Table 9. Summary of Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/ritonavir 200 mg +600/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)
Fosamprenavir/ritonavir 700 mg/100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Tipranavir/ritonavir 500/200 mg twice daily	50 mg once daily	14	0.54 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)

Antacid (MAALOX) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Boceprevir 800 mg every 8 h	50 mg once daily	13	1.05 (0.96 to 1.15)	1.07 (0.95 to 1.20)	1.08 (0.91 to 1.28)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1,200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16[c]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[a] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)

Rifampin[b] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

[a] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.

[b] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.

[c] The number of subjects represents the maximum number of subjects that were evaluated.

Abacavir or Lamivudine: The drug interactions described are based on trials conducted with abacavir or lamivudine as single entities.

Effect of Abacavir and Lamivudine on the Pharmacokinetics of Other Agents: In vitro studies have shown that abacavir has potential to inhibit CYP1A1 and limited potential to inhibit metabolism mediated by CYP3A4. Lamivudine does not inhibit or induce CYP3A4. Abacavir and lamivudine do not inhibit or induce other CYP enzymes (such as CYP2C9 or CYP2D6). Based on in vitro study results, abacavir and lamivudine at therapeutic drug exposures are not expected to affect the pharmacokinetics of drugs that are substrates of the following transporters: OATP1B1/3, BCRP or P-gp, OCT1, OCT2, OCT3 (lamivudine only), or MATE1 and MATE2-K.

Abacavir, Dolutegravir, and Lamivudine: Coadministration of a single dose of riociguat (0.5 mg) to HIV-1–infected subjects receiving TRIUMEQ is reported to increase riociguat $AUC_{(\infty)}$ compared with riociguat $AUC_{(\infty)}$ reported in healthy subjects due to CYP1A1 inhibition by abacavir. The exact magnitude of increase in riociguat exposure has not been fully characterized based on findings from two studies *[see Drug Interactions (7.3)]*.

Effect of Other Agents on the Pharmacokinetics of Abacavir or Lamivudine: In vitro, abacavir is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, MATE1, MATE2-K, MRP2 or MRP4; therefore, drugs that modulate these transporters are not expected to affect abacavir plasma concentrations. Abacavir is a substrate of BCRP and P-gp in vitro; however, considering its absolute bioavailability (83%), modulators of these transporters are unlikely to result in a clinically relevant impact on abacavir concentrations.

Lamivudine is a substrate of MATE1, MATE2-K, and OCT2 in vitro. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations. This interaction is not considered clinically significant as no dose adjustment of lamivudine is needed.

Lamivudine is a substrate of P-gp and BCRP; however, considering its absolute bioavailability (87%), it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore, coadministration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Ethanol: Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure.

Interferon Alfa: There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a trial of 19 healthy male subjects.

Methadone: 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)]*. The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir.

Ribavirin: 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.

Sorbitol (Excipient): Lamivudine and sorbitol solutions were coadministered to 16 healthy adult subjects in an open-label, randomized-sequence, 4-period, crossover trial. Each subject received a single 300-mg dose of lamivudine oral solution alone or coadministered with a single dose of 3.2 g, 10.2 g, or 13.4 g of sorbitol in solution. Coadministration of lamivudine with sorbitol resulted in dose-dependent decreases of 20%, 39%, and 44% in the $AUC_{(0\text{-}24)}$; 14%, 32%, and 36% in the $AUC_{(\infty)}$; and 28%, 52%, and 55% in the C_{max}; of lamivudine, respectively.

Abacavir, Lamivudine, Zidovudine: 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.

Lamivudine and Zidovudine: No clinically significant alterations in 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 every 12 hours).

The effects of other coadministered drugs on abacavir or lamivudine are provided in Table 10.

Table 10. 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
			AUC	Variability	
Ethanol 0.7 g/kg	Abacavir Single 600 mg	24	↑41%	90% CI: 35% to 48%	↔[a]
Nelfinavir 750 mg every 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 Single 300 mg	14	↑43%	90% CI: 32% to 55%	↔

↑ = Increase; ↔ = No significant change.

[a] The drug-drug interaction was only evaluated in males.

12.4 Microbiology

Mechanism of Action

Dolutegravir: Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified recombinant HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

Abacavir: Abacavir is a carbocyclic synthetic nucleoside analogue. 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.

Lamivudine: Lamivudine is a synthetic nucleoside analogue. 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 RT via DNA chain termination after incorporation of the nucleotide analogue.

Antiviral Activity in Cell Culture

Dolutegravir: Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentration of drug necessary to affect viral replication by 50% (EC_{50}) values of 0.5 nM (0.21 ng/mL) to 2.1 nM (0.85 ng/mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a median EC_{50} value of 0.54 nM (range: 0.41 to 0.60 nM) in a viral susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates with median EC_{50} values of 0.18 nM (n = 3, range: 0.09 to 0.5 nM), 0.08 nM (n = 5, range: 0.05 to

2.14 nM), 0.12 nM (n = 4, range: 0.05 to 0.51 nM), 0.17 nM (n = 3, range: 0.16 to 0.35 nM), 0.24 nM (n = 3, range: 0.09 to 0.32 nM), 0.17 nM (n = 4, range: 0.07 to 0.44 nM), 0.2 nM (n = 3, range: 0.02 to 0.87 nM), and 0.42 nM (n = 3, range: 0.41 to 1.79 nM) for clades A, B, C, D, E, F, and G, and group O viruses, respectively. Dolutegravir EC_{50} values against three HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Abacavir: The antiviral activity of abacavir against HIV-1 was assessed in a number of cell lines including in primary monocytes/macrophages and PBMCs. EC_{50} values ranged from 3,700 to 5,800 nM (1 nM = 0.28 ng/mL) and 70 to 1,000 nM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and the mean EC_{50} value was 260 ± 180 nM against 8 clinical isolates. The median EC_{50} values of abacavir were 344 nM (range: 14.8 to 676 nM), 16.9 nM (range: 5.9 to 27.9 nM), 8.1 nM (range: 1.5 to 16.7 nM), 356 nM (range: 35.7 to 396 nM), 105 nM (range: 28.1 to 168 nM), 47.6 nM (range: 5.2 to 200 nM), 51.4 nM (range: 7.1 to 177 nM), and 282 nM (range: 22.4 to 598 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B), respectively. The EC_{50} values against HIV-2 isolates (n = 4), ranged from 24 to 490 nM.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC_{50} values were in the range of 3 to 15,000 nM (1 nM = 0.23 ng/mL). The median EC_{50} values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B) respectively. The EC_{50} values against HIV-2 isolates (n = 4) from 3 to 120 nM in PBMCs. Ribavirin (50,000 nM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

Antiviral Activity in Combination with Other Antiviral Agents

Neither dolutegravir, abacavir, nor lamivudine were antagonistic to all tested anti-HIV agents. See full prescribing information for ZIAGEN (abacavir), TIVICAY (dolutegravir), and EPIVIR (lamivudine).

Resistance in Cell Culture

Dolutegravir: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold.

Abacavir and Lamivudine: HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have been selected in cell culture with amino acid substitutions K65R, L74V, Y115F, and M184V/I in HIV-1 RT. M184V or I substitutions resulted in high-level resistance to lamivudine and approximately 2-fold decrease in susceptibility to abacavir. Substitutions K65R, L74V, or Y115F with M184V or I conferred a 7- to 8-fold reduction in

abacavir susceptibility, and combinations of three substitutions were required to confer more than an 8-fold reduction in susceptibility.

Resistance in Clinical Subjects

No subjects in the treatment arm receiving dolutegravir + EPZICOM in SINGLE (treatment-naive trial) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 11 with HIV-1 RNA >400 copies/mL at failure or last visit and having resistance data). Two virologic failure subjects in SINGLE had treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1 subject with 275 copies/mL HIV-1 RNA had a treatment-emergent Q157Q/P integrase substitution detected at Week 24. None of these subjects had a corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to abacavir and lamivudine, components of TRIUMEQ and TRIUMEQ PD, was observed in the arm receiving dolutegravir + EPZICOM in the SINGLE trial through Week 144.

Cross-Resistance

Dolutegravir: Cross-resistance has been observed among INSTIs. The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a >2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a >2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

Abacavir and Lamivudine: Cross-resistance has been observed among NRTIs. The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with a K65R substitution with or without an M184V/I substitution, viruses with L74V plus the M184V/I substitution, and viruses with thymidine analog mutation (TAM) substitutions (M41L, D67N, K70R, L210W, T215Y/F, K219 E/R/H/Q/N) plus M184V. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Dolutegravir: Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg/kg, and rats were administered doses of up to 50 mg/kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures

approximately 26-fold higher than those in humans at the recommended dose of 50 mg once daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 17-fold and 30-fold higher in males and females, respectively, than those in humans at the recommended dose of 50 mg once daily.

Abacavir: Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 7 to 28 times the human exposure at the recommended dose of 600 mg.

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 12 times (mice) and 57 times (rats) the human exposures at the recommended dose of 300 mg.

Mutagenicity

Dolutegravir: Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the in vivo rodent micronucleus assay.

Abacavir: Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Lamivudine: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Impairment of Fertility

Dolutegravir, abacavir, or lamivudine did not affect male or female fertility in rats at doses associated with exposures approximately 44, 9, or 112 times (respectively) higher than the exposures in humans at the doses of 50 mg, 600 mg, and 300 mg (respectively).

13.2 Animal Toxicology and/or Pharmacology

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 21 times the expected systemic exposure in humans at a dose of 600 mg. The clinical relevance of this finding has not been determined.

14 CLINICAL STUDIES

14.1 Adult Subjects

The efficacy of TRIUMEQ is supported by data from a randomized, controlled trial (double-blind through 96 weeks and open-label phase from 96 to 144 weeks) in antiretroviral treatment-naive subjects, SINGLE (ING114467, NCT01263015) and other trials in treatment-naive subjects. See full prescribing information for TIVICAY. The efficacy of dolutegravir, in combination with at least two active background regimens in treatment-experienced, INSTI-naive subjects is supported by data from SAILING (ING111762, NCT01231516) (refer to the prescribing information for TIVICAY).

Treatment-Naive Subjects

In SINGLE, 833 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily with fixed-dose abacavir and lamivudine (EPZICOM) or fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate (ATRIPLA). At baseline, the median age of subjects was 35 years, 16% female, 32% non-white, 7% had hepatitis C co-infection (hepatitis B virus co-infection was excluded), 4% were CDC Class C (AIDS), 32% had HIV-1 RNA >100,000 copies/mL, and 53% had CD4+ cell count <350 cells/mm^3; these characteristics were similar between treatment groups.

Week 144 (open-label-phase analysis which followed the Week 96 double-blind phase) outcomes for SINGLE are provided in Table 11.

Table 11. Virologic Outcomes of Randomized Treatment in SINGLE at 144 Weeks (Snapshot Algorithm)

	TIVICAY + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)
HIV-1 RNA <50 copies/mL	71%	63%
Treatment difference[a]	8.3% (95% CI: 2.0%, 14.6%)[d]	
Virologic nonresponse	10%	7%
Data in window not <50 copies/mL	4%	<1%
Discontinued for lack of efficacy	3%	3%
Discontinued for other reasons while not suppressed	3%	4%
No virologic data	18%	30%
Reasons		
Discontinued study/study drug due to adverse event or death[b]	4%	14%
Discontinued study/study drug for other reasons[c]	12%	13%
Missing data during window but on study	2%	3%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤100,000	73%	64%
≥100,000	69%	61%
Gender		
Male	72%	66%
Female	69%	48%
Race		
White	72%	71%
African American/African Heritage/Other	71%	47%

[a] Adjusted for pre-specified stratification factors.

[b] Includes subjects who discontinued due to an adverse event or death at any time point if this resulted in no virologic data on treatment during the analysis window.

[c] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

[d] The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving TIVICAY and 81% in the ATRIPLA group, with a treatment difference of 7.4% and 95% CI of (2.5%, 12.3%).

Treatment differences were maintained across baseline characteristics including baseline viral load, CD4+ cell count, age, gender, and race. The adjusted mean changes in CD4+ cell counts from baseline were 378 cells per mm^3 in the group receiving TIVICAY + EPZICOM and 332 cells per mm^3 for the ATRIPLA group at 144 weeks. The adjusted difference between treatment arms and 95% CI was 46.9 cells per mm^3 (15.6 cells per mm^3, 78.2 cells per mm^3)

(adjusted for pre-specified stratification factors: baseline HIV-1 RNA, and baseline CD4+ cell count).

Treatment-Experienced

In SAILING, there were 715 subjects included in the efficacy and safety analyses (see full prescribing information for TIVICAY). At Week 48, 71% of subjects randomized to TIVICAY plus background regimen versus 64% of subjects randomized to raltegravir plus background regimen had HIV-1 RNA <50 copies/mL (treatment difference and 95% CI: 7.4% [0.7%, 14.2%]).

14.2 Pediatric Subjects

The efficacy of the individual components of TRIUMEQ and 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).

16 HOW SUPPLIED/STORAGE AND HANDLING

TRIUMEQ tablets

TRIUMEQ tablets are purple, oval, film-coated, biconvex tablets debossed with “572 Tri” on one side and contain 600 mg of abacavir (as abacavir sulfate), 50 mg of dolutegravir (as dolutegravir sodium), and 300 mg lamivudine.

Bottle of 30 tablets with desiccant and child-resistant closure. NDC 49702-231-13.

Store and dispense in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F to 86°F). [See USP Controlled Room Temperature].

TRIUMEQ PD tablets for oral suspension

TRIUMEQ PD tablets for oral suspension, are yellow, capsule-shaped, strawberry cream flavored, film-coated, biconvex tablets debossed with "SV WTU" on one side and contain 60 mg of abacavir (as abacavir sulfate), 5 mg of dolutegravir (as dolutegravir sodium), and 30 mg lamivudine.

Bottle of 90 tablets (NDC 49702-272-59) with desiccant and child-resistant closure. Each bottle is packaged as a kit (NDC 49702-258-37) with one 40-mL dosing cup.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Store and dispense in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Drug Interactions

TRIUMEQ or TRIUMEQ PD may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort *[see Contraindications (4), Warnings and Precautions (5.6), Drug Interactions (7)]*.

Hypersensitivity Reaction

Inform patients:

- that a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of TRIUMEQ or TRIUMEQ PD, and instruct the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about TRIUMEQ or TRIUMEQ PD. The complete text of the Medication Guide is reprinted at the end of this document.
- to carry the Warning Card with them.
- how to identify a hypersensitivity reaction *[see Warnings and Precautions (5.1), Medication Guide]*.
- that if they develop symptoms consistent with a hypersensitivity reaction they should call their healthcare provider right away to determine if they should stop taking TRIUMEQ or TRIUMEQ PD.

- that a hypersensitivity reaction can worsen and lead to hospitalization or death if TRIUMEQ or TRIUMEQ PD is not immediately discontinued.
- to not restart TRIUMEQ or TRIUMEQ PD or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.
- that if they have a hypersensitivity reaction, they should dispose of any unused TRIUMEQ or TRIUMEQ PD to avoid restarting abacavir.
- that a hypersensitivity reaction is usually reversible if it is detected promptly and TRIUMEQ or TRIUMEQ PD is stopped right away.
- that if they have interrupted TRIUMEQ or TRIUMEQ PD for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.
- to not restart TRIUMEQ or TRIUMEQ PD or any other abacavir-containing product without medical consultation and only if medical care can be readily accessed by the patient or others.
- to not restart TRIUMEQ or TRIUMEQ PD or any other dolutegravir-containing product following a hypersensitivity reaction to TRIUMEQ or TRIUMEQ PD.

Hepatotoxicity

Inform patients that hepatotoxicity has been reported with dolutegravir, a component of TRIUMEQ and TRIUMEQ PD *[see Warnings and Precautions (5.3), Adverse Reactions (6.1)]*. Inform patients that monitoring for hepatotoxicity during therapy with TRIUMEQ or TRIUMEQ PD is recommended.

Severe Acute Exacerbations of Hepatitis in Patients with HBV Co-infection

Advise all patients with HIV-1 to be tested for the presence of HBV prior to or when initiating TRIUMEQ or TRIUMEQ PD. Advise patients co-infected with HIV-1 and HBV that worsening of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Advise patients to discuss any changes in regimen with their physician *[see Warnings and Precautions (5.2)]*.

Lactic Acidosis/Hepatomegaly

Inform patients that some HIV medicines, including TRIUMEQ and TRIUMEQ PD, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) *[see Boxed Warning, Warnings and Precautions (5.5)]*.

Embryo-Fetal Toxicity

Advise adolescents and adults of childbearing potential, including those actively trying to become pregnant, to discuss the risks and benefits of TRIUMEQ with their healthcare provider

to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy. If pregnancy is confirmed in the first trimester, advise patients to contact their healthcare provider *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)]*.

Adolescents and adults of childbearing potential taking TRIUMEQ should be counseled on the consistent use of effective contraception *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs and symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when TRIUMEQ or TRIUMEQ PD is started *[see Warnings and Precautions (5.7)]*.

TRIUMEQ Tablets and TRIUMEQ PD Tablets for Oral Suspension Are Not Bioequivalent

Advise patients that TRIUMEQ and TRIUMEQ PD are not bioequivalent and are not interchangeable on a milligram-per-milligram basis. Advise patients or their care provider that patients switching from the tablets for oral suspension to the tablets must adjust the dose *[see Dosage and Administration (2.3) and Warnings and Precautions (5.8)]*.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to TRIUMEQ during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct mothers with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *[see Use in Specific Populations (8.2)]*.

Administration Instructions

To avoid a dosing error from using the wrong formulation of TRIUMEQ, strongly advise patients and caregivers to visually inspect the tablets to verify the correct formulation each time the prescription is filled *[see Dosage and Administration (2), Warnings and Precautions (5.8), How Supplied/Storage and Handling (16)]*.

Inform patients and caregivers that TRIUMEQ PD tablets for oral suspension should be dispersed in drinking water and should not be chewed, cut or crushed *[see Dosage and Administration (2.5)]*.

Instruct patients and caregivers that if a dose of TRIUMEQ or TRIUMEQ PD is missed, to take it as soon as they remember. Advise patients and caregivers not to double the next dose or take more than the prescribed dose *[see Dosage and Administration (2)]*.

Availability of Medication Guide

Instruct patients and caregivers to read the Medication Guide before starting TRIUMEQ or TRIUMEQ PD and to re-read it each time the prescription is renewed. Instruct patients to inform their physician or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Storage

Instruct patients and caregivers to store TRIUMEQ and TRIUMEQ PD tablets for oral suspension in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

Manufactured for:

ViiV Healthcare
Durham, NC 27701

by:

GlaxoSmithKline
Durham, NC 27701

TRM:xxPI

MEDICATION GUIDE

TRIUMEQ (TRI-u-meck) **(abacavir, dolutegravir, and lamivudine)** **tablets**	**TRIUMEQ PD (TRI-u-meck Pe De)** **(abacavir, dolutegravir, and lamivudine)** **tablets for oral suspension**

What is the most important information I should know about TRIUMEQ and TRIUMEQ PD?

TRIUMEQ and TRIUMEQ PD can cause serious side effects, including:

- **Serious allergic reactions (hypersensitivity reaction)** that can cause death have happened with TRIUMEQ or TRIUMEQ PD and other abacavir-containing products. Your risk of this allergic reaction to abacavir is much higher if you have a gene variation called HLA-B*5701. Your healthcare provider can determine with a blood test if you have this gene variation.

  If you get a symptom from 2 or more of the following groups while taking TRIUMEQ or TRIUMEQ PD, call your healthcare provider right away to find out if you should stop taking TRIUMEQ or TRIUMEQ PD.

	Symptom(s)
Group 1	**Fever**
Group 2	**Rash**
Group 3	**Nausea, vomiting, diarrhea, abdominal (stomach area) pain**
Group 4	**Generally ill feeling, extreme tiredness, or achiness**
Group 5	**Shortness of breath, cough, sore throat**

  A list of these symptoms is on the Warning Card your pharmacist gives you. **Carry this Warning Card with you at all times.**

  If you stop TRIUMEQ or TRIUMEQ PD because of an allergic reaction, never take TRIUMEQ, TRIUMEQ PD (abacavir, dolutegravir and lamivudine), or any other medicine that contains abacavir or dolutegravir (DOVATO, EPZICOM, JULUCA, TIVICAY, TIVICAY PD, TRIZIVIR, or ZIAGEN) again.

  - If you have an allergic reaction, dispose of any unused TRIUMEQ or TRIUMEQ PD. Ask your pharmacist how to properly dispose of medicines.
  - If you take TRIUMEQ, TRIUMEQ PD or any other abacavir-containing medicine again after you have had an allergic reaction, **within hours** you may get **life-threatening symptoms** that may include **very low blood pressure** or **death.**
  - If you stop TRIUMEQ or TRIUMEQ PD for any other reason, even for a few days, and you are not allergic to TRIUMEQ or TRIUMEQ PD, talk with your healthcare provider before taking it again. Taking TRIUMEQ or TRIUMEQ PD again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before.

If your healthcare provider tells you that you can take TRIUMEQ or TRIUMEQ PD again, start taking it when you are around medical help or people who can call a healthcare provider if you need one.

- **Worsening of Hepatitis B virus (HBV) infection.** Your healthcare provider will test you for HBV infection before you start treatment with TRIUMEQ or TRIUMEQ PD. If you have HBV infection and take TRIUMEQ or TRIUMEQ PD, your HBV may get worse (flare-up) if you stop taking TRIUMEQ or TRIUMEQ PD. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.
  - Do not run out of TRIUMEQ or TRIUMEQ PD. Refill your prescription or talk to your healthcare provider before your TRIUMEQ or TRIUMEQ PD is all gone.
  - Do not stop TRIUMEQ or TRIUMEQ PD without first talking to your healthcare provider.
  - If you stop taking TRIUMEQ or TRIUMEQ PD, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver function and monitor your HBV infection. It may be necessary to give you a medicine to treat hepatitis B. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking TRIUMEQ or TRIUMEQ PD.
- **Resistant HBV.** If you have human immunodeficiency virus-1 (HIV-1) and HBV, the HBV can change (mutate) during your treatment with TRIUMEQ or TRIUMEQ PD and become harder to treat (resistant). Your healthcare provider may give you other medicines to treat HBV infection if you have HIV-1 and HBV infections and take TRIUMEQ or TRIUMEQ PD.
- **For more information about side effects, see "What are the possible side effects of TRIUMEQ or TRIUMEQ PD?"**

What is TRIUMEQ and TRIUMEQ PD?

TRIUMEQ and TRIUMEQ PD are prescription medicines used to treat HIV-1 infection in adults and children who weigh at least 22 pounds (10 kg).

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

TRIUMEQ and TRIUMEQ PD contain the prescription medicines abacavir, dolutegravir, and lamivudine.

- TRIUMEQ or TRIUMEQ PD should not be used by itself in people who have resistance to certain types of medicines.

It is not known if TRIUMEQ PD is safe and effective in children who weigh less than 22 pounds (10 kg).

Do not take TRIUMEQ or TRIUMEQ PD if you:

- have a certain type of gene variation called the HLA-B*5701 allele. Your healthcare provider will test you for this before prescribing treatment with TRIUMEQ or TRIUMEQ PD.
- are allergic to abacavir, dolutegravir, lamivudine, or any of the ingredients in TRIUMEQ or TRIUMEQ PD. See the end of this Medication Guide for a complete list of ingredients in TRIUMEQ and TRIUMEQ PD.

- take dofetilide. Taking TRIUMEQ or TRIUMEQ PD and dofetilide can cause side effects that may be serious or life-threatening.
- have certain liver problems.

Before you take TRIUMEQ or TRIUMEQ PD, tell your healthcare provider about all of your medical conditions, including if you:

- have been tested and know whether or not you have a particular gene variation called HLA-B*5701.
- have or have had liver problems, including hepatitis B or C virus infection.
- have kidney problems.
- have heart problems, smoke, or have diseases that increase your risk of heart disease such as high blood pressure, high cholesterol, or diabetes.
- drink alcohol or take medicines that contain alcohol.
- are pregnant or plan to become pregnant. One of the medicines in TRIUMEQ and TRIUMEQ PD called dolutegravir may harm your unborn baby.
    - Your healthcare provider may prescribe a different medicine than TRIUMEQ if you are planning to become pregnant or if pregnancy is confirmed during the first 12 weeks of pregnancy.
    - If you can become pregnant, your healthcare provider may perform a pregnancy test before you start treatment with TRIUMEQ.
    - If you can become pregnant, you and your healthcare provider should talk about the use of effective birth control (contraception) during treatment with TRIUMEQ.
    - Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with TRIUMEQ.

Pregnancy Registry. There is a pregnancy registry for individuals who take TRIUMEQ and TRIUMEQ PD during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take TRIUMEQ.**
    - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
    - TRIUMEQ and TRIUMEQ PD pass to your baby in your breastmilk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines interact with TRIUMEQ or TRIUMEQ PD. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine**.**

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with TRIUMEQ or TRIUMEQ PD.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take TRIUMEQ or TRIUMEQ PD with other medicines.

How should I take TRIUMEQ or TRIUMEQ PD?

Read the Instructions for Use at the end of this Medication Guide for detailed instructions on how to prepare a dose of TRIUMEQ PD tablets for oral suspension.

- **Take TRIUMEQ or TRIUMEQ PD exactly as your healthcare provider tells you to take it.**
- Do not change your dose, switch medicines or stop taking TRIUMEQ or TRIUMEQ PD without talking with your healthcare provider first.
- **TRIUMEQ tablets are not the same as TRIUMEQ PD tablets for oral suspension and cannot be substituted for each other. Check to make sure you receive the correct dosage form each time you or your child's prescription is filled to avoid using the wrong medicine.**
- Your child's healthcare provider will prescribe TRIUMEQ or TRIUMEQ PD based on your child's weight.
- TRIUMEQ PD tablets for oral suspension should be dispersed in drinking water.
- Do **not** chew, cut, or crush TRIUMEQ tablets or TRIUMEQ PD tablets for oral suspension.
- TRIUMEQ or TRIUMEQ PD may be taken with or without food.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, TRIUMEQ or TRIUMEQ PD should be taken at least 2 hours before or 6 hours after you take these medicines.
- If you need to take iron or calcium supplements by mouth during treatment with TRIUMEQ or TRIUMEQ PD:
  - If you take TRIUMEQ or TRIUMEQ PD with food, you may take these supplements at the same time that you take TRIUMEQ or TRIUMEQ PD.
  - If you do not take TRIUMEQ or TRIUMEQ PD with food, take TRIUMEQ or TRIUMEQ PD at least 2 hours before or 6 hours after you take these supplements.
- If you miss a dose of TRIUMEQ or TRIUMEQ PD, take it as soon as you remember. Do not take 2 doses at the same time or take more than your healthcare provider tells you to take.
- Stay under the care of a healthcare provider during treatment with TRIUMEQ or TRIUMEQ PD.
- Do not run out of TRIUMEQ or TRIUMEQ PD. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too much TRIUMEQ or TRIUMEQ PD, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of TRIUMEQ or TRIUMEQ PD?

TRIUMEQ or TRIUMEQ PD can cause serious side effects, including:

- **See "What is the most important information I should know about TRIUMEQ and TRIUMEQ PD?"**
- **Liver problems.** People with a history of hepatitis B or C virus may have an increased risk of developing new or worsening changes in certain liver function tests during treatment with TRIUMEQ

- The bottle of TRIUMEQ and TRIUMEQ PD contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not remove the desiccant packet from the bottle.

Keep TRIUMEQ, TRIUMEQ PD, and all medicines out of the reach of children.

General information about the safe and effective use of TRIUMEQ or TRIUMEQ PD.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TRIUMEQ or TRIUMEQ PD for a condition for which it was not prescribed. Do not give TRIUMEQ or TRIUMEQ PD to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TRIUMEQ or TRIUMEQ PD that is written for health professionals.

What are the ingredients in TRIUMEQ and TRIUMEQ PD?

Active ingredients: abacavir, dolutegravir, and lamivudine

Inactive ingredients:

TRIUMEQ tablets: D-mannitol, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. Tablet film-coating contains: iron oxide black, iron oxide red, macrogol/PEG, polyvinyl alcohol–part hydrolyzed, talc, and titanium oxide.

TRIUMEQ PD tablets for oral suspension: acesulfame potassium, crospovidone, mannitol, microcrystalline cellulose, povidone K29/32, silicified microcrystalline cellulose, sodium starch glycolate, sodium stearyl fumarate, strawberry cream flavor, and sucralose.

Tablet film-coating contains: ferric oxide yellow, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

Manufactured for:

ViiV Healthcare

Durham, NC 27701

by:

GlaxoSmithKline

Durham, NC 27701

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For more information go to www.TRIUMEQ.com or call 1-877-844-8872.

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