TIVICAY PD- dolutegravir sodium tablet, for suspension
TIVICAY- dolutegravir sodium tablet, film coated
ViiV Healthcare Company

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TIVICAY safely and effectively. See full prescribing information for TIVICAY.
TIVICAY (dolutegravir) tablets, for oral use
TIVICAY PD (dolutegravir) tablets for oral suspension
Initial U.S. Approval: 2013

RECENT MAJOR CHANGES

Indications and Usage (1)	8/2026
Dosage and Administration (2.1, 2.3)	8/2026

INDICATIONS AND USAGE

TIVICAY and TIVICAY PD are an HIV-1 integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults (treatment-naïve or -experienced) and in pediatric patients (treatment-naïve or -experienced but INSTI- naïve) weighing at least 2 kg. (1)
TIVICAY is indicated in combination with rilpivirine as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure or known substitutions associated with resistance to either antiretroviral agent. (1)

DOSAGE AND ADMINISTRATION

- May be taken without regard to food. (2.2)

Adult Population	Recommended Dose
Treatment-naïve or treatment-experienced INSTI-naïve or virologically suppressed (HIV-1 RNA <50 copies per mL) adults switching to dolutegravir plus rilpivirine[a] (2.1)	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A or CYP3A inducers (2.1, 7.2, 7.3)	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[b] (2.1, 12.4)	50 mg twice daily

UGT = uridine diphosphate glucuronosyltransferase; CYP = cytochrome P450.
[a] Rilpivirine dose is 25 mg once daily for those switching to dolutegravir plus rilpivirine.
[b] Alternative combinations that do not include metabolic inducers should be considered where possible.

Pediatric Patients: Treatment-naïve or treatment-experienced INSTI-naïve patients weighing at least 2 kg. See Tables 2, 3, and 4 for complete pediatric dosing recommendations. (2.3).

- TIVICAY and TIVICAY PD are not bioequivalent and are not substitutable on a milligram-per-milligram basis.
- Pediatric Patients ≥4 weeks of age: if certain UGT1A or CYP3A inducers are coadministered, then adjust the weight-based dose of TIVICAY or TIVICAY PD to twice daily. (2.3, 7.2, 7.3)

TIVICAY PD Tablets for Oral Suspension (Table 2 and Table 3):
Term Neonates ≥2 kg (from birth to <4 weeks of age):

- Birth to 14 Days: 1 tablet every other day
- 15 Days to <4 Weeks: 1 tablet once daily

Pediatric Population (≥4 Weeks of Age)	Recommended Dose TIVICAY PD

Body Weight	Tablets for Oral Suspension
3 kg to less than 6 kg	1 tablet once daily
6 kg to less than 10 kg	3 tablets once daily
10 kg to less than 14 kg	4 tablets once daily
14 kg to less than 20 kg	5 tablets once daily
20 kg and greater	6 tablets once daily

TIVICAY Tablets (Table 4):
Alternative dosing recommendations for TIVICAY tablets for patients weighing at least 14 kg:

- 14 kg to less than 20 kg: 4 x 10 mg tablets once daily.
- 20 kg and greater: 1 x 50 mg tablet once daily.

DOSAGE FORMS AND STRENGTHS

- TIVICAY tablets: 10 mg, 25 mg, and 50 mg (3)
- TIVICAY PD tablets for oral suspension: 5 mg (3)

CONTRAINDICATIONS

- Previous hypersensitivity reaction to dolutegravir. (4)
- Coadministration with dofetilide. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported. Discontinue TIVICAY or TIVICAY PD and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop, as a delay in stopping treatment may result in a life-threatening reaction. (5.1)
- Hepatotoxicity has been reported in patients receiving dolutegravir-containing regimens. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations. Monitoring for hepatotoxicity is recommended. (5.2)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.4)
- TIVICAY tablets and TIVICAY PD tablets for oral suspension are not substitutable. (2.2, 5.5)

ADVERSE REACTIONS

The most common adverse reactions of moderate to severe intensity and incidence at least 2% (in those receiving TIVICAY in any one adult trial) are insomnia, fatigue, and headache. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Refer to the full prescribing information for important drug interactions with TIVICAY or TIVICAY PD. (4, 7)
- Drugs that are metabolic inducers may decrease the plasma concentrations of dolutegravir. (7.2, 7.3)
- TIVICAY or TIVICAY PD should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications. When taken with food, TIVICAY and supplements containing calcium or iron can be taken at the same time. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
Revised: 8/2026

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TIVICAY and TIVICAY PD are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults (treatment-naïve or -experienced) and in pediatric patients (treatment-naïve or -experienced but integrase strand transfer inhibitor [INSTI]-naïve) weighing at least 2 kg *[see Microbiology (12.4)]*.

TIVICAY is indicated in combination with rilpivirine as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure or known substitutions associated with resistance to either antiretroviral agent.

2 DOSAGE AND ADMINISTRATION

2.1 Overview of Different Dosage Forms and Important Dosage Considerations

TIVICAY is available in two dosage forms:

- TIVICAY
    - Available as 10 mg, 25 mg, and 50 mg tablets.
    - Recommended for adults and pediatric patients weighing at least 14 kg.
    - Do not use TIVICAY tablets in patients weighing less than 14 kg *[see Dosage and Administration (2.3)]*.
- TIVICAY PD
    - See Instructions for Use for details on preparation and administration of TIVICAY PD *[see Dosage and Administration (2.4)]*.
    - Available as 5 mg tablets for oral suspension.
    - Recommended for pediatric patients weighing at least 2 kg. TIVICAY PD is the only recommended dosage form for pediatric patients weighing less than 14 kg.
    - TIVICAY PD is preferred over TIVICAY tablets in patients weighing at least 14 kg to less than 20 kg *[see Dosage and Administration (2.3)]*.

Do not substitute TIVICAY tablets and TIVICAY PD tablets for oral suspension on a milligram-per-milligram basis due to differing pharmacokinetic profiles *[see Dosage and Administration (2.3), Warnings and Precautions (5.5), Clinical Pharmacology (12.3)]*. If switching from the tablets to the tablets for oral suspension, follow the recommended dosage in Table 3. If switching from the tablets for oral suspension to the tablets, follow the recommended dosage in Table 4. See administration instructions *[see Dosage and Administration (2.4)]*.

Take TIVICAY and TIVICAY PD with or without food in combination with other antiretrovirals *[see Dosage and Administration (2.2, 2.3), Clinical Pharmacology (12.3)]*.

2.2 Recommended Dosage in Adults

TIVICAY tablets may be taken with or without food in combination with other antiretrovirals *[see Clinical Pharmacology (12.3)].* Refer to Table 1 for dosage recommendation for adults using TIVICAY tablets.

Table 1. Dosing Recommendations for TIVICAY Tablets in Adult Patients

Population	Recommended Dosage
Treatment-naïve or treatment-experienced INSTI-naïve or virologically suppressed (HIV-1 RNA <50 copies/mL) adults switching to dolutegravir plus rilpivirine[a]	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A) or cytochrome P450 (CYP)3A inducers *[see Drug Interactions (7.2, 7.3)]*	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[b] *[see Microbiology (12.4)]*	50 mg twice daily

INSTI = integrase strand transfer inhibitor.

[a] Rilpivirine dose is 25 mg once daily for those switching to dolutegravir plus rilpivirine.

[b] Alternative combinations that do not include metabolic inducers should be considered where possible *[see Drug Interactions (7.3)]*.

2.3 Recommended Dosage in Pediatric Patients

The recommended dosages of TIVICAY PD tablets for oral suspension and TIVICAY tablets in pediatric patients (in treatment-naïve, or treatment-experienced but naïve to INSTI treatment) are displayed in Tables 2, 3, and 4.

In pediatric patients weighing **14 kg or greater**, either TIVICAY PD tablets for oral suspension (Table 3) or TIVICAY tablets (Table 4) can be used. Note that TIVICAY PD is preferred over TIVICAY tablets in pediatric patients weighing at least 14 kg to less than 20 kg.

Do not use **TIVICAY** tablets in patients weighing **less than 14 kg**. See administration instructions in *Dosage and Administration (2.4)*.

No data are available in preterm neonates.

TIVICAY PD Tablets for Oral Suspension

Table 2. Recommended Dosage of TIVICAY PD in Pediatric Patients Including Term Neonatesa (at Least 37 Weeks of Gestation) Less Than 4 Weeks of Age and Weighing at Least 2 kg

Pediatric Patient Population	TIVICAY PD Tablets for Oral Suspension	Total Daily Dosage
Birth to 14 days	1 tablet every other day	5 mg every other day
15 days to less than 4 weeks	1 tablet once daily	5 mg once daily

[a] No data are available in preterm neonates

Table 3. Recommended Dosage of TIVICAY PD in Pediatric Patients at Least 4 Weeks of Age and Weighing at Least 3 kg

Body Weight	TIVICAY PD Tablets for Oral Suspension	Total Daily Dosage
3 kg to less than 6 kg	1 tablet once daily	5 mg once daily
6 kg to less than 10 kg	3 tablets once daily	15 mg once daily
10 kg to less than 14 kg	4 tablets once daily	20 mg once daily
14 kg to less than 20 kg	5 tablets once daily	25 mg once daily
20 kg or greater	6 tablets once daily	30 mg once daily

TIVICAY Tablets

Table 4. Recommended Dosage of TIVICAY in Pediatric Patients Weighing at Least 14 kg

Body Weight	TIVICAY Tablets	Total Daily Dosage
14 kg to less than 20 kg	4 x 10 mg tablets once daily	40 mg once daily
20 kg and greater	1 x 50 mg tablet once daily	50 mg once daily

Dosage Modifications for Co-administration with Certain UGT1A or CYP3A Inducers in Pediatric Patients at Least 4 Weeks of Age

If certain uridine diphosphate glucuronosyltransferase (UGT)1A or cytochrome P450 (CYP)3A inducers are co-administered, then administer the corresponding dose of TIVICAY PD (see Table 3) or TIVICAY (see Table 4) twice daily instead of once daily (i.e., double the total daily dosage) *[see Drug Interactions (7.2, 7.3)]*.

2.4 Preparation and Administration Instructions for TIVICAY PD

Take TIVICAY PD daily with or without food in combination with other antiretrovirals *[see Clinical Pharmacology (12.3)]*. Do not chew, cut, or crush TIVICAY PD *[see Instructions for Use]*. Instruct patients (or instruct caregivers) to either:

- Swallow the tablets for oral suspension whole (if more than one tablet is required, swallow one tablet at a time to reduce the risk of choking), or
- Fully disperse the tablets for oral suspension in 5 mL of drinking water (if using 1 or 3 tablets for oral suspension) or 10 mL (if using 4, 5, or 6 tablets for oral suspension) in the supplied cup; swirl the suspension so that no lumps remain. After full dispersion, administer the oral suspension within 30 minutes of mixing *[see Instructions for Use]*.

3 DOSAGE FORMS AND STRENGTHS

TIVICAY Tablets:

10 mg: Each tablet contains 10 mg of dolutegravir (as dolutegravir sodium). Tablets are white, round, film-coated, biconvex tablets debossed with “SV 572” on one side and “10” on the other side.

25 mg: Each tablet contains 25 mg of dolutegravir (as dolutegravir sodium). Tablets are pale yellow, round, film-coated, biconvex tablets debossed with “SV 572” on one side and “25” on the other side.

50 mg: Each tablet contains 50 mg of dolutegravir (as dolutegravir sodium). Tablets are yellow, round, film-coated, biconvex tablets debossed with “SV 572” on one side and “50” on the other side.

TIVICAY PD Tablets for Oral Suspension:

Each tablet contains 5 mg of dolutegravir (as dolutegravir sodium). Tablets are white, round, strawberry cream flavored, film-coated, biconvex tablets debossed with “SV H7S” on one side and “5” on the other side.

4 CONTRAINDICATIONS

TIVICAY and TIVICAY PD are contraindicated in patients:

- with previous hypersensitivity reaction to dolutegravir *[see Warnings and Precautions (5.1)]*.
- receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events *[see Drug Interactions (7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of participants receiving TIVICAY in Phase III clinical trials. Discontinue TIVICAY or TIVICAY PD and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with TIVICAY or TIVICAY PD or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. TIVICAY and TIVICAY PD are contraindicated in patients who have experienced a previous hypersensitivity reaction to dolutegravir.

5.2 Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TIVICAY or TIVICAY PD *[see Adverse Reactions (6.1)]*. In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver

failure have been reported in patients receiving a dolutegravir-containing regimen without pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with TRIUMEQ (abacavir, dolutegravir, and lamivudine). Monitoring for hepatotoxicity is recommended.

5.3 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of TIVICAY or TIVICAY PD and other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4), Drug Interactions (7.3)]*:

- Loss of therapeutic effect of TIVICAY or TIVICAY PD and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

For concomitant drugs for which the interaction can be mitigated, please see Table 8 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with TIVICAY or TIVICAY PD; review concomitant medications during therapy with TIVICAY or TIVICAY PD; and monitor for the adverse reactions associated with the concomitant drugs.

5.4 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including TIVICAY or TIVICAY PD. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

5.5 Different Formulations Are Not Substitutable

TIVICAY and TIVICAY PD are not bioequivalent and are not substitutable on a milligram-per-milligram basis *[see Clinical Pharmacology (12.3)]*. If a pediatric patient switches from one formulation to the other, the dose must be adjusted for the new dosage formulation *[see Dosage and Administration (2.2)]*. Incorrect dosing of a given formulation may result in underdosing and loss of therapeutic effect and possible development of resistance or possible clinically significant adverse reactions from greater exposure of dolutegravir.

6 ADVERSE REACTIONS

The following serious adverse drug reactions are discussed in other sections of the

labeling:

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials Experience in Adult Participants

Treatment-Naïve Participants: The safety assessment of TIVICAY in treatment naïve participants with HIV-1 is based on the analyses of data from 2 international, multicenter, double-blind trials, SPRING-2 (ING113086) and SINGLE (ING114467) and data from the international, multicenter, open-label FLAMINGO (ING114915) trial.

In SPRING-2, 822 participants 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 nucleoside reverse transcriptase inhibitor (NRTI) treatment (either abacavir sulfate and lamivudine [EPZICOM] or emtricitabine/tenofovir [TRUVADA]). There were 808 participants included in the efficacy and safety analyses. Through 96 weeks, the rate of adverse events leading to discontinuation was 2% in both treatment arms.

In SINGLE, 833 participants were randomized and received at least 1 dose of either TIVICAY 50 mg with fixed-dose abacavir sulfate and lamivudine (EPZICOM) once daily or fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA) once daily (study treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rates of adverse events leading to discontinuation were 4% in participants receiving TIVICAY 50 mg once daily + EPZICOM and 14% in participants receiving ATRIPLA once daily.

Treatment-emergent adverse reactions of moderate to severe intensity observed in at least 2% of participants in either treatment arm in SPRING-2 and SINGLE trials are provided in Table 5. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 5. Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment-Naïve Participants in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

	SPRING-2		SINGLE	
System Organ Class/ Preferred Term	**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)**
Psychiatric				
Insomnia	<1%	<1%	3%	3%

Depression	<1%	<1%	1%	2%
Abnormal dreams	<1%	<1%	<1%	2%
Nervous System				
Dizziness	<1%	<1%	<1%	5%
Headache	<1%	<1%	2%	2%
Gastrointestinal				
Nausea	1%	1%	<1%	3%
Diarrhea	<1%	<1%	<1%	2%
Skin and Subcutaneous Tissue				
Rash[a]	0	<1%	<1%	6%
General Disorders				
Fatigue	<1%	<1%	2%	2%
Ear and Labyrinth				
Vertigo	0	<1%	0	2%

NRTI = Nucleoside Reverse Transcriptase Inhibitor.

[a] Includes pooled terms: rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and drug eruption.

In addition, Grade 1 insomnia was reported by 1% and less than 1% of participants receiving TIVICAY and raltegravir, respectively, in SPRING-2; whereas in SINGLE the rates were 7% and 4% for TIVICAY and ATRIPLA, respectively. These events were not treatment limiting.

In a multicenter, open-label trial (FLAMINGO), 243 participants received TIVICAY 50 mg once daily versus 242 participants who received darunavir 800 mg/ritonavir 100 mg once daily, both in combination with investigator-selected NRTI background regimen (either EPZICOM or TRUVADA). There were 484 participants included in the efficacy and safety analyses. Through 96 weeks, the rates of adverse events leading to discontinuation were 3% in participants receiving TIVICAY and 6% in participants receiving darunavir/ritonavir. The adverse reactions observed in FLAMINGO were generally consistent with those seen in SPRING-2 and SINGLE.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Participants: In an international, multicenter, double-blind trial (ING111762, SAILING), 719 participants with HIV-1, 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 one fully active agent. Participants were antiretroviral treatment-experienced adults. At 48 weeks, the rates of adverse events leading to discontinuation were 3% in participants receiving TIVICAY 50 mg once daily + background regimen and 4% in participants receiving raltegravir 400 mg twice daily + background regimen.

The only treatment-emergent adverse reaction of moderate to severe intensity with at least 2% frequency in either treatment group was diarrhea, 2% (6 of 354) in participants receiving TIVICAY 50 mg once daily + background regimen and 1% (5 of 361) in participants receiving raltegravir 400 mg twice daily + background regimen.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Participants: In

a multicenter, open-label, single-arm trial (ING112574, VIKING-3), 183 participants with HIV-1 received TIVICAY 50 mg twice daily with the current failing background regimen for 7 days and with optimized background therapy from Day 8. Participants were antiretroviral treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance. The rate of adverse events leading to discontinuation was 4% of participants at Week 48.

Treatment-emergent adverse reactions in VIKING-3 were generally similar compared with observations with the 50-mg once-daily dose in adult Phase III trials.

Virologically Suppressed Participants: The adverse reactions observed for TIVICAY plus rilpivirine in the Week 48 analysis of pooled data from 2 identical, international, multicenter, open-label trials (SWORD-1 and SWORD-2) of 513 virologically suppressed participants with HIV-1, switching from their current antiretroviral regimen to TIVICAY plus rilpivirine, were consistent with the adverse reaction profiles and severities for the individual components when administered with other antiretroviral agents. There were no adverse reactions (Grades 2 to 4) with an incidence of at least 2% in either treatment arm at Week 48. The safety profile during the additional follow-up period through Week 148 were consistent with Week 48. The rate of adverse events leading to discontinuation through Week 48 was 4% in participants receiving TIVICAY plus rilpivirine once daily and less than 1% in participants who remained on their current antiretroviral regimen. In the pooled analyses, the proportion of participants receiving TIVICAY plus rilpivirine who discontinued treatment due to an adverse event through Week 148 was 8%.

Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials: The following adverse reactions occurred in less than 2% of treatment-naïve or treatment-experienced participants receiving TIVICAY in a combination regimen in any one trial. These events have been included because of their seriousness and assessment of potential causal relationship.

Gastrointestinal Disorders: Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting.

Hepatobiliary Disorders: Hepatitis.

Musculoskeletal Disorders: Myositis.

Psychiatric Disorders: Suicidal ideation, attempt, behavior, or completion. These events were observed primarily in participants with a pre-existing history of depression or other psychiatric illness.

Renal and Urinary Disorders: Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus.

Laboratory Abnormalities:

Treatment-Naïve Participants: Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of participants are presented in Table 6. The mean change from baseline observed for selected lipid values is presented in Table 7. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 6. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Participants in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

Laboratory Parameter Preferred Term	SPRING-2		SINGLE	
	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)
ALT				
Grade 2 (>2.5-5.0 x ULN)	4%	4%	3%	5%
Grade 3 to 4 (>5.0 x ULN)	2%	2%	1%	<1%
AST				
Grade 2 (>2.5-5.0 x ULN)	5%	3%	3%	4%
Grade 3 to 4 (>5.0 x ULN)	3%	2%	1%	3%
Total Bilirubin				
Grade 2 (1.6-2.5 x ULN)	3%	2%	<1%	<1%
Grade 3 to 4 (>2.5 x ULN)	<1%	<1%	<1%	<1%
Creatine kinase				
Grade 2 (6.0-9.9 x ULN)	2%	5%	5%	3%
Grade 3 to 4 (≥10.0 x ULN)	7%	4%	7%	8%
Hyperglycemia				
Grade 2 (126-250 mg/dL)	6%	6%	9%	6%
Grade 3 (>250 mg/dL)	<1%	2%	2%	<1%
Lipase				
Grade 2 (>1.5-3.0 x ULN)	7%	7%	11%	11%
Grade 3 to 4 (>3.0 x ULN)	2%	5%	5%	4%
Total neutrophils				
Grade 2 (0.75-0.99 x 10^9)	4%	3%	4%	5%
Grade 3 to 4 (<0.75 x 10^9)	2%	2%	3%	3%

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; NRTI = Nucleoside Reverse Transcriptase Inhibitor; ULN = Upper limit of normal.

Table 7. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Participants in SPRING-2 (Week 96 Analysis[a]) and SINGLE Trials (Week 144 Analysis[a])

Laboratory Parameter Preferred Term	SPRING-2		SINGLE	
	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)
Cholesterol (mg/dL)	8.1	10.1	24.0	26.7
HDL cholesterol (mg/dL)	2.0	2.3	5.4	7.2
LDL cholesterol (mg/dL)	5.1	6.1	16.0	14.6
Triglycerides (mg/dL)	6.7	6.6	13.6	31.9

HDL = High density lipoprotein; LDL = Low density lipoprotein; NRTI = Nucleoside Reverse Transcriptase Inhibitor.

[a] Participants on lipid-lowering agents at baseline were excluded from these analyses (19 participants in each arm in SPRING-2, and in SINGLE: TIVICAY + EPZICOM n = 30 and ATRIPLA n = 27). Ninety-four participants initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless of whether they discontinued the agent (SPRING-2: TIVICAY n = 9, raltegravir n = 13; SINGLE: TIVICAY + EPZICOM n = 36, ATRIPLA n = 36).

Laboratory abnormalities observed in the FLAMINGO trial were generally consistent with observations in SPRING-2 and SINGLE.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Participants: Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naïve (SPRING-2 and SINGLE) trials.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Participants: The most common treatment-emergent laboratory abnormalities (greater than 5% for Grades 2 to 4 combined) observed in VIKING-3 at Week 48 were elevated ALT (9%), AST (8%), cholesterol (10%), creatine kinase (6%), hyperglycemia (14%), and lipase (10%). Two percent (4 of 183) of participants had a Grade 3 to 4 treatment-emergent hematology laboratory abnormality, with neutropenia (2% [3 of 183]) being the most frequently reported.

Virologically Suppressed Adults: Laboratory abnormalities observed in SWORD-1 and SWORD-2 were generally similar compared with observations seen in the other Phase III trials.

Hepatitis B and/or Hepatitis C Virus Co-infection: In Phase III trials, participants with hepatitis B and/or C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal. Overall, the safety profile in participants with hepatitis B and/or C virus co-infection was similar to that

observed in participants without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C virus co-infection for all treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected compared with HIV mono-infected participants receiving TIVICAY were observed in 18% vs. 3% with the 50-mg once-daily dose and 13% vs. 8% with the 50-mg twice-daily dose. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some participants with hepatitis B and/or C at the start of therapy with TIVICAY, particularly in the setting where anti-hepatitis therapy was withdrawn *[see Warnings and Precautions (5.2)]*.

Changes in Serum Creatinine: Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function *[see Clinical Pharmacology (12.2)]*. Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 96 weeks. In treatment-naïve participants, a mean change from baseline of 0.15 mg/dL (range: -0.32 mg/dL to 0.65 mg/dL) was observed after 96 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced participants.

Clinical Trials Experience in Pediatric Participants

Children and Adolescent Participants with HIV-1: The safety and pharmacokinetics of TIVICAY and TIVICAY PD in pediatric participants with HIV-1 aged at least 4 weeks and weighing at least 3 kg was evaluated in the IMPAACT P1093 trial and 2 weight-band-based pharmacokinetic substudies of the ODYSSEY trial *[see Use in Specific Populations (8.4), Clinical Pharmacology (12.3)]*. Overall, the safety data in these pediatric studies were similar to those seen in adults, and there was no clinically significant difference in dolutegravir exposure *[see Clinical Pharmacology (12.3)]*.

IMPAACT P1093 is a multicenter, open-label, non-comparative trial of pediatric participants with HIV-1 aged 4 weeks to less than 18 years *[see Use in Specific Populations (8.4), Clinical Pharmacology (12.3), Clinical Studies (14.3)]*.

The safety analysis based on participants (n = 75) who received the recommended dose (determined by weight and age) through Week 24 showed that 11% of participants experienced drug-related clinical adverse reactions. The only Grade 1 to 2 drug-related clinical adverse reactions reported by more than one participant was immune reconstitution inflammatory syndrome (IRIS) (n = 2). There were no Grade 3 or 4 drug-related adverse reactions reported. No adverse reactions led to discontinuation.

The Grade 3 or 4 laboratory abnormalities reported in more than one participant were decreased neutrophil count (n = 11), decreased blood bicarbonate (n = 4), decreased hemoglobin (n = 3), increased lipase (n = 2), and increased blood potassium (n = 2). These laboratory events were not considered to be drug-related. Median laboratory values were similar at baseline and Week 24. Changes in median serum creatinine were similar to those observed in adults.

Neonates Exposed to HIV-1: Forty-eight term neonates exposed to HIV-1 (from birth and weighing at least 2 kg) received dolutegravir for up to 6 weeks, and followed for a total of 16 weeks in IMPAACT 2023. The safety profile in neonates was similar to that observed in older populations and there were no new safety findings identified *[see Use in Specific Populations (8.4)]*.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic Systems

Sideroblastic anemia.

Hepatobiliary Disorders

Acute liver failure, hepatotoxicity.

Investigations

Weight increased.

Musculoskeletal

Arthralgia, myalgia.

Psychiatric

Anxiety.

7 DRUG INTERACTIONS

7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC_{50} = 1.93 microM) and multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 microM). In vivo, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide, dalfampridine, and metformin, Table 8) *[see Contraindications (4), Drug Interactions (7.3)]*.

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC_{50} = 2.12 microM) and OAT3 (IC_{50} = 1.97 microM). However, in vivo, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

In vitro, dolutegravir did not inhibit (IC_{50} greater than 50 microM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyltransferase (UGT)1A1, UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. In vitro, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4. Based on these data and the results of drug interaction trials, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir

Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir

is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp in vitro. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir.

Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentration.

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir (Table 8) *[see Drug Interactions (7.3), Clinical Pharmacology (12.3)]*.

In vitro, dolutegravir was not a substrate of OATP1B1 or OATP1B3.

7.3 Established and Other Potentially Significant Drug Interactions

Table 8 provides clinical recommendations as a result of drug interactions with TIVICAY or TIVICAY PD. These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy *[see Dosage and Administration (2), Clinical Pharmacology (12.3)]*.

Table 8. Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interactions [see Dosage and Administration (2)]

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir and/or Concomitant Drug	Clinical Comment
HIV-1 Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirine[a]	↓Dolutegravir	Use of TIVICAY or TIVICAY PD with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓Dolutegravir	Adjust dose of TIVICAY to twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients (at least 4 weeks of age), increase the weight-based dose of TIVICAY or TIVICAY PD to twice daily (Tables 3 and 4). Use alternative combinations that do not include metabolic inducers where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]
Non-nucleoside reverse transcriptase	↓Dolutegravir	Avoid coadministration with nevirapine because there are insufficient data to make

inhibitor: Nevirapine		dosing recommendations.
Protease inhibitors: Fosamprenavir/ritonavir[a] Tipranavir/ritonavir[a]	↓Dolutegravir	Adjust dose of TIVICAY to twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients (at least 4 weeks of age), increase the weight-based dose of TIVICAY or TIVICAY PD to twice daily (Tables 3 and 4). Use alternative combinations that do not include metabolic inducers where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]
Other Agents		
Dofetilide	↑Dofetilide	Coadministration is contraindicated with TIVICAY or TIVICAY PD *[see Contraindications (4)]*.
Carbamazepine[a]	↓Dolutegravir	Adjust dose of TIVICAY to twice daily in treatment-naïve or treatment-experienced, INSTI-naïve adult patients. In pediatric patients (at least 4 weeks of age), increase the weight-based dose of TIVICAY or TIVICAY PD to twice daily (Tables 3 and 4). Use alternative treatment that does not include carbamazepine where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]
Oxcarbazepine Phenytoin Phenobarbital St. John's wort (*Hypericum perforatum*)	↓Dolutegravir	Avoid coadministration with TIVICAY or TIVICAY PD because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer TIVICAY or TIVICAY PD 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron[a]	↓Dolutegravir	When taken with food, TIVICAY and supplements or multivitamins containing calcium or iron can be taken at the same time. Under fasting conditions, TIVICAY or TIVICAY PD should be taken 2 hours before or 6 hours after taking supplements containing calcium or iron.

Potassium channel blocker: Dalfampridine	↑Dalfampridine	Elevated levels of dalfampridine increase the risk of seizures. The potential benefits of taking dalfampridine concurrently with TIVICAY or TIVICAY PD should be considered against the risk of seizures in these patients.
Metformin	↑Metformin	Refer to the prescribing information for metformin for assessing the benefit and risk of concomitant use of TIVICAY or TIVICAY PD and metformin.
Rifampin[a]	↓Dolutegravir	Adjust dose of TIVICAY to twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients (at least 4 weeks of age), increase the weight-based dose of TIVICAY or TIVICAY PD to twice daily (Tables 3 and 4). Use alternatives to rifampin where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]

INSTI = integrase strand transfer inhibitor.

[a] *See Clinical Pharmacology (12.3) Table 11 or Table 12 for magnitude of interaction.*

[b] The lower dolutegravir exposures observed in INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance *[see Microbiology (12.4)]*) upon coadministration with certain inducers may result in loss of therapeutic effect and development of resistance to TIVICAY or other coadministered antiretroviral agents.

7.4 Drugs without Clinically Significant Interactions with Dolutegravir

Based on drug interaction trial results, the following drugs can be coadministered with dolutegravir without a dose adjustment: atazanavir/ritonavir, darunavir/ritonavir, elbasvir/grazoprevir, methadone, midazolam, omeprazole, oral contraceptives containing norgestimate and ethinyl estradiol, prednisone, rifabutin, rilpivirine, sofosbuvir/velpatasvir, and tenofovir *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to TIVICAY or TIVICAY PD during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Data from two, ongoing birth outcome surveillance studies in Botswana and Eswatini

which together include over 14,000 individuals evaluated during pregnancy show similar prevalence of neural tube defects among infants born to individuals taking dolutegravir at the time of conception compared to those born to individuals taking non-dolutegravir-containing regimens at conception or infants born to HIV-negative individuals. *(see Data)*.

There are insufficient human data on the use of dolutegravir during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. However, available human data from the APR do not indicate an increased risk of birth defects *(see Data)*. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In animal reproduction studies, no evidence of adverse developmental outcomes (including neural tube defects) was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD) of TIVICAY *(see Data)*.

Data

Human Data:

Observational studies: The first interim analysis from an ongoing birth outcome surveillance study in Botswana identified an association between dolutegravir and an increased risk of neural tube defects when dolutegravir was administered at the time of conception and in early pregnancy. A subsequent analysis was conducted based on a larger cohort from the birth outcome surveillance study in Botswana and included over 9,460 individuals exposed to dolutegravir at conception, 23,664 individuals exposed to non-dolutegravir-containing regimens, and 170,723 HIV-negative pregnant individuals. The prevalence of neural tube defects in infants delivered to individuals taking dolutegravir at conception was 0.11% (95% CI: 0.05-0.19%). The observed prevalence rate did not differ significantly from that of infants delivered to individuals taking non-dolutegravir-containing regimens (0.11%, 95% CI: 0.07-0.16%), or to HIV-negative individuals (0.06%, 95% CI: 0.05-0.08%).

The Eswatini birth outcome surveillance study includes 9,743 individuals exposed to dolutegravir at conception, 1,838 individuals exposed to non-dolutegravir-containing regimens, and 32,259 HIV-negative pregnant individuals. The prevalence of neural tube defects in infants delivered to individuals taking dolutegravir at conception was 0.08% (95% CI: 0.04-0.16%). The observed prevalence rate did not differ significantly from that of infants delivered to individuals taking non-dolutegravir-containing regimens (0.22%, 95% CI: 0.06-0.56%) or to HIV-negative individuals (0.08%, 95% CI: 0.06-0.12%). The observed prevalence of neural tube defects in infants delivered to individuals taking non-dolutegravir-containing regimens had a wide confidence interval due to low sample size.

Limitations of these birth outcome surveillance studies include insufficient data to determine if baseline characteristics were balanced between the study groups or to assess other factors such as the use of folic acid during the preconception or first trimester periods.

Antiretroviral Pregnancy Registry: Based on prospective reports to the APR, of 1,377 exposures to dolutegravir during pregnancy resulting in live births (including 874 exposed in the first trimester), the prevalence of defects in live births was 3.3% (95% CI:

2.2% to 4.7%) following first-trimester exposure to dolutegravir-containing regimens and 5.0% (95% CI: 3.2% to 7.3%) following second-/third-trimester exposure to dolutegravir-containing regimens. In the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP), the background birth defect rate was 2.7%.

Dolutegravir has been shown to cross the placenta. In a clinical trial in Uganda and South Africa in women during the last trimester of pregnancy receiving dolutegravir 50 mg once daily, the ratio of median dolutegravir concentration in fetal umbilical cord to that in maternal peripheral plasma was 1.21 (range 0.51 to 2.11) (n = 15).

Animal Data: Dolutegravir was administered orally at up to 1,000 mg/kg daily to pregnant rats and rabbits on Gestation Days 6 to 17 and 6 to 18, respectively, and to rats on Gestation Day 6 to Lactation/Postpartum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed at up to the highest dose tested. During organogenesis, systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the MRHD and in rats were approximately 27 times the exposure in humans at the MRHD. In the rat pre/postnatal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 27 times human exposure at the MRHD).

8.2 Lactation

Risk Summary

Dolutegravir is present in human milk. It is not known whether dolutegravir affects human milk production or has effects on the breastfed infant.

Potential risks of breastfeeding include: (1) HIV-1 transmission (in HIV-1–negative infants), (2) developing viral resistance (in HIV-1–positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults.

8.4 Pediatric Use

Children and Adolescent Participants with HIV 1

The safety, pharmacokinetics, and effectiveness of TIVICAY and TIVICAY PD were evaluated in 75 treatment-naïve or treatment-experienced, INSTI-naïve pediatric and adolescent participants with HIV-1 aged 4 weeks to less than 18 years weighing at least 3 kg in an open-label, multicenter, dose-finding clinical trial, IMPAACT P1093 *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.3)]*. Additional pharmacokinetics data were evaluated in 2 pharmacokinetic substudies in ODYSSEY, an open-label, randomized, non-inferiority trial to evaluate the safety, efficacy, and pharmacokinetic parameters of TIVICAY or TIVICAY PD plus two NRTIs compared with standard of care in pediatric participants with HIV-1 younger than 18 years *[see Clinical Pharmacology (12.3)]*.

Overall, the safety data in pediatric participants from the IMPAACT P1093 trial were comparable to those observed in adults *[see Adverse Reactions (6.1)]*. The pharmacokinetic parameters of TIVICAY or TIVICAY PD in pediatric participants from IMPAACT P1093 and ODYSSEY were comparable to those of adults receiving 50 mg once daily or twice daily *[see Clinical Pharmacology (12.3)]*. The effectiveness observed in IMPAACT P1093 is comparable to that of treatment-experienced adult participants.

Neonates Exposed to HIV-1

The safety and pharmacokinetics of dolutegravir were evaluated in 48 term HIV-1 exposed neonates in a Phase I, open-label, multicenter clinical study (IMPAACT 2023). Dolutegravir was orally administered in 2 cohorts of neonates exposed to HIV-1, weighing at least 2 kg, receiving standard of care antiretroviral prophylaxis in the first 4 to 6 weeks of life. All enrolled neonates were followed for safety data for a duration of 16 weeks. Neonates in cohorts 1 and 2 were grouped based on dolutegravir exposure *in utero*. Cohort 1 included 18 neonates (12 were exposed, and 6 were unexposed to dolutegravir *in utero*) and received 2 single doses of dolutegravir: the first dose was administered within 5 days of birth, and the second dose 7 days later. Cohort 2 included 30 neonates (16 were exposed, and 14 were unexposed to dolutegravir *in utero*) who received a chronic dolutegravir dosing regimen through 4 to 6 weeks of life. Demographics included 63% female; 54% Black, 33% Asian, 6% White, 4% unknown, and 2% multi-racial. Among the 43 neonates with HIV test results available at Week 16 (End of Study), all were HIV-1 negative. Estimated dolutegravir exposures in neonates were higher compared to older pediatric and adult populations receiving dolutegravir once daily; however, the safety profile was similar *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3)]*.

Safety and effectiveness of TIVICAY or TIVICAY PD have not been established in pre-term neonates, pediatric patients weighing less than 2 kg, or in any pediatric patients who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs (e.g., raltegravir, elvitegravir).

8.5 Geriatric Use

Clinical trials of TIVICAY did not include sufficient numbers of participants aged 65 and older to determine whether they respond differently from younger participants. In general, caution should be exercised in the administration of TIVICAY in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

No clinically important pharmacokinetic differences between participants with moderate hepatic impairment and matching healthy participants were observed. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied. Therefore, TIVICAY and TIVICAY PD are not recommended for use in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Dolutegravir plasma concentrations were decreased in participants with severe renal impairment compared with those in matched healthy controls. However, no dosage adjustment is necessary for treatment-naïve or treatment-experienced and INSTI-naïve patients with mild, moderate, or severe renal impairment or for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance) with mild or moderate renal impairment. Caution is warranted for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or

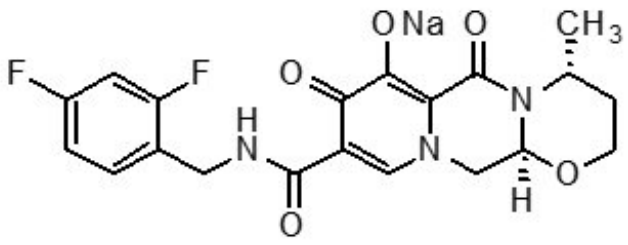
clinically suspected INSTI resistance *[see Microbiology (12.4)]*) with severe renal impairment, as the decrease in dolutegravir concentrations may result in loss of therapeutic effect and development of resistance to TIVICAY, TIVICAY PD, or other coadministered antiretroviral agents *[see Clinical Pharmacology (12.3)]*. There is inadequate information to recommend appropriate dosing of dolutegravir in patients requiring dialysis.

10 OVERDOSAGE

There is no known specific treatment for overdose with TIVICAY or TIVICAY PD. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

11 DESCRIPTION

TIVICAY contains dolutegravir, as dolutegravir sodium, an HIV INSTI. The chemical name of dolutegravir sodium is sodium (4*R*,12a*S*)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate. The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$, and the molecular weight is 441.36 g/mol. It has the following structural formula:



Dolutegravir sodium is a white to light yellow powder and is slightly soluble in water.

Each film-coated tablet of TIVICAY for oral administration contains 10.5, 26.3, or 52.6 mg of dolutegravir sodium, which is equivalent to 10, 25, or 50 mg dolutegravir free acid, respectively, and the following inactive ingredients: 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 (25-mg and 50-mg tablets only), macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

Each TIVICAY PD tablet for oral suspension contains 5.26 mg of dolutegravir sodium, which is equivalent to 5 mg dolutegravir free acid, and the following inactive ingredients: 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dolutegravir is an HIV-1 antiretroviral agent *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Effects on Electrocardiogram

In a randomized, placebo-controlled, cross-over trial, 42 healthy participants received single-dose oral administrations of placebo, dolutegravir 250-mg suspension (exposures approximately 3–fold of the 50-mg once-daily dose at steady state), and moxifloxacin 400 mg (active control) in random sequence. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) for dolutegravir was 2.4 msec (1-sided 95% upper CI: 4.9 msec). TIVICAY did not prolong the QTc interval over 24 hours postdose.

Effects on Renal Function

The effect of dolutegravir on renal function was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled trial in healthy participants (n = 37) who received dolutegravir 50 mg once daily (n = 12), dolutegravir 50 mg twice daily (n = 13), or placebo once daily (n = 12) for 14 days. A decrease in creatinine clearance, as determined by 24-hour urine collection, was observed with both doses of dolutegravir after 14 days of treatment in participants who received 50 mg once daily (9% decrease) and 50 mg twice daily (13% decrease). Neither dose of dolutegravir had a significant effect on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol) or effective renal plasma flow (determined by the clearance of probe drug, para-amino hippurate) compared with the placebo.

12.3 Pharmacokinetics

The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult participants and adult participants with HIV-1. Exposure to dolutegravir was generally similar between healthy participants and participants with HIV-1. The non-linear exposure of dolutegravir following 50 mg twice daily compared with 50 mg once daily in participants with HIV-1 (Table 9) was attributed to the use of metabolic inducers in the background antiretroviral regimens of participants receiving dolutegravir 50 mg twice daily in clinical trials.

Table 9. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in Adult Participants With HIV-1

Parameter	50 mg Once Daily Geometric Mean[a] (%CV)	50 mg Twice Daily Geometric Mean[b] (%CV)
$AUC_{(0-24)}$ (mcg·h/mL)	53.6 (27)	75.1 (35)
C_{max} (mcg/mL)	3.67 (20)	4.15 (29)
C_{min} (mcg/mL)	1.11 (46)	2.12 (47)

[a] Based on population pharmacokinetic analyses using data from SPRING-1 and SPRING-2.

[b] Based on population pharmacokinetic analyses using data from VIKING (ING112961) and VIKING-3.

TIVICAY tablets and TIVICAY PD tablets for oral suspension are not bioequivalent. The relative bioavailability of TIVICAY PD is approximately 1.6-fold higher than TIVICAY; therefore, the 2 dosage forms are not substitutable on a milligram-per-milligram basis *[see Dosage and Administration (2.1)].*

Absorption

Following oral administration of dolutegravir, peak plasma concentrations were observed 1 to 3 hours postdose. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and $C_{24\ h}$ ranging from 1.2 to 1.5.

Dolutegravir plasma concentrations increased in a less than dose-proportional manner above 50 mg. Dolutegravir is a P-gp substrate in vitro. The absolute bioavailability of dolutegravir has not been established.

Effect of Food: TIVICAY or TIVICAY PD may be taken with or without food. Food increased the extent of absorption and slowed the rate of absorption of dolutegravir following a 50-mg dose of TIVICAY. Low-, moderate-, and high-fat meals increased dolutegravir $AUC_{(0\text{-}\infty)}$ by 33%, 41%, and 66%; increased C_{max} by 46%, 52%, and 67%; and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively.

Distribution

Dolutegravir is highly bound (greater than or equal to 98.9%) to human plasma proteins based on in vivo data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50-mg once-daily administration is estimated at 17.4 L based on a population pharmacokinetic analysis.

Cerebrospinal Fluid (CSF): In 12 treatment-naïve participants on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 13.2 ng/mL (range: 3.74 ng/mL to 18.3 ng/mL) 2 to 6 hours postdose after 16 weeks of treatment. The clinical relevance of this finding has not been established.

Elimination

Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L/h based on population pharmacokinetic analyses.

Metabolism: Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A.

Polymorphisms in Drug Metabolizing Enzymes: In a meta-analysis of healthy participant trials, participants with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with participants with genotypes associated with normal metabolism via UGT1A1 (n = 41).

Excretion: After a single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose was excreted unchanged in feces. Thirty-one percent of the total oral dose was excreted in urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was low (less than 1% of the dose).

Specific Populations

Pediatric Patients: The pharmacokinetics of dolutegravir were evaluated in the IMPAACT P1093 trial and in 2 weight-band-based pharmacokinetic substudies from the ODYSSEY trial. Steady-state plasma exposure at doses by weight band are summarized in Table 10 *[see Clinical Studies (14.3)]*.

Geometric mean dolutegravir $AUC_{0\text{-}24h}$ and C_{24h} in pediatric participants with HIV-1 were comparable to those in adults after 50 mg once daily or 50 mg twice daily. Geometric mean C_{max} is higher in pediatrics, but the increase is not considered clinically significant as the safety profiles were similar in pediatric and adult participants *[see Use in Specific Populations (8.4)]*.

The pharmacokinetics of dolutegravir in term neonates exposed to HIV-1, from birth and weighing at least 2 kg, were evaluated in the IMPAACT 2023 study. Geometric mean dolutegravir C_{trough} in pediatric participants exposed to HIV-1 were comparable to those in older pediatric and adult participants with HIV-1. Geometric mean $AUC_{0\text{-}tau}$ and C_{max} is higher in neonates, but the increase is not considered clinically significant as the safety profiles were similar to older pediatric and adult participants.

Table 10. Summary of Pharmacokinetic Parameters in Pediatric Participants (Based on IMPAACT 2023, IMPAACT P1093, and ODYSSEY[a] Trials)

Weight Band	Dose[b] of TIVICAY or TIVICAY PD	n	Pharmacokinetic Parameter Geometric Mean (%CV)		
			C_{max} (mcg/mL)	$AUC_{0\text{-}tau}$ (mcg·h/mL)	C_{trough} (ng/mL)
Term Neonates Exposed to HIV-1					
≥2 kg	TIVICAY PD 5 mg every other day[c]	25	4.92 (35.8)	121 (54.7)	1,000 (168)
≥2 kg	TIVICAY PD 5 mg once daily[d]	22	5.62 (40.1)	90.3 (60.5)	2,250 (114)
Pediatric Participants with HIV-1					
3 kg to <6 kg	TIVICAY PD 5 mg once daily	8	3.80 (34)	49.37 (49)	962 (98)
6 kg to <10 kg	TIVICAY PD 15 mg once daily	17	5.27 (50)	57.17 (76)	706 (177)
10 kg to <14 kg	TIVICAY PD 20 mg once daily	13	5.99 (33)	68.75 (48)	977 (100)
14 kg to <20 kg	TIVICAY PD 25 mg once daily	19	5.97 (42)	58.97 (44)	725 (75)
20 kg to <25 kg	TIVICAY PD 30 mg once daily	9	7.16 (26)	71.53 (26)	759 (73)
≥20 kg	TIVICAY 50 mg once daily	49	4.92 (40)	54.98 (43)	778 (62)

[a] Data from 2 weight-band-based pharmacokinetic substudies in the ODYSSEY trial.

[b] The bioavailability of TIVICAY PD tablets for oral suspension is ~1.6-fold that of TIVICAY tablets.

[c] Day 1 to day 14 after birth

[d] Day 15 to day 28 after birth

Geriatric Patients: Population pharmacokinetic analysis indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir.

Patients with Hepatic Impairment: In a trial comparing 8 participants with moderate hepatic impairment (Child-Pugh Score B) with 8 matched healthy controls, exposure of dolutegravir from a single 50-mg dose was similar between the 2 groups. The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied.

Patients with Renal Impairment: In a trial evaluating the pharmacokinetics of a single 50-mg tablet of dolutegravir comparing 8 participants with severe renal impairment (CrCl less than 30 mL/min) with 8 matched healthy controls, AUC, C_{max}, and C_{24} of dolutegravir were lower by 40%, 23%, and 43%, respectively, compared with those in matched healthy participants. Population pharmacokinetic analysis using data from SAILING and VIKING-3 trials indicated that mild and moderate renal impairment had no clinically relevant effect on the exposure of dolutegravir. There is inadequate information to recommend appropriate dosing of dolutegravir in patients requiring dialysis.

HBV or HCV Co-infected Patients: Population analyses using pooled pharmacokinetic data from adult trials indicated no clinically relevant effect of HCV co-infection on the pharmacokinetics of dolutegravir. There were limited data on HBV co-infection.

Gender and Race: Population analyses using pooled pharmacokinetic data from adult trials indicated gender and race had no clinically relevant effect on the exposure of dolutegravir.

Drug Interaction Studies

Drug interaction trials were performed with TIVICAY and other drugs likely to be coadministered or commonly used as probes for pharmacokinetic interactions. The effects of dolutegravir on the exposure of coadministered drugs are summarized in Table 11 and the effects of coadministered drugs on the exposure of dolutegravir are summarized in Table 12.

Dosing or regimen recommendations as a result of established and other potentially significant drug-drug interactions with TIVICAY are provided in Table 8 *[see Dosage and Administration (2.2), Drug Interactions (7.3)]*.

Table 11. Summary of Effect of Dolutegravir on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	**Dose of TIVICAY**	**n**	**Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00**		
			C_{max}	**AUC**	**C_{τ} or C_{24}**
Elbasvir 50 mg once daily	50 mg single dose	12	0.97 (0.89, 1.05)	0.98 (0.93, 1.04)	0.98 (0.93, 1.03)
Ethinyl estradiol	50 mg	15	0.99	1.03	1.02

0.035 mg	twice daily		(0.91 to 1.08)	(0.96 to 1.11)	(0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	12	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	–
Metformin 500 mg twice daily	50 mg twice daily	15[a]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	–
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0.94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	–	0.95 (0.79 to 1.15)	–
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Sofosbuvir 400 mg once daily	50 mg once daily	24	0.88 (0.80, 0.98)	0.92 (0.85, 0.99)	NA
Metabolite (GS-331007)			1.01 (0.93, 1.10)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)
Velpatasvir 100 mg once daily	50 mg once daily	24	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)

[a] The number of participants represents the maximum number of participants that were evaluated.

Table 12. Summary of Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

Coadministered Drug(s) and Dose(s)	Dose of TIVICAY	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	C_T 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	30 mg	15	0.89	0.78	0.62

600/100 mg twice daily	once daily		(0.83 to 0.97)	(0.72 to 0.85)	(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)
Elbasvir/grazoprevir 50/200 mg once daily	50 mg single dose	12	1.22 (1.05, 1.40)	1.16 (1.00, 1.34)	1.14 (0.95, 1.36)
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)
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[a]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
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 participants represents the maximum number of participants 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/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 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 Participants: No participant 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 participants in SINGLE had treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1 participant with 275 copies/mL HIV-1 RNA had a treatment-emergent Q157Q/P integrase substitution detected at Week 24. None of these participants 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 Participants: In the dolutegravir arm of the SAILING trial for treatment-experienced and INSTI-naïve participants (n = 354), treatment-emergent integrase substitutions were observed in 6

of 28 (21%) participants who had virologic failure and resistance data. In 5 of the 6 participants' 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 participant isolates was less than 2-fold. One participant 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%) participants 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 Participants: SWORD-1 and SWORD-2 are identical trials in virologically suppressed participants 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 participants (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 participant 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 participant 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 participants meeting confirmed virologic failure in the comparative current antiretroviral regimen arms at Week 48.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Participants: VIKING-3 examined the efficacy of dolutegravir 50 mg twice daily plus optimized background therapy in participants 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 participants 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 Participants 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 participants 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 participants with available baseline phenotypes through Week 48 (n = 163) (Table 14). These baseline phenotypic groups are based on participants 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 Participants 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 participants with virologic failure on the dolutegravir twice-daily regimen in VIKING-3 with HIV-1 RNA greater than 400 copies/mL at the failure timepoint, Week 48 or beyond, or the last timepoint on trial. Thirty-nine participants 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 participants 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 participants' 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 participants in the Week 48 resistance analysis**.**

In VIKING-4 (ING116529), 30 participants 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 participants 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/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 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/kg/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 Participants with HIV1

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,	SAILING (ING111762) (NCT01231516)	TIVICAY + BR (n = 354) Raltegravir + BR (n = 361)	48

INSTI-naïve			
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; BR = Background regimen; INSTI = integrase strand transfer inhibitor; OBT = Optimized background therapy; CAR = Current antiretroviral regimen.

14.2 Adult Participants

Treatment-Naïve Participants

In SPRING-2, 822 participants 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 participants included in the efficacy and safety analyses. At baseline, the median age of participants 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/mm^3, and 39% received EPZICOM; these characteristics were similar between treatment groups.

In SINGLE, 833 participants 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 participants 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/mL, and 53% had CD4+ cell count less than 350 cells/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 Participants 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	77%	75%	71%	47%

Heritage/Other				

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 participants 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/mm^3 in the group receiving TIVICAY and 264 cells/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/mm^3 in the group receiving TIVICAY + EPZICOM and 332 cells/mm^3 for the ATRIPLA group at 144 weeks. The adjusted difference between treatment arms and 95% CI was 46.9 cells/mm^3 (15.6 cells/mm^3, 78.2 cells/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 participants 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 participants included in the efficacy and safety analyses. At baseline, the median age of participants 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/mL, and 35% had CD4+ cell count less than 350 cells/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 participants 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 participants 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 Participants

In the international, multicenter, double-blind trial (SAILING), 719 participants with HIV-1 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. These participants were antiretroviral treatment-experienced adults. There were 715 participants 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/mL, and 72% had CD4+ cell count less than 350 cells/mm^3; these characteristics were similar between treatment groups. All participants had at least 2-class antiretroviral treatment resistance, and 49% of participants 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/mm^3 in the group receiving TIVICAY and 153 cells/mm^3 in the raltegravir group.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Participants

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 adult participants with HIV-1 received TIVICAY 50 mg twice daily with the current failing background regimen for 7 days, then received TIVICAY with OBT from Day 8. These participants were antiretroviral treatment-experienced, with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance. A total of 183 participants enrolled: 133 participants with INSTI resistance at screening and 50 participants with only historical evidence of resistance (and not at screening). At baseline, median age of participants 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/mm^3, median duration of prior antiretroviral treatment was 13 years, and 56% were CDC Class C. Participants 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, participants 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.

Participants 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/mm^3 at Week 48.

Virologically Suppressed Participants

SWORD-1 and SWORD-2 are identical 148-week, Phase III, randomized, multicenter, parallel-group, non-inferiority trials. A total of 1,024 adult participants with HIV-1 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/mL), with no history of treatment failure and no known substitutions associated with resistance to dolutegravir or rilpivirine received treatment in the trials. Participants 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). Participants 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 participants with plasma HIV-1 RNA less than 50 copies/mL at Week 48. The proportion of participants with HIV-1 RNA less than 50 copies/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 participants with HIV-1 RNA greater than or equal to 50 copies/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 participants who received TIVICAY plus rilpivirine from study start had plasma HIV-1 RNA less than 50 copies/mL (Snapshot algorithm). In participants 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 participants 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 Participants

IMPAACT P1093 is a Phase I/II, multicenter, open-label trial to evaluate the pharmacokinetic parameters, safety, tolerability, and efficacy of TIVICAY or TIVICAY PD in combination treatment regimens in infants, children, and adolescents with HIV-1 aged at least 4 weeks to 18 years. Participants 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 participants received the recommended dose (determined by weight and age) of TIVICAY or TIVICAY PD *[see*

Dosage and Administration (2.1, 2.3, 2.4)].

These 75 participants 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/mL, median CD4+ cell count was 1,225 cells/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/mL and 12% had a CDC HIV clinical classification of category C. The majority (80%) of participants were treatment-experienced, but all were INSTI-naïve. Most participants had previously used at least 1 NNRTI (44%) or 1 PI (76%).

Virologic outcomes from IMPAACT P1093 include participants 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 participants achieved HIV-1 RNA less than 50 copies/mL and 86% achieved HIV-1 RNA less than 400 copies/mL (Snapshot algorithm). The median CD4 count (percent) increase from baseline to Week 24 was 105 cells/mm^3 (5%). At Week 48, 69% of participants achieved HIV-1 RNA less than 50 copies/mL and 79% achieved HIV-1 RNA less than 400 copies/mL (Snapshot algorithm). The median CD4 count (percent) increase from baseline to Week 48 was 141 cells/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.

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 (5.4)]*.

Different Formulations Are Not Bioequivalent

Advise patients that TIVICAY and TIVICAY PD are not bioequivalent and are not substitutable 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 (2.2) and Warnings and Precautions (5.5)].*

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

Inform individuals with HIV-1 infection that the potential risks of breastfeeding include: (1) HIV-1 transmission (in HIV-1–negative infants), (2) developing viral resistance (in HIV-

1–positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults *[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 (5.5), 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

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TVC:21PI

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

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

What are 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 and children weighing at least 4.4 pounds (2 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 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 premature newborn babies, children who weigh less than 4.4 pounds (2 kg), or in children who have received certain types of HIV-1 medicine.

Who should not take TIVICAY or TIVICAY PD?
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 hepatitis C.
- are pregnant or plan to become pregnant.
  - Talk to your healthcare provider about the benefits and risks of treatment with TIVICAY or TIVICAY PD during pregnancy.
  - **Pregnancy Exposure Registry.** There is a pregnancy exposure registry for those who take TIVICAY or TIVICAY PD during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. TIVICAY and TIVICAY PD pass to your baby in your breast milk. Talk to your healthcare provider about the following risks to your baby from breastfeeding during treatment with TIVICAY and TIVICAY PD:
  - the HIV-1 virus may pass to your baby if your baby does not have HIV-1.
  - the HIV-1 virus may become harder to treat if your baby has HIV-1.
  - your baby may get side effects from TIVICAY or TIVICAY PD.

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.**
- **Do not** change your dose, switch medicines or stop taking TIVICAY or TIVICAY PD without talking to your healthcare provider first.
- Take TIVICAY or TIVICAY PD with or without food.
- Children should keep scheduled healthcare provider's visits because their dosage may be adjusted as they get older or gain weight.
- 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.**
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, take TIVICAY or TIVICAY PD at least 2 hours before or 6 hours after you take these medicines.
- If you take iron or calcium supplements by mouth during treatment with TIVICAY or TIVICAY PD:
    - If you take TIVICAY or TIVICAY PD with food, you may take these supplements at the same time that you take TIVICAY or TIVICAY PD.
    - 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.** Tell 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
- extreme 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 hepatitis 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. **Tell 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 in the upper 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 develop new symptoms of infection after you start treatment with TIVICAY or TIVICAY PD.
- **The most common side effects of TIVICAY or TIVICAY PD 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 PD 5 mg tablets for oral suspension at room temperature below 86°F (30°C).
- Store TIVICAY 10 mg tablets and TIVICAY PD 5 mg tablets for oral suspension 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 that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TIVICAY or TIVICAY PD that is written for health professionals.

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

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TVC:16PIL

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

This Patient Information has been approved by the U.S. Revised: 8/2026
Food and Drug Administration.

INSTRUCTIONS FOR USE
TIVICAY PD (TIV-eh-kay Pe De)
(dolutegravir)
tablets for oral suspension

This Instructions for Use contains information on how to prepare and give TIVICAY PD as a liquid (oral suspension).

Read this Instructions for Use before giving TIVICAY PD.

Follow the steps below, using clean drinking water to prepare and give a dose to an infant or a child who cannot swallow the tablets.

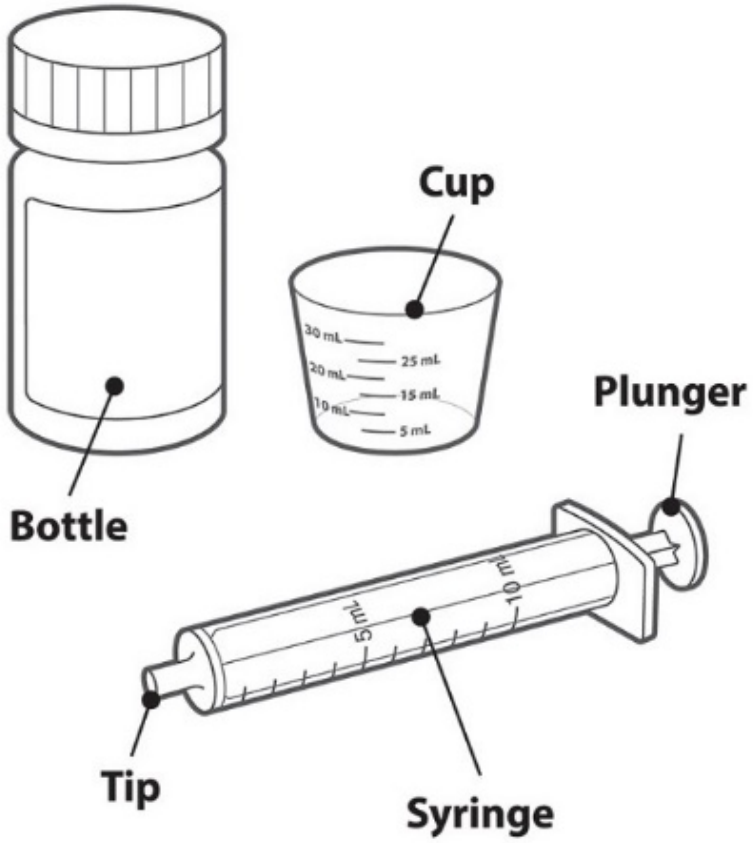
Important Information You Need to Know Before Preparing and Giving TIVICAY PD.

Always give this medicine exactly as your healthcare provider tells you. Talk to your healthcare provider if you are not sure.

- TIVICAY PD is for oral use only (taken by mouth).
- Take TIVICAY PD with or without food.
- TIVICAY PD may be swallowed whole or prepared as an oral suspension.
- **Do not** chew, cut, or crush the tablets.

- If you forget to give a dose of medicine, give it as soon as you remember. Do not give 2 doses at the same time or give more than your healthcare provider has prescribed.
- If your child does not or cannot take the full dose, tell your healthcare provider.
- If you give too much medicine, get emergency medical help right away.
- If your child is able and prefers to swallow the tablets, then you may skip the following steps.

Your pack contains:



- A bottle containing 60 **TIVICAY PD** tablets for oral suspension.
- Dosing kit:
  - **Cup:** Use this to prepare and give the medicine to **children.**
  - **Syringe:** Use this to give the medicine to **infants.**

You will also need clean drinking water.

Getting Ready
Step 1. Pour water

Water Volume Guide					
Number of tablets	1	3	4	5	6
Volume of water	5 mL		10 mL		



Figure A

- Pour clean drinking water into the cup.
  The Water Volume Guide in Figure A shows the amount of water needed for the prescribed dose.
  See Figure A.

Use drinking water only.
Do not use any other drink or food to prepare the dose.

Step 2. Prepare the medicine

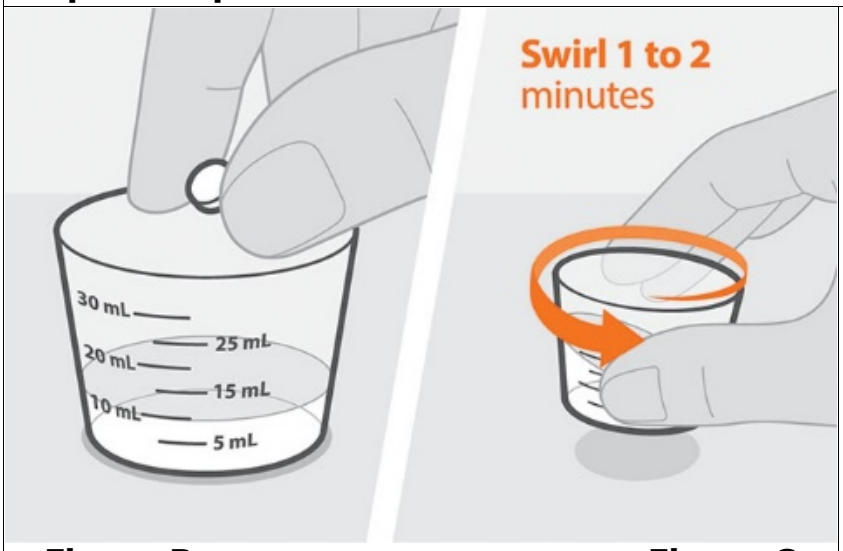


Figure B **Figure C**

- Add the prescribed number of tablets to the water. **See Figure B.**
- Swirl the cup gently for 1 to 2 minutes to disperse the tablets. The medicine will be cloudy. Take care not to spill any of the medicine. **See Figure C.**
- Check that the medicine is ready. If there are any lumps of tablets, swirl the cup until they are gone.

If you spill any medicine, clean up the spill.
Throw away the rest of the prepared medicine and make a new dose.
You must give the dose of medicine within 30 minutes of preparing the dose. If it has been more than 30 minutes, wash away all the dose in the cup using water and prepare a new dose of medicine.

Giving the medicine
Step 3. Give the medicine

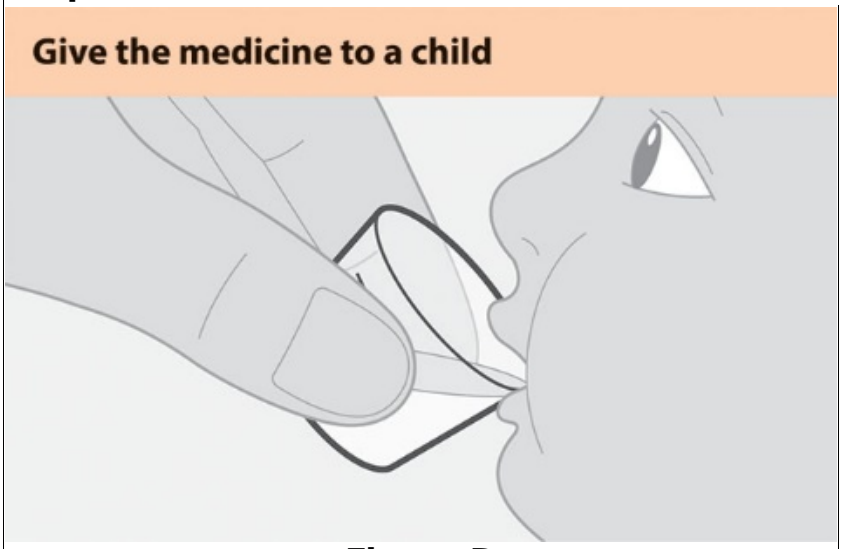


Figure D

- Make sure that the child is upright. Give all the prepared medicine to the child. **See Figure D.**
- Add another 5 mL of drinking water to the cup, swirl, and give it all to the child.
- **Repeat if any medicine remains in the cup to make sure the child gets the full dose.**

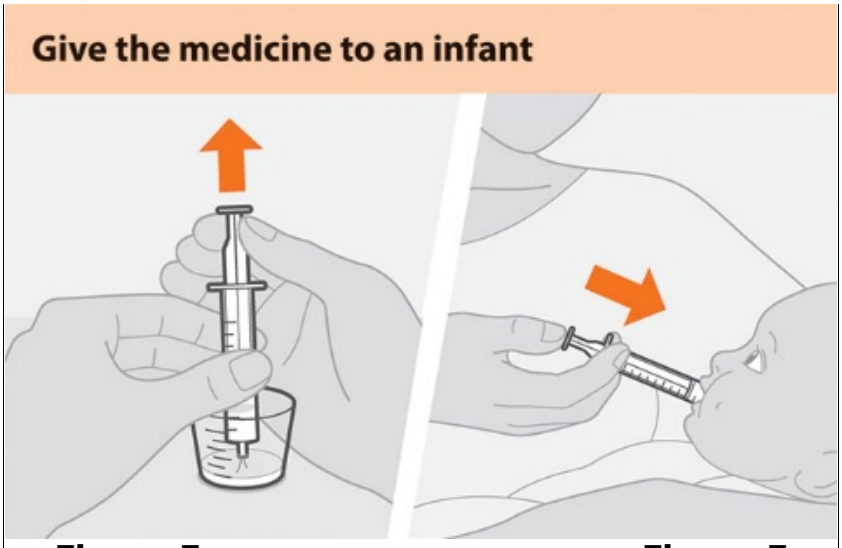


Figure E **Figure F**

- 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 Up
Step 4. Clean the dosing items

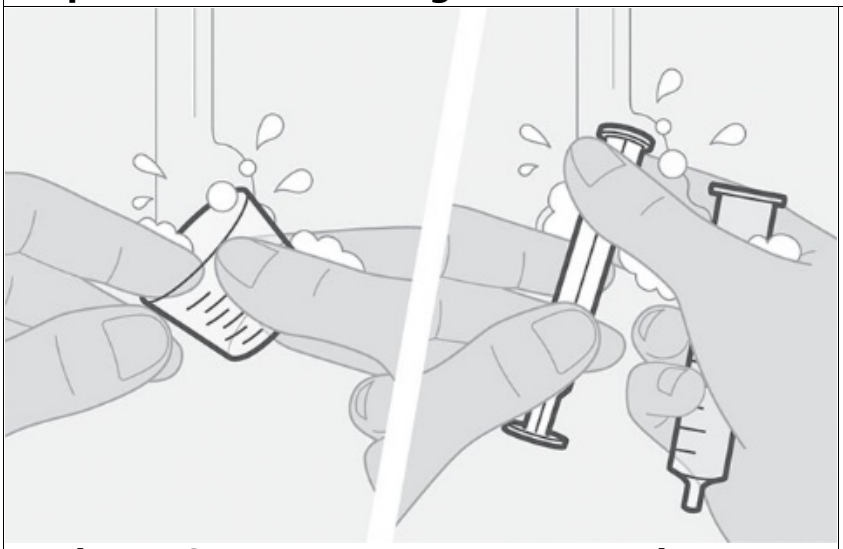


Figure G **Figure H**

- Wash the cup with water. **See Figure G.**
- Pull the plunger out of the syringe and wash the syringe parts separately with 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.

Storing TIVICAY PD

- Store TIVICAY PD tablets for oral suspension at room temperature below 86°F (30°C).
- Store TIVICAY PD tablets for oral suspension 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.

Disposing of TIVICAY PD

- When all the tablets in the bottle have been taken or are no longer needed, throw away the bottle, cup, and syringe based on your local household waste guidelines.
- You will get a new cup and syringe in your next pack.

Manufactured for:
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Durham, NC 27701
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TVC: 4IFU

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 8/2026

PRINCIPAL DISPLAY PANEL

NDC 49702-255-37

Tivicay PD

(dolutegravir) Tablets for Oral Suspension

5 mg

Rx Only

Tivicay and Tivicay PD are not interchangeable.

Each tablet contains 5 mg of dolutegravir equivalent to 5.26 mg of dolutegravir sodium.

Do not chew, cut, or crush tablet for oral suspension.

Do not accept if security seal is missing or broken.

See prescribing information for dosage information.

Contents:

- 1 Bottle of 60 tablets
- 1 Oral dosing syringe
- 1 Dosing cup
- Prescribing Information
- Instruction for Use

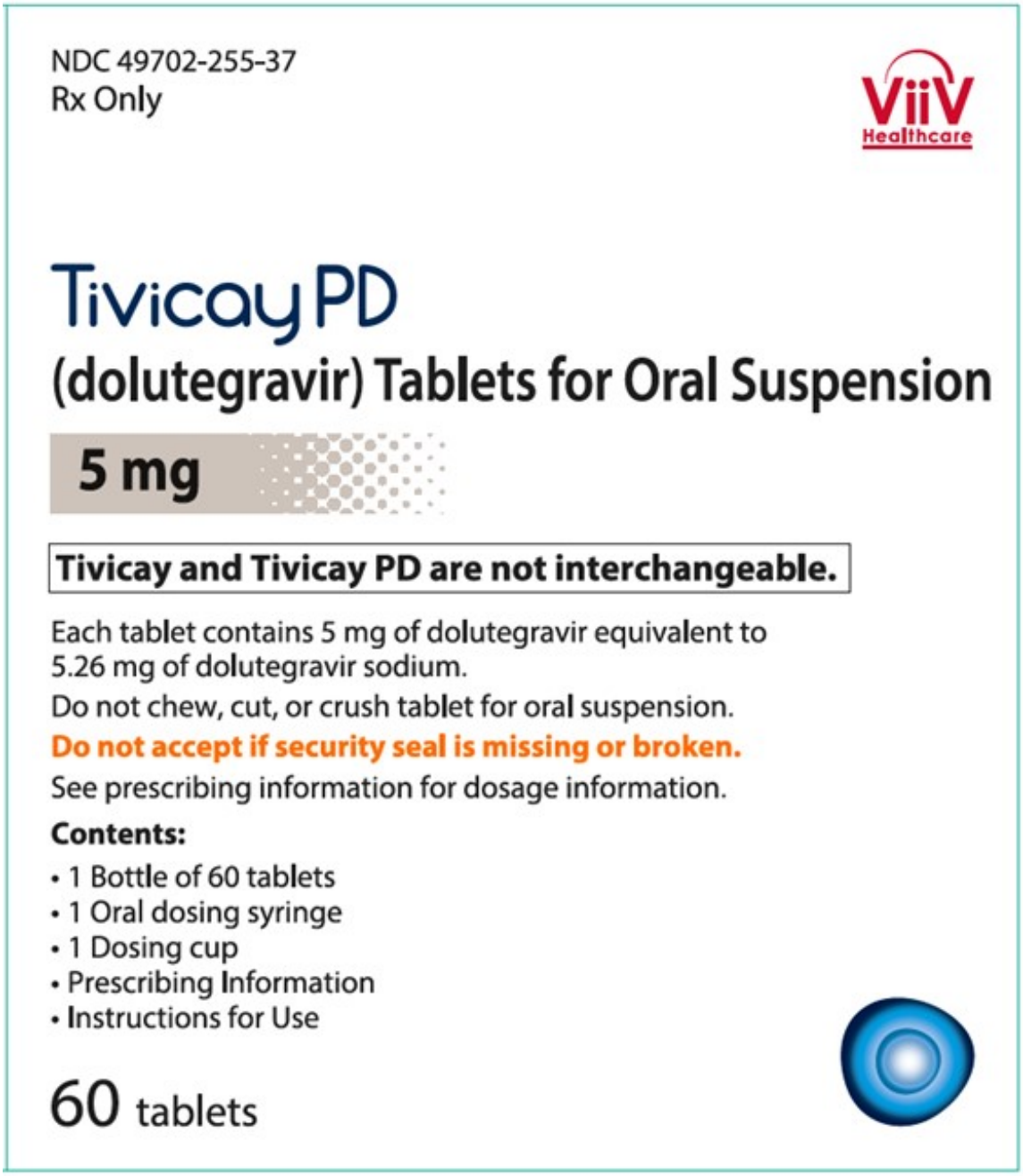
60 tablets

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Made in Japan

Rev. 1/2024

62000000091728



PRINCIPAL DISPLAY PANEL

NDC 49702-226-13

Tivicay

(dolutegravir)

Tablets

10 mg

Rx Only

Each film-coated tablet contains dolutegravir sodium equivalent to 10 mg of dolutegravir.

30 Tablets

Keep out of reach of children.

Store in original package at controlled room temperature of 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP].

Keep bottle tightly closed; protect from moisture. Do not remove desiccant.

Do not accept if membrane seal under cap is missing or broken.

See prescribing information for dosage information.

Manufactured for:

ViiV Healthcare

Durham, NC 27701

by:

GlaxoSmithKline

Durham, NC 27701

Made in Japan

Rev. 2/23

62000000085469



PRINCIPAL DISPLAY PANEL

NDC 49702-227-13

Tivicay

(dolutegravir)

Tablets

25 mg

Rx Only

Each film-coated tablet contains dolutegravir sodium equivalent to 25 mg of dolutegravir.

30 Tablets

Keep out of reach of children.

Store at controlled room temperature of 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP].

Do not accept if membrane seal under cap is missing or broken.

See prescribing information for dosage information.

Manufactured for:

ViiV Healthcare

Durham, NC 27701

by:

GlaxoSmithKline

Durham, NC 27701

Made in Japan

Rev. 2/23

62000000085470



PRINCIPAL DISPLAY PANEL

NDC 49702-228-13

Tivicay

(dolutegravir)

Tablets

50 mg

Rx Only

Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg of dolutegravir.

30 Tablets

Keep out of reach of children.

Store at controlled room temperature of 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP].

Do not accept if membrane seal under cap is missing or broken.

See prescribing information for dosage information.

Manufactured for:

ViiV Healthcare

Durham, NC 27701

by:

GlaxoSmithKline

Durham, NC 27701

Made in Japan

Rev. 2/23

62000000085468



TIVICAY PD

dolutegravir sodium tablet, for suspension

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:49702-255
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DOLUTEGRAVIR SODIUM (UNII: 1Q1V9V5WYQ) (DOLUTEGRAVIR - UNII:DKO1W9H7M1)	DOLUTEGRAVIR	5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CALCIUM SULFATE DIHYDRATE (UNII: 4846Q921YM)	
CROSPOVIDONE, UNSPECIFIED (UNII: 2S7830E561)	
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE K30 (UNII: U725QWY32X)	
SODIUM STARCH GLYCOLATE TYPE A CORN (UNII: AG9B65PV6B)	
SUCRALOSE (UNII: 96K6UQ3ZD4)	
SODIUM STEARYL FUMARATE (UNII: 7CV7WJK4UI)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor	STRAWBERRY (Strawberry Cream)	**Imprint Code**	SV;H75;5
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:49702-255-37	1 in 1 CARTON	06/12/2020	
1		60 in 1 BOTTLE; Type 1: Convenience Kit of Co-Package		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA213983	06/12/2020	

TIVICAY

dolutegravir sodium tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:49702-226
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DOLUTEGRAVIR SODIUM (UNII: 1Q1V9V5WYQ) (DOLUTEGRAVIR - UNII:DKO1W9H7M1)	DOLUTEGRAVIR	10 mg

Inactive Ingredients

Ingredient Name	Strength
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SODIUM STARCH GLYCOLATE TYPE A CORN (UNII: AG9B65PV6B)	
SODIUM STEARYL FUMARATE (UNII: 7CV7WJK4UI)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	SV;572;10
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49702-226-13	30 in 1 BOTTLE; Type 0: Not a Combination Product	06/09/2016	08/31/2027

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA204790	06/09/2016	08/31/2027

TIVICAY

dolutegravir sodium tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:49702-227
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DOLUTEGRAVIR SODIUM (UNII: 1Q1V9V5WYQ) (DOLUTEGRAVIR - UNII:DKO1W9H7M1)	DOLUTEGRAVIR	25 mg

Inactive Ingredients

Ingredient Name	Strength
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SODIUM STARCH GLYCOLATE TYPE A CORN (UNII: AG9B65PV6B)	
SODIUM STEARYL FUMARATE (UNII: 7CV7WJK4UI)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	YELLOW	**Score**	no score
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	SV;572;25
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49702-227-13	30 in 1 BOTTLE; Type 0: Not a Combination Product	06/09/2016	05/31/2027

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA204790	06/09/2016	05/31/2027

TIVICAY

dolutegravir sodium tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:49702-228
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DOLUTEGRAVIR SODIUM (UNII: 1Q1V9V5WYQ) (DOLUTEGRAVIR - UNII:DKO1W9H7M1)	DOLUTEGRAVIR	50 mg

Inactive Ingredients

Ingredient Name	Strength
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SODIUM STARCH GLYCOLATE TYPE A CORN (UNII: AG9B65PV6B)	
SODIUM STEARYL FUMARATE (UNII: 7CV7WJK4UI)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	YELLOW	**Score**	no score
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	SV;572;50
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49702-228-13	30 in 1 BOTTLE; Type 0: Not a Combination Product	08/13/2013	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA204790	08/13/2013	

Labeler - ViiV Healthcare Company (027295585)

Revised: 8/2026 ViiV Healthcare Company