NDA/Supplement	205551 Supplement 11
Submission Type	Efficacy Supplement
Applicant Name	ViiV Healthcare
Submission Dates	05/31/2017
Generic Name	Triumeq®
Dosage Form (Strength)	Abacavir (ABC) 600 mg, dolutegravir (DTG) 50 mg, lamivudine (3TC) 300 mg tablets
Indication	Treatment of HIV-1 infection in pediatric patients weighing at least 40 kg
Review Team	Amal Ayyoub, PhD, Shirley Seo, PhD

1 Contents

2 Executive Summary

2.1 Background

Triumeq®; a fixed-dose combination (FDC) of dolutegravir (DTG; integrase strand transfer inhibitor [INSTI]), and the nucleoside analogue reverse transcriptase inhibitors (NRTIs) abacavir (ABC) and lamivudine (3TC), was approved for the treatment of HIV-1 infection in adults in 2014. The recommended dose for adults is one tablet daily with or without food. Triumeq® is not currently approved for use in pediatric patients, however, each individual component of Triumeq® has been approved for use in some pediatric subpopulations. Additionally, Epzicom® dual combination tablet (ABC/3TC) also has approved pediatric uses. The original approval of Triumeq® included the Post-Marketing Requirement (PMR) 2768-3 under the Pediatric Research Equity Act (PREA) outlined below:

"Evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in HIV infected pediatric subjects 12 years to less than 18 years of age and weighing at least 40 kg. The safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 12 to less than 18 years of age and weighing at least 40 kg may not be required if dosing recommendation for the FDC tablets can be supported by pediatric trials already conducted with the individual drug products".

The basis of approval for the adolescent dosing is the existing adolescent dosing for Tivicay® (DTG) and Epzicom® (ABC/3TC). Therefore, no new data was included is this submission.

2.2 Recommendations

The Office of Clinical Pharmacology review team finds this application acceptable and fulfils PMR 2768-3.

2.3 Labeling Recommendations

Based on cross-labeling comparisons with Tivicay® and Epzicom®, labeling negotiations with the Applicant resulted in the following final additions/changes (shown below in *red*):

I. In **HIGHLIGHTS OF PRESCRIBING INFORMATION**, the following sections were updated:

- under **INDICATIONS AND USAGE:**
  "TRIUMEQ, a combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), abacavir, and lamivudine (both nucleoside analogue reverse transcriptase inhibitors) is indicated for the treatment of HIV-1 infection in adults *and in pediatric patients weighing at least 40 kg*. (1)"

- under **DOSAGE AND ADMINISTRATION**:

  "Adults *and pediatric patients weighing at least 40 kg:* One tablet daily. May be taken with or without food. (2.2)"

- under **USE IN SPECIFIC POPULATION:**

  "Pediatrics: Not recommended for patients weighing less than 40 kg. (8.4)"

II. In **Section 2.2, Recommended Dosage**, the following text was edited:

"TRIUMEQ is a fixed-dose combination product containing 600 mg of abacavir, 50 mg of dolutegravir, and 300 mg of lamivudine. The recommended dosage regimen of TRIUMEQ in *adults and pediatric patients weighing at least 40 kg* is one tablet once daily orally with or without food"

III. In **Section 8.4, Pediatric Use**, the following text was added:

"The clinical data supporting use of TRIUMEQ in HIV-1 infected pediatric patients weighing at least 40 kg is derived from the following previously conducted pediatric trials using the individual components of TRIUMEQ:
• The safety and efficacy of once-daily abacavir and lamivudine were established with a randomized, multicenter trial (ARROW [COL105677]) in HIV-1–infected, treatment-naïve subjects aged 3 months to 17 years with a first-line regimen containing abacavir and lamivudine, using either the combination of EPIVIR and ZIAGEN or EPZICOM [see Adverse Reactions (6.2), Clinical Studies (14.2)].
• The safety and antiviral activity (efficacy) of dolutegravir was established through a 48-week, open-label, multicenter, dose-finding clinical trial (IMPAACT P1093), in which 23 treatment-experienced, INSTI-naïve, HIV-1–infected subjects aged 12 to less than 18 years were treated with

dolutegravir (TIVICAY) plus optimized background therapy [see Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.2)].”

IV. In Section **12.3, Pharmacokinetics -** Specific Populations **-** *Pediatric Patients,* the following text was added:

“*The pharmacokinetics for the individual components of TRIUMEQ (abacavir, dolutegravir, and lamivudine) have been evaluated in pediatric subjects.*

Dolutegravir: The pharmacokinetics of dolutegravir in HIV-1–infected children (n = 14) weighing at least 40 kg were similar to those observed in HIV-1–infected adults who received dolutegravir 50 mg once daily (Table 7) [see Clinical Studies (14.2)].

Table 7. Dolutegravir Steady-State Pharmacokinetic Parameters in Pediatric Subjects

		Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (%CV)		
Weight (n)	***Dose of TIVICAY***	***C_{max} (mcg/mL))***	***$AUC_{(0-24)}$ (mcg.h/mL)***	***C_{24} (mcg/mL)***
≥40 kg (n = 14)	*50 mg once daily*	*3.89 (43)*	*50.1 (53)*	*0.99 (66)*

Abacavir and Lamivudine: The pharmacokinetic data for abacavir and lamivudine once daily following administration of EPZICOM in pediatric subjects weighing at least 40 kg are limited. The dosing recommendations in this population are based on the safety and efficacy established in a controlled trial conducted using either the combination of EPIVIR and ZIAGEN or EPZICOM. Refer to the prescribing information for EPIVIR and ZIAGEN for pharmacokinetic information on the individual products in pediatric patients [see Dosage and Administration (2.2), Clinical Studies (14.2)].”

2.4 Reviewer Comments and Conclusion

The Applicant utilized the 2013 version of the Tivicay® label to populate Sections 8.4 and 12.3 of the Triumeq® label. During labeling negotiations, the Clinical Pharmacology team requested that the Applicant uses the most recent Tivicay® label for cross-referencing purposes. The final labeling additions reflected in the supplement included herein are consistent with the labeling changes requested by the FDA.

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

/s/

AMAL AYYOUB
10/25/2017

SHIRLEY K SEO
10/25/2017