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

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

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

12.4 Microbiology

Mechanism of Action

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 HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

Antiviral Activity in Cell Culture

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0.52 nM in a viral integrase 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 (3 in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC_{50} values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC_{50} values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Antiviral Activity in Combination with Other Antiviral Agents

The antiviral activity of dolutegravir was not antagonistic when combined with the INSTI, raltegravir; non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz or nevirapine; the NRTIs, abacavir or stavudine; the protease inhibitors (PIs), amprenavir or lopinavir; the CCR5 co-receptor antagonist, maraviroc; or the fusion inhibitor, enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor, adefovir, or inhibited by the antiviral, ribavirin.

Resistance

Cell Culture: 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. Passage of mutant viruses containing the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutions included T97A, E138K, G140S, and M154I. Passage of mutant viruses containing both G140S and Q148H selected for L74M, E92Q, and N155H.

Treatment-Naïve Subjects: No subject who received dolutegravir 50-mg once-daily in the treatment-naïve trials SPRING-2 (96 weeks) and SINGLE (144 weeks) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 12 with HIV-1 RNA greater than 400 copies per 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 per 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 the background regimen was observed in the dolutegravir arm in either the SPRING-2 or SINGLE trials. No treatment-emergent primary resistance substitutions were observed in either treatment group in the FLAMINGO trial through Week 96.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In the dolutegravir arm of the SAILING trial for treatment-experienced and INSTI-naïve subjects (n = 354), treatment-emergent integrase substitutions were observed in 6 of 28 (21%) subjects who had virologic failure and resistance data. In 5 of the 6 subjects' isolates emergent INSTI substitutions included L74L/M/I, Q95Q/L, V151V/I (n = 1 each), and R263K (n = 2). The change in dolutegravir phenotypic susceptibility for these 5 subject isolates was less than 2-fold. One subject isolate had pre-existing raltegravir resistance substitutions E138A, G140S, and Q148H at baseline and had additional emergent INSTI-resistance substitutions T97A and E138A/T with a corresponding 148-fold reduction in dolutegravir susceptibility at failure. In the comparator raltegravir arm, 21 of 49 (43%) subjects with post-baseline resistance data had evidence of emergent INSTI-resistance substitutions (L74M, E92Q, T97A, E138Q, G140S/A, Y143R/C, Q148H/R, V151I, N155H, E157Q, and G163K/R) and raltegravir phenotypic resistance.

Virologically Suppressed Subjects: SWORD-1 and SWORD-2 are identical trials in virologically suppressed subjects receiving 2 NRTIs plus either an INSTI, an NNRTI, or a PI, that switched to dolutegravir plus rilpivirine (n = 513) or remained on their current antiviral regimen (n = 511). In the pooled SWORD-1 and SWORD-2 trials, 12 subjects (7 in SWORD-1 and 5 in SWORD-2) had confirmed virologic failure (HIV-1 RNA greater than 200 copies/mL) while receiving dolutegravir plus rilpivirine at any time through Week 148. Ten of the confirmed virologic failures had post-baseline resistance data, with 6 isolates showing evidence of rilpivirine resistance, and 2 with evidence of dolutegravir resistance substitutions. Six isolates showed genotypic and/or phenotypic resistance to rilpivirine with emergent NNRTI-resistance substitutions E138E/A (rilpivirine 1.6-fold change), M230M/L (rilpivirine 2-fold change), L100L/I, K101Q, and E138A (rilpivirine 4.1-fold change), K101K/E (rilpivirine 1.2-fold change), K101K/E, M230M/L (rilpivirine 2-fold change), and L100L/V/M, M230M/L (rilpivirine 31-fold change). In addition, 1 virologic failure subject had NNRTI-resistance substitutions K103N and V179I at Week 88 with rilpivirine phenotypic fold change of 5.2 but had no baseline sample.

One virologic failure isolate had emergent INSTI-resistance substitution V151V/I present post-baseline with baseline INSTI-resistance substitutions N155N/H and G163G/R (by exploratory HIV proviral DNA archive sequencing); no integrase phenotypic data were available for this isolate at virologic failure. One other subject had the dolutegravir resistance substitution G193E at baseline and virologic failure, but no detectable phenotypic resistance (fold change = 1.02) at Week 24.

No resistance-associated substitutions were observed for the 2 subjects meeting confirmed virologic failure in the comparative current antiretroviral regimen arms at Week 48.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: VIKING-3 examined the efficacy of dolutegravir 50 mg twice daily plus optimized background therapy in subjects with prior or current virologic failure on an INSTI- (elvitegravir or raltegravir) containing regimen. Use of TIVICAY in INSTI-experienced patients should be guided by the

number and type of baseline INSTI substitutions. The efficacy of TIVICAY 50 mg twice daily is reduced in patients with an INSTI-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions, including T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R.

Response by Baseline Genotype

Of the 183 subjects with baseline data, 30% harbored virus with a substitution at Q148, and 33% had no primary INSTI-resistance substitutions (T66A/I/K, E92Q/V, Y143R/C/H, Q148H/R/K, and N155H) at baseline, but had historical genotypic evidence of INSTI-resistance substitutions, phenotypic evidence of elvitegravir or raltegravir resistance, or genotypic evidence of INSTI-resistance substitutions at screening.

Response rates by baseline genotype were analyzed in an "as-treated" analysis at Week 48 (n = 175) (Table 13). The response rate at Week 48 to dolutegravir-containing regimens was 47% (24 of 51) when Q148 substitutions were present at baseline; Q148 was always present with additional INSTI-resistance substitutions (Table 13). In addition, a diminished virologic response of 40% (6 of 15) was observed when the substitution E157Q or K was present at baseline with other INSTI-resistance substitutions but without a Q148H or R substitution.

Table 13. Response by Baseline Integrase Genotype in Subjects with Prior Experience to an Integrase Strand Transfer Inhibitor in VIKING-3

Baseline Genotype	Week 48 (<50 copies/mL) n = 175
Overall Response	66% (116/175)
No Q148 substitution[a]	74% (92/124)
Q148H/R + G140S/A/C without additional INSTI-resistance substitution[b]	61% (17/28)
Q148H/R + ≥2 INSTI-resistance substitutions[b,c]	29% (6/21)

INSTI = integrase strand transfer inhibitor.

[a] Includes INSTI-resistance substitutions Y143R/C/H and N155H.

[b] INSTI-resistance substitutions included T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R. Two additional subjects had baseline genotypes of Q148Q/R plus L74L/I/M (virologic failure) and Q148R plus E138K (responder).

[c] The most common pathway with Q148H/R + greater than or equal to 2 INSTI-resistance substitutions had Q148+G140+E138 substitutions (n = 16).

Response by Baseline Phenotype

Response rates by baseline phenotype were analyzed in an as-treated analysis using all subjects with available baseline phenotypes through Week 48 (n = 163) (Table 14). These baseline phenotypic groups are based on subjects enrolled in VIKING-3 and are not meant to represent

definitive clinical susceptibility cut points for dolutegravir. The data are provided to guide clinicians on the likelihood of virologic success based on pretreatment susceptibility to dolutegravir in INSTI-resistant patients.

Table 14. Response by Baseline Dolutegravir Phenotype (Fold-Change from Reference) in Subjects with Prior Experience to an Integrase Strand Transfer Inhibitor in VIKING-3

Baseline Dolutegravir Phenotype (Fold-Change from Reference)	Response at Week 48 (<50 copies/mL) Subset n = 163
Overall Response	64% (104/163)
<3-fold change	72% (83/116)
3- <10-fold change	53% (18/34)
≥10-fold change	23% (3/13)

Integrase Strand Transfer Inhibitor Treatment-Emergent Resistance

There were 50 subjects with virologic failure on the dolutegravir twice-daily regimen in VIKING-3 with HIV-1 RNA greater than 400 copies per mL at the failure timepoint, Week 48 or beyond, or the last timepoint on trial. Thirty-nine subjects with virologic failure had resistance data that were used in the Week 48 analysis. In the Week 48 resistance analysis 85% (33 of 39) of the subjects with virologic failure had treatment-emergent INSTI-resistance substitutions in their isolates. The most common treatment-emergent INSTI-resistance substitution was T97A. Other frequently emergent INSTI-resistance substitutions included L74M, I or V, E138K or A, G140S, Q148H, R or K, M154I, or N155H. Substitutions E92Q, Y143R or C/H, S147G, V151A, and E157E/Q each emerged in 1 to 3 subjects' isolates. At failure, the median dolutegravir fold-change from reference was 61-fold (range: 0.75 to 209) for isolates with emergent INSTI-resistance substitutions (n = 33).

Resistance to one or more background drugs in the dolutegravir twice-daily regimen also emerged in 49% (19 of 39) of subjects in the Week 48 resistance analysis.

In VIKING-4 (ING116529), 30 subjects with current virological failure on an INSTI-containing regimen and genotypic evidence of INSTI-resistance substitutions at screening were randomized to receive either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days and then all subjects received open-label dolutegravir plus optimized background regimen from Day 8. Virologic responses at Week 48 by baseline genotypic and phenotypic INSTI-resistance categories and the INSTI resistance-associated substitutions that emerged on dolutegravir treatment in VIKING-4 were consistent with those seen in VIKING-3.

Cross-Resistance

Site-Directed Integrase Strand Transfer Inhibitor-Resistant Mutant HIV-1 and HIV-2 Strains: The susceptibility of dolutegravir was tested against 60 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) and 6 INSTI-

resistant site-directed mutant HIV-2 viruses. The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 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 greater than 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.

Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent antiviral activity against 2 NNRTI-resistant, 3 NRTI-resistant, and 2 PI-resistant HIV-1 mutant clones compared with the wild-type strain.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg per kg, and rats were administered doses of up to 50 mg per 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 14 times higher than those in humans at the maximum recommended dose. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 10 times and 15 times higher in males and females, respectively, than those in humans at the maximum recommended dose.

Mutagenesis

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

Impairment of Fertility

In a study conducted in rats, there were no effects on mating or fertility with dolutegravir up to 1,000 mg per kg per day. This dose is associated with an exposure that is approximately 24 times higher than the exposure in humans at the maximum recommended dose.

14 CLINICAL STUDIES

14.1 Description of Clinical Studies

The efficacy and safety of TIVICAY or TIVICAY PD were evaluated in the studies summarized in Table 15.

Table 15. Trials Conducted with TIVICAY or TIVICAY PD in HIV-1–Infected Subjects

Population	Trial	Trial Arms	Timepoint (Week)
Adults: Treatment-naïve	SPRING-2 (ING113086) (NCT01227824)	TIVICAY + 2 NRTIs (n = 403) Raltegravir + 2 NRTIs (n = 405)	96
	SINGLE (ING114467) (NCT01263015)	TIVICAY + EPZICOM (n = 414) ATRIPLA (n = 419)	144
	FLAMINGO (ING114915) (NCT01449929)	TIVICAY + NRTI BR (n = 243) Darunavir/ritonavir + NRTI BR (n = 242)	96
Treatment-experienced, INSTI-naïve	SAILING (ING111762) (NCT01231516)	TIVICAY + BR (n = 354) Raltegravir + BR (n = 361)	48
INSTI-experienced	VIKING-3 (ING112574) (NCT01328041)	TIVICAY + OBT (n = 183)	48
Virologically suppressed	SWORD-1 (NCT02429791) SWORD-2 (NCT02422797)	Pooled presentation TIVICAY + Rilpivirine (n = 513) CAR (n = 511)	48
Pediatrics: 4 weeks and older and weighing at least 3 kg without INSTI resistance	IMPAACT P1093 (NCT01302847)	TIVICAY or TIVICAY PD + BR (n = 75)	24

NRTI = nucleoside reverse transcriptase inhibitor; INSTI = integrase strand transfer inhibitor; BR = Background regimen; CAR = Current antiretroviral regimen; OBT = Optimized background therapy.

14.2 Adult Subjects

Treatment-Naïve Subjects

In SPRING-2, 822 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual NRTI treatment (either abacavir sulfate and lamivudine [EPZICOM] or emtricitabine/tenofovir [TRUVADA]). There were 808 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 36 years, 13% female, 15% non-white, 11% had hepatitis B and/or C virus co-infection, 2% were CDC Class C (AIDS), 28% had HIV-1 RNA greater than 100,000 copies per mL, 48% had CD4+ cell count less than 350 cells per mm^3, and 39% received EPZICOM; these characteristics were similar between treatment groups.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily with fixed-dose abacavir sulfate and lamivudine (EPZICOM) or fixed-dose

efavirenz/emtricitabine/tenofovir (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 greater than 100,000 copies per mL, and 53% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment groups.

Outcomes for SPRING-2 (Week 96 analysis) and SINGLE (Week 144 open-label phase analysis which followed the Week 96 double-blind phase) are provided in Table 16. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 16. Virologic Outcomes of Randomized Treatment in SPRING-2 at Week 96 and SINGLE at Week 144 (Snapshot Algorithm)

	SPRING-2 Week 96		**SINGLE Week 144**	
	TIVICAY 50 mg Once Daily + 2 NRTIs (n = 403)	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**TIVICAY 50 mg + EPZICOM Once Daily (n = 414)**	**ATRIPLA Once Daily (n = 419)**
HIV-1 RNA <50 copies/mL	82%	78%	71%	63%
Treatment difference[a]	4.9% (95% CI: -0.6%, 10.3%)[b]		8.3% (95% CI: 2.0%, 14.6%)[c]	
Virologic nonresponse	5%	10%	10%	7%
Data in window not <50 copies/mL	1%	3%	4%	<1%
Discontinued for lack of efficacy	2%	3%	3%	3%
Discontinued for other reasons while not suppressed	<1%	3%	3%	4%
Change in ART regimen	<1%	<1%	0	0
No virologic data	12%	12%	18%	30%
Reasons				
Discontinued study/study drug due to adverse event or death[d]	2%	2%	4%	14%
Discontinued study/study drug for other reasons[e]	8%	9%	12%	13%
Missing data during window but on study	2%	<1%	2%	3%

Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category				
Plasma viral load (copies/mL)				
≤100,000	84%	83%	73%	64%
>100,000	79%	63%	69%	61%
Gender				
Male	84%	79%	72%	66%
Female	70%	68%	69%	48%
Race				
White	83%	78%	72%	71%
African-American/African Heritage/Other	77%	75%	71%	47%

NRTI = nucleoside reverse transcriptase inhibitor

[a] Adjusted for pre-specified stratification factors.

[b] The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving TIVICAY and 86% in the raltegravir group, with a treatment difference of 2.6% and 95% CI of (-1.9%, 7.2%).

[c] 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%).

[d] 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.

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

SPRING-2: Virologic outcomes were also comparable across baseline characteristics including CD4+ cell count, age, and use of EPZICOM or TRUVADA as NRTI background regimen. The median change in CD4+ cell counts from baseline was 276 cells per mm^3 in the group receiving TIVICAY and 264 cells per mm^3 for the raltegravir group at 96 weeks.

There was no treatment-emergent resistance to dolutegravir or to the NRTI background.

SINGLE: 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).

There was no treatment-emergent resistance to dolutegravir, abacavir, or lamivudine.

FLAMINGO: In FLAMINGO, 485 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily (n = 243) or darunavir + ritonavir 800 mg/100 mg once daily (n = 242), both in combination with investigator-selected NRTI background regimen (either fixed-dose abacavir and lamivudine [EPZICOM] or fixed-dose emtricitabine/tenofovir disoproxil fumarate [TRUVADA]). There were 484 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 34 years, 15% female, 28% non-white, 10% had hepatitis B and/or C virus co-infection, 3% were CDC Class C (AIDS), 25% had HIV-1 RNA greater than 100,000 copies per mL, and 35% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment groups. Overall response rates by Snapshot algorithm through Week 96 were 80% for TIVICAY and 68% for darunavir/ritonavir. The proportion of subjects who were non-responders (HIV-1 RNA greater than or equal to 50 copies per mL) at Week 96 was 8% and 12% in the arms receiving TIVICAY and darunavir + ritonavir, respectively; no virologic data were available for 12% and 21% for subjects treated with TIVICAY and darunavir + ritonavir, respectively. The adjusted overall response rate difference in proportion and 95% CI was 12.4% (4.7%, 20.2%). No treatment-emergent primary resistance substitutions were observed in either treatment group.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects

In the international, multicenter, double-blind trial (SAILING), 719 HIV-1–infected, antiretroviral treatment-experienced adults were randomized and received either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least 1 fully active agent. There were 715 subjects included in the efficacy and safety analyses. At baseline, the median age was 43 years, 32% were female, 50% non-white, 16% had hepatitis B and/or C virus co-infection, 46% were CDC Class C (AIDS), 20% had HIV-1 RNA greater than 100,000 copies per mL, and 72% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment groups. All subjects had at least 2-class antiretroviral treatment resistance, and 49% of subjects had at least 3-class antiretroviral treatment resistance at baseline. Week 48 outcomes for SAILING are shown in Table 17.

Table 17. Virologic Outcomes of Randomized Treatment in SAILING at 48 Weeks (Snapshot Algorithm)

	TIVICAY 50 mg Once Daily + BR[a] (n = 354)	Raltegravir 400 mg Twice Daily + BR[a] (n = 361)
HIV-1 RNA <50 copies/mL	71%	64%
Adjusted[b] treatment difference	7.4% (95% CI: 0.7%, 14.2%)	
Virologic nonresponse	20%	28%
No virologic data	9%	9%
Reasons		
Discontinued study/study drug due to adverse event or death	3%	4%
Discontinued study/study drug for other reasons[c]	5%	4%
Missing data during window but on study	2%	1%
Proportion (%) with HIV-1 RNA <50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤50,000 copies/mL	75%	71%
>50,000 copies/mL	62%	47%
Background regimen		
No darunavir use	67%	60%
Darunavir use with primary PI substitutions	85%	67%
Darunavir use without primary PI substitutions	69%	70%
Gender		
Male	70%	66%
Female	74%	60%
Race		
White	75%	71%
African-American/African Heritage/Other	67%	57%

[a] BR = Background regimen. Background regimen was restricted to less than or equal to 2 antiretroviral treatments with at least 1 fully active agent.

[b] Adjusted for pre-specified stratification factors.

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

Treatment differences were maintained across the baseline characteristics including CD4+ cell count and age.

The mean changes in CD4+ cell counts from baseline were 162 cells per mm^3 in the group receiving TIVICAY and 153 cells per mm^3 in the raltegravir group.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects

VIKING-3 examined the effect of TIVICAY 50 mg twice daily over 7 days of functional monotherapy, followed by OBT with continued treatment of TIVICAY 50 mg twice daily.

In the multicenter, open-label, single-arm VIKING-3 trial, 183 HIV-1–infected, antiretroviral treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received TIVICAY 50 mg twice daily with the current failing background regimen for 7 days, then received TIVICAY with OBT from Day 8. A total of 183 subjects enrolled: 133 subjects with INSTI resistance at screening and 50 subjects with only historical evidence of resistance (and not at screening). At baseline, median age of subjects was 48 years; 23% were female, 29% non-white, and 20% had hepatitis B and/or C virus co-infection. Median baseline CD4+ cell count was 140 cells per mm^3, median duration of prior antiretroviral treatment was 13 years, and 56% were CDC Class C. Subjects showed multiple-class antiretroviral treatment resistance at baseline: 79% had greater than or equal to 2 NRTI, 75% greater than or equal to 1 NNRTI, and 71% greater than or equal to 2 PI major substitutions; 62% had non-R5 virus.

Mean reduction from baseline in HIV-1 RNA at Day 8 (primary endpoint) was 1.4 $\log_{10}$ (95% CI: 1.3 $\log_{10}$, 1.5 $\log_{10}$). Response at Week 48 was affected by baseline INSTI substitutions *[see Microbiology (12.4)]*.

After the functional monotherapy phase, subjects had the opportunity to re-optimize their background regimen when possible. Week 48 virologic outcomes for VIKING-3 are shown in Table 18.

Table 18. Virologic Outcomes of Treatment of VIKING-3 at 48 Weeks (Snapshot Algorithm)

	TIVICAY 50 mg Twice Daily + OBT (n = 183)
HIV-1 RNA <50 copies/mL	63%
Virologic nonresponse	32%
No virologic data Reasons Discontinued study/study drug due to adverse event or death	3%
Proportion (%) with HIV-1 RNA <50 copies/mL by Baseline Category	
Gender	
Male	63%
Female	64%
Race	
White	63%
African-American/African Heritage/Other	64%

OBT = Optimized Background Therapy.

Subjects harboring virus with Q148 and with additional Q148-associated secondary substitutions also had a reduced response at Week 48 in a stepwise fashion *[see Microbiology (12.4)]*.

The median change in CD4+ cell count from baseline was 80 cells per mm^3 at Week 48.

Virologically Suppressed Subjects

SWORD-1 and SWORD-2 are identical 148-week, Phase 3, randomized, multicenter, parallel-group, non-inferiority trials. A total of 1,024 adult HIV-1–infected subjects who were on a stable suppressive antiretroviral regimen (containing 2 NRTIs plus either an INSTI, an NNRTI, or a PI) for at least 6 months (HIV-1 RNA less than 50 copies per mL), with no history of treatment failure and no known substitutions associated with resistance to dolutegravir or rilpivirine received treatment in the trials. Subjects were randomized 1:1 to continue their current antiretroviral regimen (n°= 511) or be switched to TIVICAY 50 mg plus rilpivirine 25 mg administered once daily (n = 513). Subjects originally assigned to continue their current antiretroviral regimen and who remained virologically suppressed at Week 48 switched to TIVICAY plus rilpivirine at Week 52 (n = 477).

The primary efficacy endpoint for the SWORD trial was the proportion of subjects with plasma HIV-1 RNA less than 50 copies per mL at Week 48. The proportion of subjects with HIV-1 RNA less than 50 copies per mL at Week 48 was 95% for both treatment groups; treatment difference and 95% CI was -0.2% (-3.0%, 2.5%). The proportion of subjects with HIV-1 RNA greater than or equal to 50 copies per mL (virologic failure) at Week 48 was 0.6% and 1.2% for the dolutegravir plus rilpivirine treatment group and the current antiretroviral regimen treatment groups, respectively; treatment difference and 95% CI was -0.6% (-1.7%, 0.6%). At Week 148 in the pooled SWORD-1 and SWORD-2 trials, 84% of subjects who received TIVICAY plus rilpivirine from study start had plasma HIV-1 RNA less than 50 copies/mL (Snapshot algorithm). In subjects who initially remained on their current antiretroviral regimen and switched to TIVICAY plus rilpivirine at Week 52, 90% had plasma HIV-1 RNA less than 50 copies/mL at Week 148 (Snapshot algorithm), which was comparable to the response rate (89%) observed at Week 100 (similar exposure duration) in subjects receiving TIVICAY plus rilpivirine from study start.

Refer to the prescribing information for JULUCA (dolutegravir and rilpivirine) tablet for complete virologic outcome information.

14.3 Pediatric Subjects

IMPAACT P1093 is an ongoing Phase 1/2, multicenter, open-label trial to evaluate the pharmacokinetic parameters, safety, tolerability, and efficacy of TIVICAY or TIVICAY PD in combination treatment regimens in HIV-1–infected infants, children, and adolescents aged at least 4 weeks to 18 years. Subjects were stratified by 5 age cohorts: Cohort 1, aged 12 to less than 18 years; Cohort 2A, aged 6 to less than 12 years; Cohort 3, aged 2 to less than 6 years; Cohort 4, aged 6 months to less than 2 years; and Cohort 5, aged 4 weeks to less than 6 months.

Seventy-five subjects received the recommended dose (determined by weight and age) of TIVICAY or TIVICAY PD *[see Dosage and Administration (2.3, 2.4, 2.5)]*.

These 75 subjects had a median age of 27 months (range: 1 to 214), were 59% female, and 68% were black or African American. At baseline, mean plasma HIV-1 RNA was 4.4 $\log_{10}$ copies per mL, median CD4+ cell count was 1,225 cells per mm^3 (range: 1 to 8,255), and median CD4+% was 23% (range: 0.3% to 49%). Overall, 33% had baseline plasma HIV-1 RNA greater than 50,000 copies per mL and 12% had a CDC HIV clinical classification of category C. The majority (80%) of subjects were treatment-experienced, but all were INSTI-naïve. Most subjects had previously used at least 1 NNRTI (44%) or 1 PI (76%).

Virologic outcomes from IMPAACT P1093 include subjects who received either TIVICAY tablets or TIVICAY PD tablets for oral suspension as per the dosing recommendations for their weight band and who had reached Week 24 (n = 58) or Week 48 (n = 42). At Week 24, 62% of subjects achieved HIV-1 RNA less than 50 copies per mL and 86% achieved HIV-1 RNA less than 400 copies per mL (Snapshot algorithm). The median CD4 count (percent) increase from baseline to Week 24 was 105 cells per mm^3 (5%). At Week 48, 69% of subjects achieved HIV-1 RNA less than 50 copies per mL and 79% achieved HIV-1 RNA less than 400 copies per mL (Snapshot algorithm). The median CD4 count (percent) increase from baseline to Week 48 was 141 cells per mm^3 (7%).

16 HOW SUPPLIED/STORAGE AND HANDLING

TIVICAY tablets, 10 mg, are white, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "10" on the other side. Bottle of 30 tablets with child-resistant closure and containing a desiccant. NDC 49702-226-13.

Store and dispense the 10-mg tablets in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

TIVICAY tablets, 25 mg, are pale yellow, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "25" on the other side. Bottle of 30 tablets with child-resistant closure. NDC 49702-227-13.

TIVICAY tablets, 50 mg, are yellow, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "50" on the other side. Bottle of 30 tablets with child-resistant closure. NDC 49702-228-13.

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

TIVICAY PD tablets for oral suspension, 5 mg, are white, round, strawberry cream flavored, film-coated, biconvex tablets debossed with "SV H7S" on one side and "5" on the other side. Bottle of 60 tablets with child-resistant closure containing a desiccant. Each bottle is packaged

with one 30-mL dosing cup and one 10-mL oral dosing syringe with 1-mL gradations. NDC 49702-255-37.

Store TIVICAY PD tablets for oral suspension below 30°C (86°F). Store and dispense the 5-mg tablets 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 (Patient Information and Instructions for Use).

Drug Interactions

TIVICAY or TIVICAY PD may interact with other 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 (5.4), Drug Interactions (7)]*.

Hypersensitivity Reactions

Advise patients to immediately contact their healthcare provider if they develop rash. Instruct patients to immediately stop taking TIVICAY or TIVICAY PD and other suspect agents, and seek medical attention if they develop a rash associated with any of the following symptoms, as it may be a sign of a more serious reaction such as severe hypersensitivity: fever; generally ill feeling; extreme tiredness; muscle or joint aches; blisters or peeling of the skin; oral blisters or lesions; eye inflammation; facial swelling; swelling of the eyes, lips, tongue, or mouth; breathing difficulty; and/or signs and symptoms of liver problems (e.g., yellowing of the skin or whites of the eyes, dark or tea-colored urine, pale-colored stools or bowel movements, nausea, vomiting, loss of appetite, or pain, aching, or sensitivity on the right side below the ribs) *[see Warnings and Precautions (5.1)]*.

Hepatotoxicity

Inform patients that hepatotoxicity has been reported with dolutegravir *[see Warnings and Precautions (5.2)]*. Advise patients that laboratory monitoring for hepatoxicity during therapy with TIVICAY or TIVICAY PD is recommended, especially for patients with liver disease, such as hepatitis B or C.

Embryo-Fetal Toxicity

Advise adolescents and adults of childbearing potential, including those actively trying to become pregnant, to discuss the risks and benefits of TIVICAY and TIVICAY PD 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 (5.3), Use in Specific Populations (8.1, 8.3)]*.

Adolescents and adults of childbearing potential taking TIVICAY or TIVICAY PD should be counseled on the consistent use of effective contraception *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs or symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when TIVICAY or TIVICAY PD is started *[see Warnings and Precautions (5.5)]*.

Different Formulations Are Not Bioequivalent

Advise patients that TIVICAY and TIVICAY PD are not bioequivalent and are not interchangeable on a milligram-per-milligram basis. Advise patients or their care provider that patients switching from one formulation to the other must adjust the dose for the new dosage formulation *[see Dosage and Administration (2.3) and Warnings and Precautions (5.6)]*.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to TIVICAY or TIVICAY PD 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 dolutegravir, 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 (5.6), How Supplied/Storage and Handling (16)]*.

Inform patients and caregivers that TIVICAY PD tablets for oral suspension may be swallowed whole or dispersed in drinking water and should not be chewed, cut or crushed. The amount of water needed to disperse the tablet will depend on the dose (number of tablets prescribed).

Instruct patients and caregivers that if a dose of TIVICAY or TIVICAY 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)]*.

Storage

Instruct patients and caregivers to store the TIVICAY 10-mg tablets and TIVICAY PD 5-mg tablets for oral suspension in the original package, keep the bottle tightly closed, and protect from moisture. Do not remove desiccant *[see How Supplied/Storage and Handling (16)]*.

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Manufactured for:

ViiV Healthcare
Durham, NC 27701

by:
GlaxoSmithKline
Durham, NC 27701

TVC:xxPI

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

TIVICAY (TIV-eh-kay) (dolutegravir) tablets	**TIVICAY PD (TIV-eh-kay Pe De) (dolutegravir) tablets for oral suspension**

What is TIVICAY and TIVICAY PD?

TIVICAY and TIVICAY PD are prescription medicines used to treat Human Immunodeficiency Virus-1 (HIV-1) infection together with:

- other HIV-1 medicines in adults who have not received HIV-1 medicines in the past or to replace their current HIV-1 medicines.
- other HIV-1 medicines in children, aged at least 4 weeks and weighing at least 6.6 pounds (3 kg), who have not received HIV-1 medicines in the past or to replace their current HIV-1 medicines when their healthcare provider determines that they meet certain requirements.

TIVICAY is used together with rilpivirine as a complete regimen to treat Human Immunodeficiency Virus-1 (HIV-1) infection in adults to replace their current HIV-1 medicines when their healthcare provider determines that they meet certain requirements.

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

It is not known if TIVICAY or TIVICAY PD is safe and effective in children who are less than 4 weeks of age and weigh less than 6.6 pounds (3 kg) or in children who have received certain types of medicine for HIV-1 infection.

Do not take TIVICAY or TIVICAY PD if you:

- have ever had an allergic reaction to a medicine that contains dolutegravir.
- take dofetilide.

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

- have or have had liver problems, including hepatitis B or C infection.
- are pregnant or plan to become pregnant. TIVICAY or TIVICAY PD may harm your unborn baby.
  - Your healthcare provider may prescribe a different medicine than TIVICAY or TIVICAY PD 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 TIVICAY or TIVICAY PD.
  - If you can become pregnant, you and your healthcare provider should talk about the use of effective birth control (contraception) during treatment with TIVICAY or TIVICAY PD.
  - 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 TIVICAY or TIVICAY PD.

Pregnancy Registry. There is a pregnancy registry for individuals who take antiretroviral medicines, including TIVICAY and TIVICAY 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 TIVICAY or TIVICAY PD.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - TIVICAY and TIVICAY PD pass to your baby in your breast milk.
    Talk with your healthcare provider about the best way to feed your baby.

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 TIVICAY or TIVICAY PD. Keep a list of your medicines and show it to 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 TIVICAY or TIVICAY 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 TIVICAY or TIVICAY PD with other medicines.

How should I take TIVICAY or TIVICAY PD?

- **Take TIVICAY or TIVICAY PD exactly as your healthcare provider tells you to take it.**
- Take TIVICAY or TIVICAY PD with or without food.
- For children who cannot swallow tablets, read the Instructions for Use at the end of this patient information for detailed instructions on how to prepare a dose of TIVICAY PD tablets for oral suspension.
- TIVICAY PD may be swallowed whole or dispersed in drinking water and should not be chewed, cut, or crushed.
- **TIVICAY tablets are not the same as TIVICAY PD tablets for oral suspension and cannot be substituted for each other. Check to make sure you receive the correct form of TIVICAY each time you or your child's prescription is filled to avoid using the wrong medicine.**
- Do not change your dose, switch medicines or stop taking TIVICAY or TIVICAY PD without talking with your healthcare provider first.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, TIVICAY or TIVICAY 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 TIVICAY or TIVICAY PD:
  - If you take TIVICAY with food, you may take these supplements at the same time that you take TIVICAY.
  - If you do not take TIVICAY or TIVICAY PD with food, take TIVICAY or TIVICAY PD at least 2 hours before or 6 hours after you take these supplements.
- Do not miss a dose of TIVICAY or TIVICAY PD.
- If you miss a dose of TIVICAY or TIVICAY PD, take it as soon as you remember. Do not take 2 doses at the same time or take more than your prescribed dose.

- Stay under the care of a healthcare provider during treatment with TIVICAY or TIVICAY PD.
- Do not run out of TIVICAY or TIVICAY 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 TIVICAY or TIVICAY PD, call your healthcare provider or go to the nearest hospital emergency room right away.

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

- **TIVICAY or TIVICAY PD can cause serious side effects including:**
- **Allergic reactions.** Call your healthcare provider right away if you develop a rash with TIVICAY or TIVICAY PD**. Stop taking TIVICAY or TIVICAY PD and get medical help right away if you develop a rash with any of the following signs or symptoms:**
  - fever
  - generally ill feeling
  - tiredness
  - muscle or joint aches
  - blisters or sores in mouth
  - blisters or peeling of the skin
  - redness or swelling of the eyes
  - swelling of the mouth, face, lips, or tongue
  - problems breathing
- **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 tests during treatment with TIVICAY or TIVICAY PD. Liver problems, including liver failure, have also happened in people without a history of liver disease or other risk factors. Your healthcare provider may do blood tests to check your liver. **Call your healthcare provider right away if you develop any of the following signs or symptoms of liver problems**:
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or “tea-colored” urine
  - light-colored stools (bowel movements)
  - nausea or vomiting
  - loss of appetite
  - pain, aching, or tenderness on the right side of your stomach area
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after you start taking TIVICAY or TIVICAY PD.
- **The most common side effects of TIVICAY include:**
  - trouble sleeping
  - tiredness
  - headache

These are not all the possible side effects of TIVICAY or TIVICAY PD. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TIVICAY or TIVICAY PD?

- Store TIVICAY 10-mg, 25-mg, and 50-mg tablets at room temperature between 68°F to 77°F (20°C to 25°C).

- Store TIVICAY 10-mg tablets in the original bottle. Keep the bottle tightly closed and protected from moisture. The bottle contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not remove the desiccant packet from the bottle.
- Store TIVICAY PD 5-mg tablets for oral suspension at room temperature below 86°F (30°C) in the original bottle. Keep the bottle tightly closed and protected from moisture. The bottle contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not remove the desiccant packet from the bottle.

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

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

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TIVICAY or TIVICAY PD for a condition for which it was not prescribed. Do not give TIVICAY or TIVICAY PD to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about TIVICAY that is written for health professionals. For more information, go to www.TIVICAY.com or call 1-877-844-8872.

What are the ingredients in TIVICAY and TIVICAY PD?

Active ingredient: dolutegravir.

Inactive ingredients:

TIVICAY tablets: D-mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, and sodium stearyl fumarate. The tablet film-coating contains the inactive ingredients iron oxide yellow (for the 25-mg and 50-mg tablets only), macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

TIVICAY PD tablets for oral suspension: calcium sulfate dihydrate, crospovidone, mannitol, microcrystalline cellulose, povidone K29/32, silicified microcrystalline cellulose, sodium starch glycolate, strawberry cream flavor, sucralose, and sodium stearyl fumarate. The tablet film-coating contains hypromellose, polyethylene glycol, and titanium dioxide.

Manufactured for:

ViiV Healthcare
Durham, NC 27701

by:

GlaxoSmithKline
Durham, NC 27701

TVC:xxPIL

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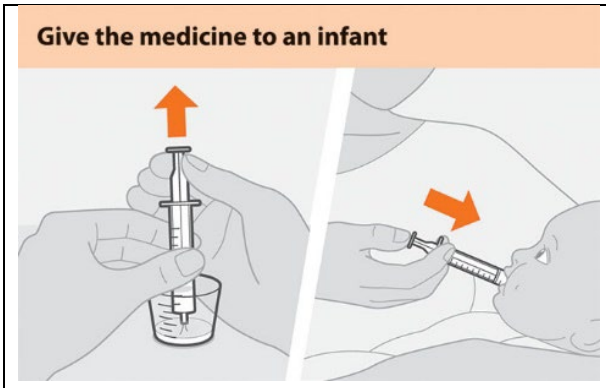

Figure E **Figure F**

- Place the tip of the syringe into the prepared medicine and draw up all the medicine into the syringe by pulling up on the plunger. **See Figure E.**
- Place the tip of the syringe against the inside of the infant's cheek. Gently push down the plunger to give the dose slowly. **See Figure F.**
- Add another 5 mL of drinking water to the cup and swirl. Draw up the remaining medicine into the syringe and give it all to the infant.
- **Repeat if any medicine remains in the syringe to make sure the infant gets the full dose.**

Allow time for the medicine to be swallowed.

Cleaning

Step 4. Clean the dosing items

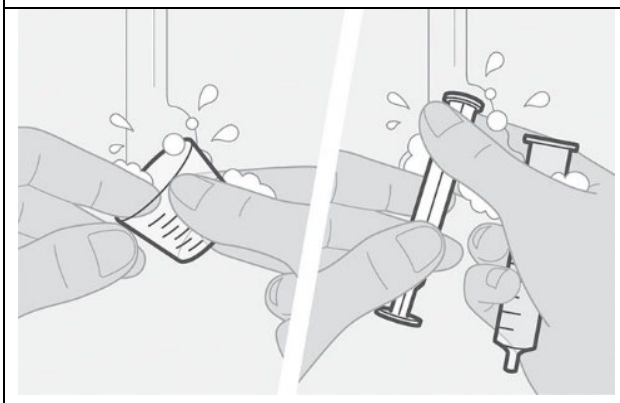

Figure G **Figure H**

- Wash the cup with water. **See Figure G.**
- **Pull the plunger out of the syringe and wash the syringe parts separately in water. Allow parts to dry completely before reassembling and storing. See Figure H**.
- All parts will need to be clean before preparing the next dose.

Storage Information

Store TIVICAY PD tablets for oral suspension at room temperature below 86°F (30°C) in the original bottle. Keep the bottle tightly closed and protect from moisture. The bottle contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not remove the desiccant packet from the bottle.

Keep TIVICAY PD and all medicines out of the reach of children.

Disposal Information

When all the tablets in the bottle have been taken or are no longer needed, throw away the bottle, cup, and syringe. Dispose of them using your local household waste guidelines.

You will get a new cup and syringe in your next pack.

Manufactured for:

ViiV Healthcare

Durham, NC 27701

by:

GlaxoSmithKline

Durham, NC 27701

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