NEW DRUG APPROVAL

Brand Name	Triumeq PD
Generic Name	abacavir, dolutegravir, and lamivudine
Drug Manufacturer	ViiV Healthcare

New Drug Approval

FDA Approval Date: March 30, 2022

Review designation: Priority

Type of review: Type 3 - New Dosage Form; New Drug Application (NDA): 215413

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

HIV (human immunodeficiency virus) is a virus that attacks cells that help the body fight infection, making a person more vulnerable to other infections and diseases. It is spread by contact with certain bodily fluids of a person with HIV, most commonly during unprotected sex (sex without a condom or HIV medicine to prevent or treat HIV), or through sharing injection drug equipment. If left untreated, HIV can lead to the disease AIDS (acquired immunodeficiency syndrome).

Approximately 1.2 million people in the U.S. have HIV. About 13 percent of them don't know it and need testing. HIV continues to have a disproportionate impact on certain populations, particularly racial and ethnic minorities and gay, bisexual, and other men who have sex with men. In 2019, an estimated 34,800 new HIV infections occurred in the United States. New HIV infections declined 8% from 37,800 in 2015 to 34,800 in 2019, after a period of general stability. In 2019, 36,801 people received an HIV diagnosis in the U.S. and 6 dependent areas—an overall 9% decrease compared with 2015 and the number of new HIV diagnoses was highest among people aged 25 to 29. From 2015 through 2019, HIV diagnoses increased among persons aged 13-24 years, 35-44 years, and 45-54 years. Diagnoses remained stable among persons aged 25-35 years and persons aged 55 years and over.

Efficacy

The efficacy of the individual components of Triumeq PD for the treatment of HIV-1 infection was evaluated in pediatric patients enrolled in the ARROW trial (NCT02028676) and IMPAACT P1093 trial (NCT01302847), as summarized below.

- Abacavir and lamivudine once daily, in combination with a third antiretroviral drug, were evaluated in a randomized, multicenter trial (ARROW) in treatment- naive pediatric subjects with HIV-1 infection. Subjects randomized to once-daily dosing (n = 336) and who weighed at least 25 kg received abacavir 600 mg and lamivudine 300 mg, as either the single entities or as EPZICOM. At Week 96, 67% of subjects receiving abacavir and lamivudine once-daily in combination with a third antiretroviral drug, had HIV-1 RNA <80 copies/mL.
- Dolutegravir (Tivicay or Tivicay PD), in combination with other antiretroviral drugs was evaluated in treatment naive or treatment-experienced, INSTI- naive, HIV-1–infected subjects aged at least 4 weeks to 18 years in an ongoing open-label, multicenter, dose-finding clinical trial, IMPAACT P1093. Subjects were stratified by age cohort; subjects aged 12 to <18 years were enrolled in Cohort I, subjects aged 6 to <12 years were enrolled in

Cohort IIA, and subjects aged 2 to <6 years were enrolled in Cohort III-DT. Subjects weighing at least 10 kg from Cohorts I (n = 19), IIA (n = 5), and III-DT (n = 3) who received the recommended dose (determined by weight and age) and formulation contributed to the efficacy analysis at Week 48. Across all 3 cohorts, 67% (18/27) of subjects weighing at least 10 kg achieved HIV-1 RNA <50 copies/mL at Week 48 (Snapshot algorithm).

Safety

ADVERSE EVENTS

The following reported adverse reactions:

- Serious and sometimes fatal hypersensitivity reaction.
- Exacerbations of hepatitis B.
- Hepatotoxicity
- Lactic acidosis and severe hepatomegaly with steatosis.
- Immune reconstitution syndrome.
- Myocardial infarction

WARNINGS & PRECAUTIONS

- Hepatotoxicity has been reported in patients receiving a dolutegravir containing regimen. Monitoring for hepatotoxicity is recommended.
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues.
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Assess the risks and benefits of Triumeq and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. Adolescents and adults of childbearing potential should be counseled on the consistent use of effective contraception.
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy.
- Triumeq tablets and Triumeq PD tablets for oral suspension are not interchangeable.

CONTRAINDICATIONS

- Presence of HLA-B*5701 allele.
- Prior hypersensitivity reaction to abacavir, dolutegravir, or lamivudine.
- Coadministration with dofetilide.
- Moderate or severe hepatic impairment.

Clinical Pharmacology

MECHANISMS OF ACTION

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-5′-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of reverse transcriptase via DNA chain termination after incorporation of the nucleotide analogue.

Dose & Administration

ADULTS

Not recommended in adults.

PEDIATRICS

The dosage and dosage form recommended for pediatric patients varies by weight as shown in Table 1 below:

Table 1. Recommended Dosage of Triumeq PD Tablets for Oral Suspension in Pediatric Patients:

Body Weight	Triumeq PD Number of Tablets	Total Daily Dose
10 kg to < 14 kg	4 tablets once daily	240 mg abacavir, 20 mg dolutegravir, and 120 mg lamivudine once daily
14 kg to < 20 kg	5 tablets once daily	300 mg abacavir, 25 mg dolutegravir, and 150 mg lamivudine once daily
20 kg to < 25 kg	6 tablets once daily	360 mg abacavir, 30 mg dolutegravir, and 180 mg lamivudine once daily
≥25 kg	Not recommended	600 mg of abacavir, 50 mg of dolutegravir, and 300 mg of lamivudine

Triumeq PD is a fixed-dose combination product containing 60 mg of abacavir, 5 mg of dolutegravir, and 30 mg of lamivudine and only recommended in pediatric patients weighing 10 kg to less than 25 kg.

GERIATRICS

Refer adult dose.

RENAL IMPAIRMENT

Triumeq PD is not recommended for patients with creatinine clearance <30 mL/min because Triumeq PD is fixed-dose combinations, and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of Triumeq PD, is required for patients with creatinine clearance <30 mL/min, then the individual components should be used.

HEPATIC IMPAIRMENT

Triumeq PD is fixed-dose combination, and the dosage of the individual components cannot be adjusted. If a dose reduction of abacavir, a component of Triumeq PD, 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 PD is contraindicated in these patients.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Triumeq PD tablets for oral suspension: 60 mg of abacavir, 5 mg of dolutegravir, and 30 mg of lamivudine.