING114580) and the proposed commercial tablets was supported by comparative dissolution profile data indicating that this image change did not have a significant effect on the drug dissolution profiles.

5) Bio-analytical method:

The bio-analytical methods used to measure concentrations of DTG, ABC and 3TC in human plasma were sensitive, selective, accurate and reproducible. The proposed bio-analytical methods are suitable and validated. The stability of each of the 3 actives was demonstrated during sample processing and long-term storage.

6) Inspection of BE Studies:

The OSI inspection report for the BE study ING 114580 is currently pending.

RECOMMENDATION:

At this time of the review process the consult report from the Office of Scientific Investigations is pending. Therefore, from the Biopharmaceutics perspective the information needed to support the approval of this NDA is incomplete and the Biopharmaceutics recommendation for NDA 205551 for Triumeq (abacavir, dolutegravir, and lamivudine) FDC Tablets (600 mg/50 mg/300 mg) is currently PENDING.

Attachment 1: Bio-Analytical Methods Summary

Abacavir

(b) (4)

Report numbers: 2012N150069, 2012N151912

Matrix	Human Plasma	
Sample Volume Required Storage Conditions Extraction Procedure	50µL of human plasma is extracted using protein precipitation at room temperature.	
Concentration Range	2.5 to 2500 ng/mL	
HPLC Procedure	Gradient A=10 mM Ammonium Formate with 0.1% formic acid in water B=Acetonitrile with 0.1% formic acid Column = Thermo Betasil Silica-100, 3.0 x 50 mm	
Detection	MS/MS	
Regression Type	Linear, 1/x ²	
Coefficient of Determination	0.9963 to 0.9994	
Between-Batch Accuracy	standards	-3.9% to 2.7%
	QCs	-8.7% to 2.1%
Between-Batch CV	standards	3.7% to 5.8%
	QCs	2.7% to 12.3%
Within Batch	Accuracy	-18.7% to 3.9%
	CV	0.9% to 17.4%
Recovery	Drug	85.2%
	Reference (IS)	82.1%
Stability in human plasma	Room temp	27.75 hours at room temperature
	Freeze/thaw	5 cycles from -20°C and -70°C
	Long term	212 days at -20°C and -70°C
Solution Stability	at room temp	27.75 hours at room temperature
	at 4°C	50 days at 2 to 8°C
Reference Solution Stability (IS)	at room temp	27.75 hours at room temperature
	at 4°C	50 days at 2 to 8°C
LLOQ (Accuracy/CV)		-8.7% (accuracy), 12.3% (CV)
Processed Stability	at 4°C	90.25 hours at 5°C
Dilution Integrity (v:v sample-blank)		5 x dilution tested

Dolutegravir

(b) (4)

Report numbers: 2012N147635, 2012N151911, 2013N161036

Matrix	Human Plasma	
Sample Volume Required Storage Conditions Extraction Procedure	25µL of human plasma is protected from light and extracted using protein precipitation.	
Concentration Range	20 to 20000 ng/mL	
HPLC Procedure	Isocratic 60:40 (water with 0.1% formic acid: acetonitrile with 0.1% formic acid) Flow rate = 0.475 mL/min Column = Waters XBridge C ₁₈ , 2.1 x 50 mm	
Detection	MS/MS	
Regression Type	Linear, 1/x ²	
Coefficient of Determination	0.9990 to 0.9995	
Between-Batch Accuracy	standards QCs	-1.4% to 1.9% -2.5% to 6.5%
Between-Batch CV	standards QCs	2.2% to 3.8% 2.9% to 8.0%
Within Batch	Accuracy CV	-7.1% to 7.5% 1.1% to 13.6%
Recovery	Drug Reference (IS)	97.6% 98.4%
Stability in human plasma	Room temp Freeze/thaw Long term	24.75 hours at room temperature 5 cycles from -20°C and -70°C 257 days at -20°C and -70°C
Solution Stability	at room temp at 4°C	At least 22.75 hours at room temperature 214 days at 2 to 8°C
Reference Solution Stability (IS)	at room temp at 4°C	At least 22.75 hours at room temperature 214 days at 2 to 8°C
LLOQ (Accuracy/CV)		6.5% (accuracy), 6.4% (CV)
Processed Stability	at 4°C	96.5 hours at 5°C
Dilution Integrity (v:v sample-blank)		5 x and 10x dilutions tested

Lamivudine

(b) (4)

Report numbers: 2012N150069, 2012N151912

Matrix	Human Plasma	
Sample Volume Required Storage Conditions Extraction Procedure	50µL of human plasma is extracted using protein precipitation at room temperature.	
Concentration Range	2.5 to 2500 ng/mL	
HPLC Procedure	Gradient A=10 mM Ammonium Formate with 0.1% formic acid in water B=Acetonitrile with 0.1% formic acid Column = Thermo Betasil Silica-100, 3.0 x 50 mm	
Detection	MS/MS	
Regression Type	Linear, $1/x^2$	
Coefficient of Determination	0.9992 to 0.9994	
Between-Batch Accuracy	standards QCs	-1.1% to 0.7% -10.8% to 3.8%
Between-Batch CV	standards QCs	2.4% to 4.5% 2.6% to 11.4%
Within Batch	Accuracy CV	-14.8% to 5.5% 1.8% to 18.9%
Recovery	Drug Reference (IS)	81.7% 80.7%
Stability in human plasma	Room temp Freeze/thaw Long term	27.75 hours at room temperature 5 cycles from -20°C and -70°C 212 days at -20°C and -70°C
Solution Stability	at room temp at 4°C	27.5 hours at room temperature 50 days at 2 to 8°C
Reference Solution Stability (IS)	at room temp at 4°C	27.5 hours at room temperature 50 days at 2 to 8°C
LLOQ (Accuracy/CV)		-10.8% (accuracy), 11.4% (CV)
Processed Stability	at 4°C	90.5 hours at 5°C
Dilution Integrity (v:v sample-blank)		5 x dilution tested

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

/s/

ELSBETH G CHIKHALE
07/07/2014

ANGELICA DORANTES
07/08/2014

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	205551	Brand Name	Triumeq (proposed)
OCP Division (I, II, III, IV, V)	DCP4	Generic Name	Dolutegravir (DTG), abacavir (ABC), and lamivudine (3TC)
Medical Division	DAVP	Drug Class	DTG: integrase strand transfer inhibitor, ABC and 3TC: nucleoside reverse transcriptase inhibitors
OCP Reviewer	Stanley Au	Indication(s)	HIV-1 infection
OCP Team Leader	Shirley Seo	Dosage Form	Tablets
Pharmacometrics Reviewer		Dosing Regimen	Once daily fixed dose combination regimen: DTG (50 mg), ABC (600 mg), 3TC (300 mg)
Date of Submission	October 22, 2013	Route of Administration	Oral
Estimated Due Date of OCP Review	June 22, 2014	Sponsor	ViiV Healthcare
Medical Division Due Date	June 29, 2014	Priority Classification	Standard
PDUFA Due Date	August 22, 2014		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary	X (section 2.7.2)			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for
NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X (b) (4)			This trial will not be reviewed.
Bioequivalence studies -				
traditional design; single / multi dose:	X (ING114580)			The bioequivalence component of the trial will be reviewed by biopharmaceutics.
replicate design; single / multi dose:				
Food-drug interaction studies	X (ING114580)			The food effect component of the trial will be reviewed by clinical pharmacology.
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X (For the clinical pharmacology review)	The adequacy of the bioequivalence assessment will be made by the biopharmaceutics reviewer.
2	Has the applicant provided metabolism and drug-drug interaction information?			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

	pharmacokinetics and exposure-response in the clinical pharmacology section of the label?				
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

 YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

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

/s/

STANLEY AU
12/17/2013

SHIRLEY K SEO
12/18/2013