Brand Name	Tivicay
Active Ingredient(s)	dolutegravir
Strength	50 mg
Dosage Form	tablet
Inactive Ingredients	D-mannitol, iron oxide yellow (25 mg and 50 mg tablets only), macrogol/PEG, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, sodium stearyl fumarate, polyvinyl alcohol – part hydrolyzed, talc, titanium dioxide
NDC	49702-228-13
DIN	02414945
Canadian Distributor	ViiV Healthcare ULC 1400 75 Rue Queen, Montreal, Quebec, Canada H3C 2N6
NDA Number	NDA204790
US Distributor (NDA Holder)	ViiV Healthcare 5 Moore Drive, Research Triangle Park, North Carolina USA 27709
Manufacturer (Final Packager)	Patheon Inc 2100 Syntex Ct, Mississauga ON L5N 7K9, Canada Janssen Cilag SpA Latina, Italy
API Manufacturer	Not available
Relationship to Sponsor	The Sponsor may have or have had agreements with the U.S. manufacturer for rebates. The Sponsor has no relationship with the foreign manufacturer.

Current FDA-approved Package Insert

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

---------- 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) aged at least 4 weeks and weighing at least 3 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 per 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----------

- Pregnancy Testing: Pregnancy testing is recommended before initiation of TIVICAY or TIVICAY PD in adolescents and adults of childbearing potential. (2.1, 5.3, 8.1, 8.3)
- May be taken without regard to food. (2.2, 2.6)

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] (2.2)	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A or CYP3A inducers (2.2, 7.2, 7.3)	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[b] (2.2, 12.4)	50 mg twice daily

[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 aged at least 4 weeks and weighing at least 3 kg. See Tables 2, 3, and 4 for complete pediatric dosing recommendations. (2.3, 2.4, 2.5). TIVICAY and TIVICAY PD are not bioequivalent and are not interchangeable on a milligram-per-milligram basis.

Pediatric Population Body Weight	Recommended Dose[a] TIVICAY PD Tablets for Oral Suspension
3 kg to less than 6 kg	5 mg once daily
6 kg to less than 10 kg	15 mg once daily
10 kg to less than 14 kg	20 mg once daily
14 kg to less than 20 kg	25 mg once daily
20 kg and greater	30 mg once daily

[a] If certain UGT1A or CYP3A inducers are coadministered, then adjust the weight-based dose of TIVICAY to twice daily. (2.4, 2.5, 7.2, 7.3)

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

- 14 kg to less than 20 kg: 40 mg once daily.
- 20 kg and greater: 50 mg 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)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Assess the risks and benefits of TIVICAY and TIVICAY PD and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. Adolescents and adults of childbearing potential should be counseled on the consistent use of effective contraception. (2.1, 5.3, 8.1, 8.3)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.5)
- TIVICAY tablets and TIVICAY PD tablets for oral suspension are not interchangeable. (2.3, 5.6)

---------- 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)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: Assess the risks and benefits of TIVICAY and TIVICAY PD and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. (2.1, 5.3, 8.1, 8.3)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
- Females and males of reproductive potential: Pregnancy testing is recommended in adolescents and adults of childbearing potential. Patients should be counseled on the consistent use of effective contraception. (8.1, 8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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) aged at least 4 weeks and weighing at least 3 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 per 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 Pregnancy Testing before Initiation

Pregnancy testing is recommended before initiation of TIVICAY or TIVICAY PD in adolescents and adults of childbearing potential *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

2.2 Recommended Dosage in Adults

TIVICAY tablets may be taken with or without food.

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 per 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 General Dosing and Administration Instructions for Pediatric Patients

Do not interchange TIVICAY tablets and TIVICAY PD tablets for oral suspension on a milligram-per-milligram basis due to differing pharmacokinetic profiles *[see Warnings and Precautions (5.6), 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 in *Dosage and Administration (2.6)*.

2.4 Recommended Dosage in Pediatric Patients Weighing 3 to 14 kg

The recommended weight-based dosage of TIVICAY PD tablets for oral suspension in **pediatric patients weighing 3 to 14 kg** (4 weeks and older, treatment-naïve, or treatment-experienced but naïve to INSTI treatment) is described in Table 2.

Do not use TIVICAY tablets in patients weighing 3 to 14 kg. See administration instructions in *Dosage and Administration (2.6).*

Table 2. Recommended Dosage of TIVICAY PD in Pediatric Patients 4 Weeks and Older Weighing 3 to 14 kg

	TIVICAY PD Tablets for Oral Suspension	
Body Weight	Daily Dose[a]	Number of 5-mg Tablets
3 kg to less than 6 kg	5 mg once daily	1
6 kg to less than 10 kg	15 mg once daily	3
10 kg to less than 14 kg	20 mg once daily	4

[a] If certain UGT1A or CYP3A inducers are coadministered, then administer TIVICAY PD twice daily *[see Drug Interactions (7.2, 7.3)]*.

2.5 Recommended Dosage in Pediatric Patients Weighing 14 kg or Greater

For **pediatric patients weighing 14 kg or greater** (4 weeks and older, treatment-naïve, or treatment-experienced but naïve to INSTI treatment) administer either:

- TIVICAY PD tablets for oral suspension (preferred in pediatric patients weighing less than 20 kg) (Table 3), or
- TIVICAY tablets for oral use (Table 4)

Table 3. Recommended Dosage of TIVICAY PD Tablets for Oral Suspension in Pediatric Patients Weighing 14 kg or Greater

	TIVICAY PD Tablets for Oral Suspension	
Body Weight	**Daily Dose[a]**	**Number of 5-mg Tablets**
14 kg to less than 20 kg	25 mg once daily	5
20 kg and greater	30 mg once daily	6

[a] If certain UGT1A or CYP3A inducers are coadministered, then administer TIVICAY PD twice daily *[see Drug Interactions (7.2, 7.3)]*.

Table 4. Recommended Dosage of TIVICAY Tablets in Pediatric Patients Weighing 14 kg or Greater

	TIVICAY Tablets	
Body Weight	**Daily Dose[a]**	**Number of Tablets**
14 kg to less than 20 kg	40 mg once daily	4 x 10-mg
20 kg and greater	50 mg once daily	1 x 50-mg

[a] If certain UGT1A or CYP3A inducers are coadministered, then administer TIVICAY twice daily *[see Drug Interactions (7.2, 7.3)]*.

2.6 Additional Administration Instructions

Administer TIVICAY tablets and TIVICAY PD tablets for oral suspension with or without food.

Administration Instructions for TIVICAY PD

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 subjects receiving TIVICAY in Phase 3 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 Embryo-Fetal Toxicity

An ongoing observational study showed 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. As there is limited understanding of the association of reported types of neural tube defects with dolutegravir use, inform adolescents and adults of childbearing potential, including those actively trying to become pregnant, about the potential increased risk of neural tube defects with TIVICAY and TIVICAY PD. Assess the risks and benefits of TIVICAY and TIVICAY PD and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester *[see Use in Specific Populations (8.1, 8.3)]*.

Pregnancy testing is recommended before initiation of TIVICAY or TIVICAY PD in adolescents and adults of childbearing potential *[see Dosage and Administration (2.1)]*.

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

TIVICAY or TIVICAY PD may be considered during the second and third trimesters of pregnancy if the expected benefit justifies the potential risk to the pregnant woman and the fetus.

5.4 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.

5.5 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.

5.6 Different Formulations Are Not Interchangeable

TIVICAY and TIVICAY PD are not bioequivalent and are not interchangeable 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 (2.3)].* 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 (5.5)]*.

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 Subjects

Treatment-Naïve Subjects: The safety assessment of TIVICAY in HIV-1–infected treatment-naïve subjects 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 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) treatment (either abacavir sulfate and lamivudine [EPZICOM] or emtricitabine/tenofovir [TRUVADA]). There were 808 subjects 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 subjects 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 subjects receiving TIVICAY 50 mg once daily + EPZICOM and 14% in subjects receiving ATRIPLA once daily.

Treatment-emergent adverse reactions of moderate to severe intensity observed in at least 2% of subjects 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 Subjects 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%

[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 subjects 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 subjects received TIVICAY 50 mg once daily versus 242 subjects 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 subjects included in the efficacy and safety analyses. Through 96 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving TIVICAY and 6% in subjects 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 Subjects: In an international, multicenter, double-blind trial (ING111762, SAILING), 719 HIV-1–infected, antiretroviral treatment-experienced adults were randomized and received either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving TIVICAY 50 mg once daily + background regimen and 4% in subjects 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 subjects receiving TIVICAY 50 mg once daily + background regimen and 1% (5 of 361) in subjects receiving raltegravir 400 mg twice daily + background regimen.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: In a multicenter, open-label, single-arm trial (ING112574, VIKING-3), 183 HIV-1–infected, antiretroviral treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received TIVICAY 50 mg twice daily with the current failing background regimen for 7 days and with optimized background therapy from Day 8. The rate of adverse events leading to discontinuation was 4% of subjects 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 3 trials.

Virologically Suppressed Subjects: 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 HIV-1–infected, virologically suppressed subjects 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 subjects receiving TIVICAY plus rilpivirine once daily and less than 1% in subjects who remained on their current antiretroviral regimen. In the pooled analyses, the proportion of subjects 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 subjects 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 subjects 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 Subjects: Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects 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 Subjects 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 amino transferase; AST = Aspartate amino transferase; ULN = Upper limit of normal.

Table 7. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects 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.

[a] Subjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SPRING-2, and in SINGLE: TIVICAY + EPZICOM n = 30 and ATRIPLA n = 27). Ninety-four subjects 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 Subjects: 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 Subjects: 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 subjects 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 3 trials.

Hepatitis B and/or Hepatitis C Virus Co-infection: In Phase 3 trials, subjects 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 subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects 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 subjects 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 subjects 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 subjects, a mean change from baseline of 0.15 mg per dL (range: -0.32 mg per dL to 0.65 mg per dL) was observed after 96 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced subjects.

Clinical Trials Experience in Pediatric Subjects

The safety and pharmacokinetics of TIVICAY and TIVICAY PD in HIV-1–infected pediatric subjects 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 an ongoing, multicenter, open-label, non-comparative trial of HIV-1–infected pediatric subjects 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 subjects (n = 75) who received the recommended dose (determined by weight and age) through Week 24 showed that 11% of subjects experienced drug-related clinical adverse reactions. The only Grade 1 to 2 drug-related clinical adverse reactions reported by more than one subject 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 subject 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.

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.

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, increase the weight-based dose of TIVICAY or TIVICAY PD to twice daily (Tables 2, 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 inhibitor: Nevirapine	↓Dolutegravir	Avoid coadministration with nevirapine because there are insufficient data to make 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, increase the weight-based dose of TIVICAY or TIVICAY PD to twice daily (Tables 2, 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, increase the weight-based dose of TIVICAY or TIVICAY PD to twice daily (Tables 2, 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, increase the weight-based dose of TIVICAY or TIVICAY PD to twice daily (Tables 2, 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, daclatasvir, 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 an ongoing birth outcome surveillance study has identified an increased risk of neural tube defects when dolutegravir is administered at the time of conception. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk.

Advise adolescents and adults of childbearing potential, including those actively trying to become pregnant, of the potential risk of neural tube defects with use of TIVICAY and TIVICAY PD. Assess the risks and benefits of TIVICAY and TIVICAY PD and discuss with the

patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester. A benefit-risk assessment should consider factors such as feasibility of switching to another antiretroviral regimen, tolerability, ability to maintain viral suppression, and risk of HIV-1 transmission to the infant against the risk of neural tube defects associated with in utero dolutegravir exposure during critical periods of fetal development *[see Warnings and Precautions (5.3)]*.

There are insufficient human data on the use of dolutegravir during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. 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 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: In a birth outcome surveillance study in Botswana, there were 7 cases of neural tube defects reported out of 3,591 deliveries (0.19%) to women who were exposed to dolutegravir-containing regimens at the time of conception. In comparison, the neural tube defect prevalence rates were 0.11% (21/19,361 deliveries) in the non-dolutegravir arm and 0.07% (87/119,630 deliveries) in the HIV-uninfected arm. Seven cases reported with dolutegravir included 3 cases of myelomeningocele, 2 cases of encephalocele, and one case each of anencephaly and iniencephaly. In the same study, no increased risk of neural tube defects was identified in women who started dolutegravir during pregnancy. Two infants out of 4,448 (0.04%) deliveries to women who started dolutegravir during pregnancy had a neural tube defect, compared with 5 infants out of 6,748 (0.07%) deliveries to women who started non-dolutegravir-containing regimens during pregnancy. The reported risks of neural tube defects by treatment groups were based on interim analyses from the ongoing surveillance study in Botswana. It is unknown if baseline characteristics were balanced between the study treatment groups. The observed trends of association could change as data accumulate.

Data analyzed to date from other sources including the APR, clinical trials, and postmarketing data are insufficient to definitively address the risk of neural tube defects with dolutegravir.

Data from the birth outcome surveillance study described above and postmarketing sources with more than 1,000 pregnancy outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes.

Based on prospective reports to the APR of 842 exposures to dolutegravir during pregnancy resulting in live births (including 512 exposed in the first trimester), the prevalence of defects in

live births was 3.3% (95% CI: 1.9% to 5.3%) following first-trimester exposure to dolutegravir-containing regimens and 4.8% (95% CI: 2.8% to 7.8%) 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 0.51-2.11) (n = 15).

Animal Data: Dolutegravir was administered orally at up to 1,000 mg per 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

The Centers for Disease Control and Prevention recommends that HIV-1–infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

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

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving dolutegravir.

8.3 Females and Males of Reproductive Potential

In adolescents and adults of childbearing potential currently on TIVICAY or TIVICAY PD who are actively trying to become pregnant or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing TIVICAY or TIVICAY PD and discuss with the patient if an alternative treatment should be considered *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing is recommended in adolescents and adults of childbearing potential before initiation of TIVICAY or TIVICAY PD *[see Dosage and Administration (2.1)]*.

Contraception

Adolescents and adults of childbearing potential who are taking TIVICAY or TIVICAY PD should be counseled on the consistent use of effective contraception.

8.4 Pediatric Use

The safety, pharmacokinetics, and effectiveness of TIVICAY and TIVICAY PD were evaluated in 75 HIV-1–infected, treatment-naïve or treatment-experienced, INSTI-naïve pediatric and adolescent subjects aged 4 weeks to less than 18 years weighing at least 3 kg in an ongoing, 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 ongoing 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 HIV-1–infected pediatric subjects younger than 18 years *[see Clinical Pharmacology (12.3)]*.

Overall, the safety data in pediatric subjects 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 subjects 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 subjects.

Safety and effectiveness of TIVICAY or TIVICAY PD have not been established in pediatric patients aged less than 4 weeks or weighing less than 3 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 subjects aged 65 and older to determine whether they respond differently from younger subjects. 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 subjects with moderate hepatic impairment and matching healthy subjects 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

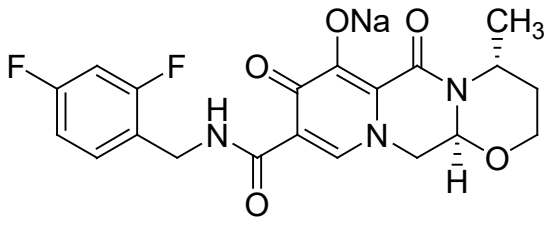
Dolutegravir plasma concentrations were decreased in subjects with severe renal impairment compared with those in matched healthy controls. However, no dosage adjustment is necessary for treatment-naïve or treatment-experienced and INSTI-naïve patients with mild, moderate, or severe renal impairment 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 per 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 subjects 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 subjects (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 subjects 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 subjects and HIV-1–infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1–infected subjects. The non-linear exposure of dolutegravir following 50 mg twice daily compared with 50 mg once daily in HIV-1–infected subjects (Table 9) was attributed to the use of metabolic inducers in the background antiretroviral regimens of subjects receiving dolutegravir 50 mg twice daily in clinical trials.

Table 9. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV-1–Infected Adults

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 interchangeable on a milligram-per-milligram basis *[see Dosage and Administration (2.3)]*.

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 $AUC_{(0-\infty)}$ 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 subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 13.2 ng per mL (range: 3.74 ng per mL to 18.3 ng per 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 per hour 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 subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects 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)]*.

Mean dolutegravir $AUC_{0\text{-}24h}$ and C_{24h} in HIV-1–infected pediatric subjects were comparable to those in adults after 50 mg once daily or 50 mg twice daily. 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 subjects *[see Use in Specific Populations (8.4)]*.

Table 10. Summary of Pharmacokinetic Parameters in Pediatric HIV-1–Infected Subjects (Pooled Analyses for 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)	$AUC_{0\text{-}24h}$ (mcg·h/mL)	C_{24h} (ng/mL)
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.

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 subjects 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 subjects with severe renal impairment (CrCl less than 30 mL per 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 subjects. 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}
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
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 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (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 Metabolite (GS-331007)	50 mg once daily	24	0.88 (0.80, 0.98) 1.01 (0.93, 1.10)	0.92 (0.85, 0.99) 0.99 (0.97, 1.01)	NA 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 subjects represents the maximum number of subjects 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_τ or C_{24}
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
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)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[c] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

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

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

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

12.4 Microbiology

Mechanism of Action

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

Antiviral Activity in Cell Culture

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

Antiviral Activity in Combination with Other Antiviral Agents

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

Resistance

Cell Culture: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold. Passage of mutant viruses containing the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutions included T97A, E138K, G140S, and M154I. Passage of mutant viruses containing both G140S and Q148H selected for L74M, E92Q, and N155H.

Treatment-Naïve Subjects: No subject who received dolutegravir 50-mg once-daily in the treatment-naïve trials SPRING-2 (96 weeks) and SINGLE (144 weeks) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 12 with HIV-1 RNA greater than 400 copies per mL at failure or last visit and having resistance data). Two virologic failure subjects in SINGLE had treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1 subject with 275 copies per mL HIV-1 RNA had a treatment-emergent Q157Q/P integrase substitution detected at Week 24. None of these subjects had a corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to the background regimen was observed in the dolutegravir arm in either the SPRING-2 or SINGLE trials. No treatment-emergent primary resistance substitutions were observed in either treatment group in the FLAMINGO trial through Week 96.

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

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

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

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

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

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

Response by Baseline Genotype

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

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

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

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

INSTI = integrase strand transfer inhibitor.

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

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

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

Response by Baseline Phenotype

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

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

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

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

Integrase Strand Transfer Inhibitor Treatment-Emergent Resistance

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

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

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

Cross-Resistance

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Description of Clinical Studies

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

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

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

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

14.2 Adult Subjects

Treatment-Naïve Subjects

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

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

efavirenz/emtricitabine/tenofovir (ATRIPLA). At baseline, the median age of subjects was 35 years, 16% female, 32% non-white, 7% had hepatitis C co-infection (hepatitis B virus co-infection was excluded), 4% were CDC Class C (AIDS), 32% had HIV-1 RNA greater than 100,000 copies per mL, and 53% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment groups.

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

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

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

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

NRTI = Nucleoside reverse transcriptase inhibitor.

[a] Adjusted for pre-specified stratification factors.

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

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

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

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

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

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

SINGLE: Treatment differences were maintained across baseline characteristics including baseline viral load, CD4+ cell count, age, gender, and race.

The adjusted mean changes in CD4+ cell counts from baseline were 378 cells per mm^3 in the group receiving TIVICAY + EPZICOM and 332 cells per mm^3 for the ATRIPLA group at 144 weeks. The adjusted difference between treatment arms and 95% CI was 46.9 cells per mm^3 (15.6 cells per mm^3, 78.2 cells per mm^3) (adjusted for pre-specified stratification factors: baseline HIV-1 RNA, and baseline CD4+ cell count).

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

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

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects

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

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

	TIVICAY 50 mg Once Daily + BR[a] (n = 354)	**Raltegravir 400 mg Twice Daily + BR[a] (n = 361)**
HIV-1 RNA <50 copies/mL	71%	64%
Adjusted[b] treatment difference	7.4% (95% CI: 0.7%, 14.2%)	
Virologic nonresponse	20%	28%
No virologic data	9%	9%
Reasons		
Discontinued study/study drug due to adverse event or death	3%	4%

Discontinued study/study drug for other reasons[c]	5%	4%
Missing data during window but on study	2%	1%
Proportion (%) with HIV-1 RNA <50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤50,000 copies/mL	75%	71%
>50,000 copies/mL	62%	47%
Background regimen		
No darunavir use	67%	60%
Darunavir use with primary PI substitutions	85%	67%
Darunavir use without primary PI substitutions	69%	70%
Gender		
Male	70%	66%
Female	74%	60%
Race		
White	75%	71%
African-American/African Heritage/Other	67%	57%

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

[b] Adjusted for pre-specified stratification factors.

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

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

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

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects

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

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

75% greater than or equal to 1 NNRTI, and 71% greater than or equal to 2 PI major substitutions; 62% had non-R5 virus.

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

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

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

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

OBT = Optimized Background Therapy.

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

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

Virologically Suppressed Subjects

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

antiretroviral regimen and who remained virologically suppressed at Week 48 switched to TIVICAY plus rilpivirine at Week 52 (n = 477).

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

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

14.3 Pediatric Subjects

IMPAACT P1093 is an ongoing Phase 1/2, multicenter, open-label trial to evaluate the pharmacokinetic parameters, safety, tolerability, and efficacy of TIVICAY or TIVICAY PD in combination treatment regimens in HIV-1–infected infants, children, and adolescents aged at least 4 weeks to 18 years. Subjects were stratified by 5 age cohorts: Cohort 1, aged 12 to less than 18 years; Cohort 2A, aged 6 to less than 12 years; Cohort 3, aged 2 to less than 6 years; Cohort 4, aged 6 months to less than 2 years; and Cohort 5, aged 4 weeks to less than 6 months. Seventy-five subjects received the recommended dose (determined by weight and age) of TIVICAY or TIVICAY PD *[see Dosage and Administration (2.3, 2.4, 2.5)]*.

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

Virologic outcomes from IMPAACT P1093 include subjects who received either TIVICAY tablets or TIVICAY PD tablets for oral suspension as per the dosing recommendations for their weight band and who had reached Week 24 (n = 58) or Week 48 (n = 42). At Week 24, 62% of

subjects achieved HIV-1 RNA less than 50 copies per mL and 86% achieved HIV-1 RNA less than 400 copies per mL (Snapshot algorithm). The median CD4 count (percent) increase from baseline to Week 24 was 105 cells per mm^3 (5%). At Week 48, 69% of subjects achieved HIV-1 RNA less than 50 copies per mL and 79% achieved HIV-1 RNA less than 400 copies per mL (Snapshot algorithm). The median CD4 count (percent) increase from baseline to Week 48 was 141 cells per mm^3 (7%).

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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

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

TIVICAY PD tablets for oral suspension, 5 mg, are white, round, strawberry cream flavored, film-coated, biconvex tablets debossed with "SV H7S" on one side and "5" on the other side. Bottle of 60 tablets with child-resistant closure containing a desiccant. Each bottle is packaged with one 30-mL dosing cup and one 10-mL oral dosing syringe with 1-mL gradations. NDC 49702-255-37.

Store TIVICAY PD tablets for oral suspension below 30°C (86°F). Store and dispense the 5-mg tablets in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

17 PATIENT COUNSELING INFORMATION

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

Drug Interactions

TIVICAY or TIVICAY PD may interact with other drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or

herbal products, including St. John's wort *[see Contraindications (4), Warnings and Precautions (5.4), Drug Interactions (7)]*.

Hypersensitivity Reactions

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

Hepatotoxicity

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

Embryo-Fetal Toxicity

Advise adolescents and adults of childbearing potential, including those actively trying to become pregnant, to discuss the risks and benefits of TIVICAY and TIVICAY PD with their healthcare provider to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy. If pregnancy is confirmed in the first trimester, advise patients to contact their healthcare provider *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

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

Immune Reconstitution Syndrome

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

Different Formulations Are Not Bioequivalent

Advise patients that TIVICAY and TIVICAY PD are not bioequivalent and are not interchangeable on a milligram-per-milligram basis. Advise patients or their care provider that

patients switching from one formulation to the other must adjust the dose for the new dosage formulation *[see Dosage and Administration (2.3) and Warnings and Precautions (5.6)]*.

Pregnancy Registry

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

Lactation

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

Administration Instructions

To avoid a dosing error from using the wrong formulation of dolutegravir, strongly advise patients and caregivers to visually inspect the tablets to verify the correct formulation each time the prescription is filled *[see Dosage and Administration (2), Warnings and Precautions (5.6), How Supplied/Storage and Handling (16)]*.

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

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

Storage

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

Manufactured for:

ViiV Healthcare

ViiV Healthcare
Durham, NC 27701

by:
GlaxoSmithKline
Durham, NC 27701

TVC:18PI

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

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

What is TIVICAY and TIVICAY PD?

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

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

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

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

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

Do not take TIVICAY or TIVICAY PD if you:

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

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

- have or have had liver problems, including hepatitis B or C infection.
- are pregnant or plan to become pregnant. TIVICAY or TIVICAY PD may harm your unborn baby.
  - Your healthcare provider may prescribe a different medicine than TIVICAY or TIVICAY PD if you are planning to become pregnant or if pregnancy is confirmed during the first 12 weeks of pregnancy
  - If you can become pregnant, your healthcare provider may perform a pregnancy test before you start treatment with TIVICAY or TIVICAY PD.
  - If you can become pregnant, you and your healthcare provider should talk about the use of effective birth control (contraception) during treatment with TIVICAY or TIVICAY PD.
  - Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with TIVICAY or TIVICAY PD.

Pregnancy Registry. There is a pregnancy registry for individuals who take antiretroviral medicines, including TIVICAY and TIVICAY PD, during pregnancy. The purpose of this registry is to collect

information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take TIVICAY or TIVICAY PD.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - TIVICAY and TIVICAY PD pass to your baby in your breast milk.
    Talk with your healthcare provider about the best way to feed your baby.

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

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

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

How should I take TIVICAY or TIVICAY PD?

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

- Stay under the care of a healthcare provider during treatment with TIVICAY or TIVICAY PD.
- Do not run out of TIVICAY or TIVICAY PD. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too much TIVICAY or TIVICAY PD, call your healthcare provider or go to the nearest hospital emergency room right away.

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

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

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

How should I store TIVICAY or TIVICAY PD?

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

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

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

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

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

What are the ingredients in TIVICAY and TIVICAY PD?

Active ingredient: dolutegravir.

Inactive ingredients:

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

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

Manufactured for:

ViiV Healthcare
Durham, NC 27701

by:

GlaxoSmithKline
Durham, NC 27701

TVC:13PIL

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 10/2022

INSTRUCTIONS FOR USE

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

Read this Instructions for Use before giving a dose of medicine.

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

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

Do not chew, cut, or crush the tablets.

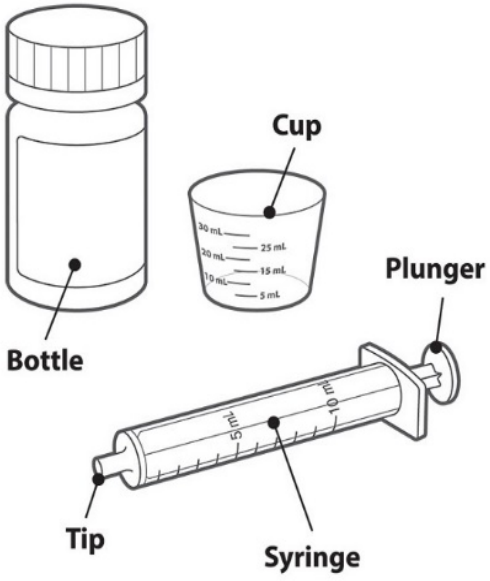
If you forget to give a dose of medicine, give it as soon as you remember. Do not give 2 doses at the same time or give more than your healthcare provider has prescribed.

If your child does not or cannot take the full dose, call 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

- Pour clean drinking water into the cup.

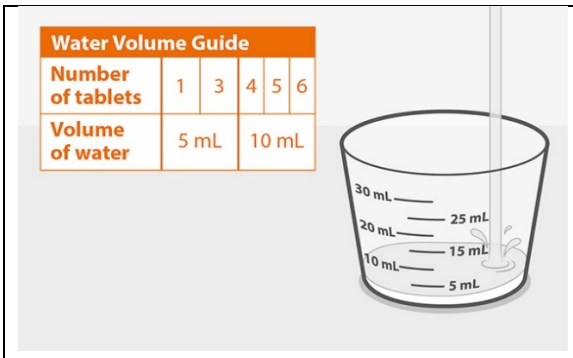


Figure A

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

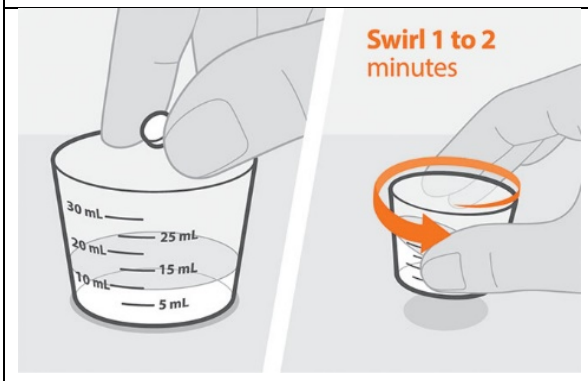


Figure B **Figure C**

- Add the prescribed number of tablet(s) to the water. **See Figure B.**
- Swirl the cup gently for 1 to 2 minutes to disperse the tablet(s). The medicine will become 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 tablet, 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

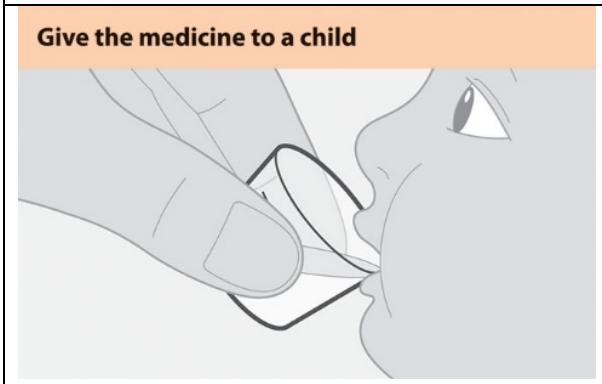


Figure D

- 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.**

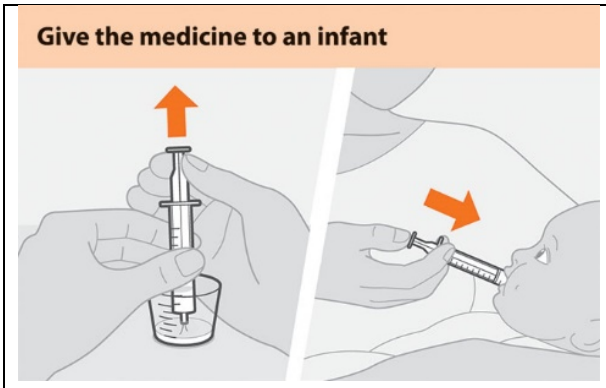


Figure E **Figure F**

- 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

Step 4. Clean the dosing items

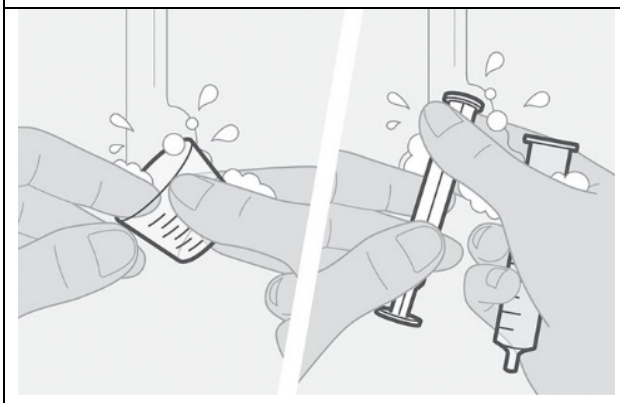


Figure G **Figure H**

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

Storage Information

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

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

Disposal Information

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

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

Manufactured for:

ViiV Healthcare
Durham, NC 27701

by:
GlaxoSmithKline
Durham, NC 27701

TVC: 2IFU

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: 10/2022

Proposed Package Insert

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
Initial U.S. Approval: 2013
The 10 mg tablets 25 mg tablets and 5 mg tablets for oral suspension (Tivicay PD) are not being imported by LifeScience Logistics.

---------- 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) aged at least 4 weeks and weighing at least 3 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 per 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----------
- Pregnancy Testing: Pregnancy testing is recommended before initiation of TIVICAY in adolescents and adults of childbearing potential. (2.1, 5.3, 8.1, 8.3)
- May be taken without regard to food. (2.2, 2.6)

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] (2.2)	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A or CYP3A inducers (2.2, 7.2, 7.3)	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[b] (2.2, 12.4)	50 mg twice daily

[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.

---------- DOSAGE FORMS AND STRENGTHS ----------
- TIVICAY tablets: 50 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)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Assess the risks and benefits of TIVICAY and TIVICAY PD and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. Adolescents and adults of childbearing potential should be counseled on the consistent use of effective contraception. (2.1, 5.3, 8.1, 8.3)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.5)
- TIVICAY tablets and TIVICAY PD tablets for oral suspension are not interchangeable. (2.3, 5.6)

---------- 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 LifeScience Logistics at 1-855-738-6171 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)

---------- USE IN SPECIFIC POPULATIONS ----------
- Pregnancy: Assess the risks and benefits of TIVICAY and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. (2.1, 5.3, 8.1, 8.3)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
- Females and males of reproductive potential: Pregnancy testing is recommended in adolescents and adults of childbearing potential. Patients should be counseled on the consistent use of effective contraception. (8.1, 8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TIVICAY 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) aged at least 4 weeks and weighing at least 3 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 per 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 Pregnancy Testing before Initiation

Pregnancy testing is recommended before initiation of TIVICAY in adolescents and adults of childbearing potential *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

2.2 Recommended Dosage in Adults

TIVICAY tablets may be taken with or without food.

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 per 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 General Dosing and Administration Instructions for Pediatric Patients

Do not interchange TIVICAY tablets and TIVICAY PD tablets for oral suspension on a milligram-per-milligram basis due to differing pharmacokinetic profiles *[see Warnings and Precautions (5.6), 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 in *Dosage and Administration (2.6)*.

2.4 Recommended Dosage in Pediatric Patients Weighing 3 to 14 kg

The recommended weight-based dosage of TIVICAY PD tablets for oral suspension in **pediatric patients weighing 3 to 14 kg** (4 weeks and older, treatment-naïve, or treatment-experienced but naïve to INSTI treatment) is described in Table 2.

Do not use TIVICAY tablets in patients weighing 3 to 14 kg. See administration instructions in *Dosage and Administration (2.6).*

Table 2. Recommended Dosage of TIVICAY PD in Pediatric Patients 4 Weeks and Older Weighing 3 to 14 kg

	TIVICAY PD Tablets for Oral Suspension	
Body Weight	Daily Dose[a]	Number of 5-mg Tablets
3 kg to less than 6 kg	5 mg once daily	1
6 kg to less than 10 kg	15 mg once daily	3
10 kg to less than 14 kg	20 mg once daily	4

[a] If certain UGT1A or CYP3A inducers are coadministered, then administer TIVICAY PD twice daily *[see Drug Interactions (7.2, 7.3)]*.

2.5 Recommended Dosage in Pediatric Patients Weighing 14 kg or Greater

For **pediatric patients weighing 14 kg or greater** (4 weeks and older, treatment-naïve, or treatment-experienced but naïve to INSTI treatment) administer:

- The 10 mg, 25 mg, 50 mg tablets and 5 mg tablets for oral suspension are not being imported by LifeScience Logistics.
- TIVICAY tablets for oral use (Table 4)

Table 3. Recommended Dosage of TIVICAY PD Tablets for Oral Suspension in Pediatric Patients Weighing 14 kg or Greater

	TIVICAY PD Tablets for Oral Suspension	
Body Weight	**Daily Dose[a]**	**Number of 5-mg Tablets**
14 kg to less than 20 kg	25 mg once daily	5
20 kg and greater	30 mg once daily	6

[a] If certain UGT1A or CYP3A inducers are coadministered, then administer TIVICAY PD twice daily *[see Drug Interactions (7.2, 7.3)]*.

The 10 mg, 25 mg, 50 mg tablets and 5 mg tablets for oral suspension are not being imported by LifeScience Logistics.

Table 4. Recommended Dosage of TIVICAY Tablets in Pediatric Patients Weighing 14 kg or Greater

	TIVICAY Tablets	
Body Weight	**Daily Dose[a]**	**Number of Tablets**
14 kg to less than 20 kg	40 mg once daily	4 x 10-mg
20 kg and greater	50 mg once daily	1 x 50-mg

[a] If certain UGT1A or CYP3A inducers are coadministered, then administer TIVICAY twice daily *[see Drug Interactions (7.2, 7.3)]*.

2.6 Additional Administration Instructions

Administer TIVICAY tablets with or without food.

The 10 mg tablets 25 mg tablets and 5 mg tablets for oral suspension (Tivicay PD) are not being imported by LifeScience Logistics.

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:

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.

The 10 mg tablets 25 mg tablets and 5 mg tablets for oral suspension (Tivicay PD) are not being imported by LifeScience Logistics.

4 CONTRAINDICATIONS

TIVICAY 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 subjects receiving TIVICAY in Phase 3 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

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 Embryo-Fetal Toxicity

An ongoing observational study showed 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. As there is limited understanding of the association of reported types of neural tube defects with dolutegravir use, inform adolescents and adults of childbearing potential, including those actively trying to become pregnant, about the potential increased risk of neural tube defects with TIVICAY and TIVICAY PD. Assess the risks and benefits of TIVICAY and TIVICAY PD and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester *[see Use in Specific Populations (8.1, 8.3)]*.

Pregnancy testing is recommended before initiation of TIVICAY or TIVICAY PD in adolescents and adults of childbearing potential *[see Dosage and Administration (2.1)]*.

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

TIVICAY or TIVICAY PD may be considered during the second and third trimesters of pregnancy if the expected benefit justifies the potential risk to the pregnant woman and the fetus.

5.4 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.

5.5 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.

5.6 Different Formulations Are Not Interchangeable

TIVICAY and TIVICAY PD are not bioequivalent and are not interchangeable 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 (2.3)].* 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 (5.5)]*.

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 Subjects

Treatment-Naïve Subjects: The safety assessment of TIVICAY in HIV-1–infected treatment-naïve subjects 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 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) treatment (either abacavir sulfate and lamivudine [EPZICOM] or emtricitabine/tenofovir [TRUVADA]). There were 808 subjects 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 subjects 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 subjects receiving TIVICAY 50 mg once daily + EPZICOM and 14% in subjects receiving ATRIPLA once daily.

Treatment-emergent adverse reactions of moderate to severe intensity observed in at least 2% of subjects 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 Subjects 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%

[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 subjects 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 subjects received TIVICAY 50 mg once daily versus 242 subjects 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 subjects included in the efficacy and safety analyses. Through 96 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving TIVICAY and 6% in subjects 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 Subjects: In an international, multicenter, double-blind trial (ING111762, SAILING), 719 HIV-1–infected, antiretroviral treatment-experienced adults were randomized and received either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving TIVICAY 50 mg once daily + background regimen and 4% in subjects 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 subjects receiving TIVICAY 50 mg once daily + background regimen and 1% (5 of 361) in subjects receiving raltegravir 400 mg twice daily + background regimen.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: In a multicenter, open-label, single-arm trial (ING112574, VIKING-3), 183 HIV-1–infected, antiretroviral treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received TIVICAY 50 mg twice daily with the current failing background regimen for 7 days and with optimized background therapy from Day 8. The rate of adverse events leading to discontinuation was 4% of subjects 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 3 trials.

Virologically Suppressed Subjects: 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 HIV-1–infected, virologically suppressed subjects 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 subjects receiving TIVICAY plus rilpivirine once daily and less than 1% in subjects who remained on their current antiretroviral regimen. In the pooled analyses, the proportion of subjects 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 subjects 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 subjects 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 Subjects: Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects 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 Subjects 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 amino transferase; AST = Aspartate amino transferase; ULN = Upper limit of normal.

Table 7. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects 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.

[a] Subjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SPRING-2, and in SINGLE: TIVICAY + EPZICOM n = 30 and ATRIPLA n = 27). Ninety-four subjects 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 Subjects: 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 Subjects: 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 subjects 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 3 trials.

Hepatitis B and/or Hepatitis C Virus Co-infection: In Phase 3 trials, subjects 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 subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects 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 subjects 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 subjects 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 subjects, a mean change from baseline of 0.15 mg per dL (range: -0.32 mg per dL to 0.65 mg per dL) was observed after 96 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced subjects.

Clinical Trials Experience in Pediatric Subjects

The safety and pharmacokinetics of TIVICAY and TIVICAY PD in HIV-1–infected pediatric subjects 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 an ongoing, multicenter, open-label, non-comparative trial of HIV-1–infected pediatric subjects 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 subjects (n = 75) who received the recommended dose (determined by weight and age) through Week 24 showed that 11% of subjects experienced drug-related clinical adverse reactions. The only Grade 1 to 2 drug-related clinical adverse reactions reported by more than one subject 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 subject 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.

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.

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, increase the weight-based dose of TIVICAY or TIVICAY PD to twice daily (Tables 2, 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 inhibitor: Nevirapine	↓Dolutegravir	Avoid coadministration with nevirapine because there are insufficient data to make 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, increase the weight-based dose of TIVICAY or TIVICAY PD to twice daily (Tables 2, 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, increase the weight-based dose of TIVICAY or TIVICAY PD to twice daily (Tables 2, 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, increase the weight-based dose of TIVICAY or TIVICAY PD to twice daily (Tables 2, 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, daclatasvir, 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 an ongoing birth outcome surveillance study has identified an increased risk of neural tube defects when dolutegravir is administered at the time of conception. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk.

Advise adolescents and adults of childbearing potential, including those actively trying to become pregnant, of the potential risk of neural tube defects with use of TIVICAY and TIVICAY PD. Assess the risks and benefits of TIVICAY and TIVICAY PD and discuss with the

patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester. A benefit-risk assessment should consider factors such as feasibility of switching to another antiretroviral regimen, tolerability, ability to maintain viral suppression, and risk of HIV-1 transmission to the infant against the risk of neural tube defects associated with in utero dolutegravir exposure during critical periods of fetal development *[see Warnings and Precautions (5.3)]*.

There are insufficient human data on the use of dolutegravir during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. 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 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: In a birth outcome surveillance study in Botswana, there were 7 cases of neural tube defects reported out of 3,591 deliveries (0.19%) to women who were exposed to dolutegravir-containing regimens at the time of conception. In comparison, the neural tube defect prevalence rates were 0.11% (21/19,361 deliveries) in the non-dolutegravir arm and 0.07% (87/119,630 deliveries) in the HIV-uninfected arm. Seven cases reported with dolutegravir included 3 cases of myelomeningocele, 2 cases of encephalocele, and one case each of anencephaly and iniencephaly. In the same study, no increased risk of neural tube defects was identified in women who started dolutegravir during pregnancy. Two infants out of 4,448 (0.04%) deliveries to women who started dolutegravir during pregnancy had a neural tube defect, compared with 5 infants out of 6,748 (0.07%) deliveries to women who started non-dolutegravir-containing regimens during pregnancy. The reported risks of neural tube defects by treatment groups were based on interim analyses from the ongoing surveillance study in Botswana. It is unknown if baseline characteristics were balanced between the study treatment groups. The observed trends of association could change as data accumulate.

Data analyzed to date from other sources including the APR, clinical trials, and postmarketing data are insufficient to definitively address the risk of neural tube defects with dolutegravir.

Data from the birth outcome surveillance study described above and postmarketing sources with more than 1,000 pregnancy outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes.

Based on prospective reports to the APR of 842 exposures to dolutegravir during pregnancy resulting in live births (including 512 exposed in the first trimester), the prevalence of defects in

live births was 3.3% (95% CI: 1.9% to 5.3%) following first-trimester exposure to dolutegravir-containing regimens and 4.8% (95% CI: 2.8% to 7.8%) 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 0.51-2.11) (n = 15).

Animal Data: Dolutegravir was administered orally at up to 1,000 mg per 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

The Centers for Disease Control and Prevention recommends that HIV-1–infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

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

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving dolutegravir.

8.3 Females and Males of Reproductive Potential

In adolescents and adults of childbearing potential currently on TIVICAY or TIVICAY PD who are actively trying to become pregnant or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing TIVICAY or TIVICAY PD and discuss with the patient if an alternative treatment should be considered *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing is recommended in adolescents and adults of childbearing potential before initiation of TIVICAY or TIVICAY PD *[see Dosage and Administration (2.1)]*.

Contraception

Adolescents and adults of childbearing potential who are taking TIVICAY or TIVICAY PD should be counseled on the consistent use of effective contraception.

8.4 Pediatric Use

The safety, pharmacokinetics, and effectiveness of TIVICAY and TIVICAY PD were evaluated in 75 HIV-1–infected, treatment-naïve or treatment-experienced, INSTI-naïve pediatric and adolescent subjects aged 4 weeks to less than 18 years weighing at least 3 kg in an ongoing, 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 ongoing 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 HIV-1–infected pediatric subjects younger than 18 years *[see Clinical Pharmacology (12.3)]*.

Overall, the safety data in pediatric subjects 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 subjects 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 subjects.

Safety and effectiveness of TIVICAY or TIVICAY PD have not been established in pediatric patients aged less than 4 weeks or weighing less than 3 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 subjects aged 65 and older to determine whether they respond differently from younger subjects. 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 subjects with moderate hepatic impairment and matching healthy subjects 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

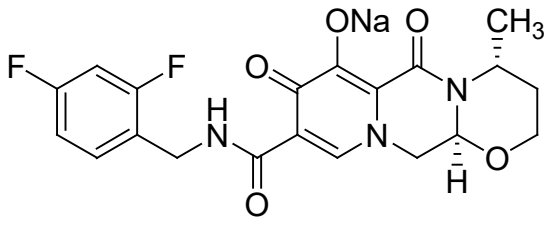
Dolutegravir plasma concentrations were decreased in subjects with severe renal impairment compared with those in matched healthy controls. However, no dosage adjustment is necessary for treatment-naïve or treatment-experienced and INSTI-naïve patients with mild, moderate, or severe renal impairment 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 per 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 subjects 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 subjects (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 subjects 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 subjects and HIV-1–infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1–infected subjects. The non-linear exposure of dolutegravir following 50 mg twice daily compared with 50 mg once daily in HIV-1–infected subjects (Table 9) was attributed to the use of metabolic inducers in the background antiretroviral regimens of subjects receiving dolutegravir 50 mg twice daily in clinical trials.

Table 9. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV-1–Infected Adults

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 interchangeable on a milligram-per-milligram basis *[see Dosage and Administration (2.3)]*.

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 $AUC_{(0-\infty)}$ 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 subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 13.2 ng per mL (range: 3.74 ng per mL to 18.3 ng per 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 per hour 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 subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects 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)]*.

Mean dolutegravir $AUC_{0\text{-}24h}$ and C_{24h} in HIV-1–infected pediatric subjects were comparable to those in adults after 50 mg once daily or 50 mg twice daily. 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 subjects *[see Use in Specific Populations (8.4)]*.

Table 10. Summary of Pharmacokinetic Parameters in Pediatric HIV-1–Infected Subjects (Pooled Analyses for 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)	$AUC_{0\text{-}24h}$ (mcg·h/mL)	C_{24h} (ng/mL)
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.

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 subjects 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 subjects with severe renal impairment (CrCl less than 30 mL per 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 subjects. 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}
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
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 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (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 Metabolite (GS-331007)	50 mg once daily	24	0.88 (0.80, 0.98) 1.01 (0.93, 1.10)	0.92 (0.85, 0.99) 0.99 (0.97, 1.01)	NA 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 subjects represents the maximum number of subjects 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_τ or C_{24}
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
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)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[c] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

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

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

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

12.4 Microbiology

Mechanism of Action

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

Antiviral Activity in Cell Culture

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

Antiviral Activity in Combination with Other Antiviral Agents

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

Resistance

Cell Culture: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold. Passage of mutant viruses containing the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutions included T97A, E138K, G140S, and M154I. Passage of mutant viruses containing both G140S and Q148H selected for L74M, E92Q, and N155H.

Treatment-Naïve Subjects: No subject who received dolutegravir 50-mg once-daily in the treatment-naïve trials SPRING-2 (96 weeks) and SINGLE (144 weeks) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 12 with HIV-1 RNA greater than 400 copies per mL at failure or last visit and having resistance data). Two virologic failure subjects in SINGLE had treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1 subject with 275 copies per mL HIV-1 RNA had a treatment-emergent Q157Q/P integrase substitution detected at Week 24. None of these subjects had a corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to the background regimen was observed in the dolutegravir arm in either the SPRING-2 or SINGLE trials. No treatment-emergent primary resistance substitutions were observed in either treatment group in the FLAMINGO trial through Week 96.

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

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

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

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

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

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

Response by Baseline Genotype

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

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

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

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

INSTI = integrase strand transfer inhibitor.

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

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

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

Response by Baseline Phenotype

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

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

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

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

Integrase Strand Transfer Inhibitor Treatment-Emergent Resistance

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

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

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

Cross-Resistance

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Description of Clinical Studies

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

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

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

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

14.2 Adult Subjects

Treatment-Naïve Subjects

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

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

efavirenz/emtricitabine/tenofovir (ATRIPLA). At baseline, the median age of subjects was 35 years, 16% female, 32% non-white, 7% had hepatitis C co-infection (hepatitis B virus co-infection was excluded), 4% were CDC Class C (AIDS), 32% had HIV-1 RNA greater than 100,000 copies per mL, and 53% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment groups.

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

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

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

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

NRTI = Nucleoside reverse transcriptase inhibitor.

[a] Adjusted for pre-specified stratification factors.

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

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

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

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

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

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

SINGLE: Treatment differences were maintained across baseline characteristics including baseline viral load, CD4+ cell count, age, gender, and race.

The adjusted mean changes in CD4+ cell counts from baseline were 378 cells per mm^3 in the group receiving TIVICAY + EPZICOM and 332 cells per mm^3 for the ATRIPLA group at 144 weeks. The adjusted difference between treatment arms and 95% CI was 46.9 cells per mm^3 (15.6 cells per mm^3, 78.2 cells per mm^3) (adjusted for pre-specified stratification factors: baseline HIV-1 RNA, and baseline CD4+ cell count).

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

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

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects

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

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

	TIVICAY 50 mg Once Daily + BR[a] (n = 354)	**Raltegravir 400 mg Twice Daily + BR[a] (n = 361)**
HIV-1 RNA <50 copies/mL	71%	64%
Adjusted[b] treatment difference	7.4% (95% CI: 0.7%, 14.2%)	
Virologic nonresponse	20%	28%
No virologic data	9%	9%
Reasons		
Discontinued study/study drug due to adverse event or death	3%	4%

Discontinued study/study drug for other reasons[c]	5%	4%
Missing data during window but on study	2%	1%
Proportion (%) with HIV-1 RNA <50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤50,000 copies/mL	75%	71%
>50,000 copies/mL	62%	47%
Background regimen		
No darunavir use	67%	60%
Darunavir use with primary PI substitutions	85%	67%
Darunavir use without primary PI substitutions	69%	70%
Gender		
Male	70%	66%
Female	74%	60%
Race		
White	75%	71%
African-American/African Heritage/Other	67%	57%

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

[b] Adjusted for pre-specified stratification factors.

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

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

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

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects

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

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

75% greater than or equal to 1 NNRTI, and 71% greater than or equal to 2 PI major substitutions; 62% had non-R5 virus.

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

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

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

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

OBT = Optimized Background Therapy.

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

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

Virologically Suppressed Subjects

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

antiretroviral regimen and who remained virologically suppressed at Week 48 switched to TIVICAY plus rilpivirine at Week 52 (n = 477).

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

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

14.3 Pediatric Subjects

IMPAACT P1093 is an ongoing Phase 1/2, multicenter, open-label trial to evaluate the pharmacokinetic parameters, safety, tolerability, and efficacy of TIVICAY in combination treatment regimens in HIV-1–infected infants, children, and adolescents aged at least 4 weeks to 18 years. Subjects were stratified by 5 age cohorts: Cohort 1, aged 12 to less than 18 years; Cohort 2A, aged 6 to less than 12 years; Cohort 3, aged 2 to less than 6 years; Cohort 4, aged 6 months to less than 2 years; and Cohort 5, aged 4 weeks to less than 6 months. Seventy-five subjects received the recommended dose (determined by weight and age) of TIVICAY or TIVICAY PD *[see Dosage and Administration (2.3, 2.4, 2.5)]*.

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

Virologic outcomes from IMPAACT P1093 include subjects who received either TIVICAY tablets as per the dosing recommendations for their weight band and who had reached Week 24 (n = 58) or Week 48 (n = 42). At Week 24, 62% of

subjects achieved HIV-1 RNA less than 50 copies per mL and 86% achieved HIV-1 RNA less than 400 copies per mL (Snapshot algorithm). The median CD4 count (percent) increase from baseline to Week 24 was 105 cells per mm^3 (5%). At Week 48, 69% of subjects achieved HIV-1 RNA less than 50 copies per mL and 79% achieved HIV-1 RNA less than 400 copies per mL (Snapshot algorithm). The median CD4 count (percent) increase from baseline to Week 48 was 141 cells per mm^3 (7%).

16 HOW SUPPLIED/STORAGE AND HANDLING

TIVICAY tablets, 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 42067-280-30.

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

The 10 mg tablets 25 mg tablets and 5 mg tablets for oral suspension (Tivicay PD) are not being imported by LifeScience Logistics.

This drug was imported from Canada without the authorization of ViiV Healthcare or GlaxoSmithKline under the State of Florida Section 804 Importation Program.
Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

17 PATIENT COUNSELING INFORMATION

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

Drug Interactions

TIVICAY 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 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 is recommended, especially for patients with liver disease, such as hepatitis B or C.

Embryo-Fetal Toxicity

Advise adolescents and adults of childbearing potential, including those actively trying to become pregnant, to discuss the risks and benefits of TIVICAY with their healthcare provider to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy. If pregnancy is confirmed in the first trimester, advise patients to contact their healthcare provider *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

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

Immune Reconstitution Syndrome

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

Different Formulations Are Not Bioequivalent

Advise patients or their care provider that

patients switching from one formulation to the other must adjust the dose for the new dosage formulation *[see Dosage and Administration (2.3) and Warnings and Precautions (5.6)]*.

Pregnancy Registry

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

Lactation

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

Administration Instructions

To avoid a dosing error from using the wrong formulation of dolutegravir, strongly advise patients and caregivers to visually inspect the tablets to verify the correct formulation each time the prescription is filled *[see Dosage and Administration (2), Warnings and Precautions (5.6), How Supplied/Storage and Handling (16)]*.

Instruct patients and caregivers that if a dose of TIVICAY 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

Do not remove desiccant *[see How Supplied/Storage and Handling (16)]*.

Manufactured for:

ViiV Healthcare
Durham, NC 27701

by:
GlaxoSmithKline
Durham, NC 27701

TVC:18PI

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

TIVICAY (TIV-eh-kay)
(dolutegravir)
tablets

What is TIVICAY? The 10 mg tablets 25 mg tablets and 5 mg tablets for oral suspension (Tivicay PD) are not being imported by LifeScience Logistics.

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

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

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

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

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

Do not take TIVICAY if you:

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

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

- have or have had liver problems, including hepatitis B or C infection.
- are pregnant or plan to become pregnant. TIVICAY may harm your unborn baby.
  - Your healthcare provider may prescribe a different medicine than TIVICAY if you are planning to become pregnant or if pregnancy is confirmed during the first 12 weeks of pregnancy
  - If you can become pregnant, your healthcare provider may perform a pregnancy test before you start treatment with TIVICAY.
  - If you can become pregnant, you and your healthcare provider should talk about the use of effective birth control (contraception) during treatment with TIVICAY.
  - Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with TIVICAY.

Pregnancy Registry. There is a pregnancy registry for individuals who take antiretroviral medicines, including TIVICAY, during pregnancy. The purpose of this registry is to collect

information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take TIVICAY.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - TIVICAY pass to your baby in your breast milk.
    Talk with your healthcare provider about the best way to feed your baby.

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

Some medicines interact with TIVICAY. 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.
- **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 with other medicines.

How should I take TIVICAY?

- **Take TIVICAY exactly as your healthcare provider tells you to take it.**
- Take TIVICAY with or without food.
- **TIVICAY tablets cannot be substituted. Check to make sure you receive the correct form of TIVICAY each time you or your child's prescription is filled to avoid using the wrong medicine.**
- Do not change your dose, switch medicines or stop taking TIVICAY without talking with your healthcare provider first.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, TIVICAY should be taken at least 2 hours before or 6 hours after you take these medicines.
- If you need to take iron or calcium supplements by mouth during treatment with TIVICAY:
  - If you take TIVICAY with food, you may take these supplements at the same time that you take TIVICAY.
  - If you do not take TIVICAY with food, take TIVICAY at least 2 hours before or 6 hours after you take these supplements.
- Do not miss a dose of TIVICAY.
- If you miss a dose of TIVICAY, 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.
- Do not run out of TIVICAY. 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, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of TIVICAY?

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

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

How should I store TIVICAY?

- Store TIVICAY 50-mg tablets at room temperature between 68°F to 77°F (20°C to 25°C). The 10 mg tablets 25 mg tablets and 5 mg tablets for oral suspension (Tivicay PD) are not being imported by LifeScience Logistics.

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

General information about the safe and effective use of TIVICAY.

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

What are the ingredients in TIVICAY?

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.

The 10 mg, 25 mg, 50 mg tablets and 5 mg tablets for oral suspension are not being imported by LifeScience Logistics.

Manufactured for:

ViiV Healthcare
Durham, NC 27701

by:

GlaxoSmithKline
Durham, NC 27701

TVC:13PIL

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 10/2022

This drug was imported from Canada without the authorization of ViiV healthcare or GlaxoSmithKline under the State of Florida Section 804 Importation Program. Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

Manufactured for:

ViiV Healthcare
Durham, NC 27701

by:
GlaxoSmithKline
Durham, NC 27701

TVC: 2IFU

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: 10/2022

This drug was imported from Canada without the authorization of ViiV healthcare or GlaxoSmithKline under the State of Florida Section 804 Importation Program. Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

Annotated Label Comparisons

PI Comparisons FDA VS. FLCPDIP
Differences
Updated information Adverse Reactions Contact
How Supplied/Storage and Handling added SIP804 language
Patient Information added SIP804 language
Listed new NDC #
Added Importation language & Importer name & address
Listed only drug strength purchased for program

FDA

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

---------- 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-naive or -experienced) and in pediatric patients (treatment-naive or -experienced but INSTI- naive) aged at least 4 weeks and weighing at least 3 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 per 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----------

- Pregnancy Testing: Pregnancy testing is recommended before initiation of TIVICAY or TIVICAY PD in adolescents and adults of childbearing potential. (2.1, 5.3, 8.1, 8.3)
- May be taken without regard to food. (2.2, 2.6)

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] (2.2)	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A or CYP3A inducers (2.2, 7.2, 7.3)	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[b] (2.2, 12.4)	50 mg twice daily

[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 aged at least 4 weeks and weighing at least 3 kg. See Tables 2, 3, and 4 for complete pediatric dosing recommendations. (2.3, 2.4, 2.5). TIVICAY and TIVICAY PD are not bioequivalent and are not interchangeable on a milligram-per-milligram basis.

Pediatric Population Body Weight	Recommended Dose* TIVICAY PD Tablets for Oral Suspension
3 kg to less than 6 kg	5 mg once daily
6 kg to less than 10 kg	15 mg once daily
10 kg to less than 14 kg	20 mg once daily
14 kg to less than 20 kg	25 mg once daily
20 kg and greater	30 mg once daily

* If certain UGT1A or CYP3A inducers are coadministered, then adjust the weight-based dose of TIVICAY to twice daily. (2.4, 2.5, 7.2, 7.3)

Alternative dosing recommendations for TIVICAY tablets for patients weighing at least 14 kg (Table 4):
- 14 kg to less than 20 kg: 40 mg once daily.
- 20 kg and greater: 50 mg 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)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Assess the risks and benefits of TIVICAY and TIVICAY PD and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. Adolescents and adults of childbearing potential should be counseled on the consistent use of effective contraception. (2.1, 5.3, 8.1, 8.3)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.5)
- TIVICAY tablets and TIVICAY PD tablets for oral suspension are not interchangeable. (2.3, 5.6)

---------- 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)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: Assess the risks and benefits of TIVICAY and TIVICAY PD and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. (2.1, 5.3, 8.1, 8.3)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
- Females and males of reproductive potential: Pregnancy testing is recommended in adolescents and adults of childbearing potential. Patients should be counseled on the consistent use of effective contraception. (8.1, 8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2022

FLSIP 804

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
Initial U.S. Approval: 2013
The 10 mg tablets 25 mg tablets and 5 mg tablets for oral suspension (Tivicay PD) are not being imported by LifeScience Logistics.

---------- 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-naive or -experienced) and in pediatric patients (treatment-naive or -experienced but INSTI- naive) aged at least 4 weeks and weighing at least 3 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 per 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----------

- Pregnancy Testing: Pregnancy testing is recommended before initiation of TIVICAY in adolescents and adults of childbearing potential. (2.1, 5.3, 8.1, 8.3)
- May be taken without regard to food. (2.2, 2.6)

Adult Population	Recommended Dose
Treatment-naive or treatment-experienced INSTI-naive or virologically suppressed (HIV-1 RNA <50 copies per mL) adults switching to dolutegravir plus rilpivirine[a] (2.2)	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A or CYP3A inducers (2.2, 7.2, 7.3)	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[b] (2.2, 12.4)	50 mg twice daily

Rilpivirine dose is 25 mg once daily for those switching to dolutegravir plus rilpivirine.
Alternative combinations that do not include metabolic inducers should be considered where possible.

---------- DOSAGE FORMS AND STRENGTHS ----------

TIVICAY tablets: 50 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)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Assess the risks and benefits of TIVICAY and TIVICAY PD and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. Adolescents and adults of childbearing potential should be counseled on the consistent use of effective contraception. (2.1, 5.3, 8.1, 8.3)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.5)
- TIVICAY tablets and TIVICAY PD tablets for oral suspension are not interchangeable. (2.3, 5.6)

---------- 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 LifeScience Logistics at 1-855-738-6171 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)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: Assess the risks and benefits of TIVICAY and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. (2.1, 5.3, 8.1, 8.3)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
- Females and males of reproductive potential: Pregnancy testing is recommended in adolescents and adults of childbearing potential. Patients should be counseled on the consistent use of effective contraception. (8.1, 8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2022

FDA

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) aged at least 4 weeks and weighing at least 3 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 per 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 Pregnancy Testing before Initiation

Pregnancy testing is recommended before initiation of TIVICAY or TIVICAY PD in adolescents and adults of childbearing potential *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

2.2 Recommended Dosage in Adults

TIVICAY tablets may be taken with or without food.

2.5 Recommended Dosage in Pediatric Patients Weighing 14 kg or Greater

For **pediatric patients weighing 14 kg or greater** (4 weeks and older, treatment-naïve, or treatment-experienced but naïve to INSTI treatment) administer either:

- TIVICAY PD tablets for oral suspension (preferred in pediatric patients weighing less than 20 kg) (Table 3), or
- TIVICAY tablets for oral use (Table 4)

Table 3. Recommended Dosage of TIVICAY PD Tablets for Oral Suspension in Pediatric Patients Weighing 14 kg or Greater

	TIVICAY PD Tablets for Oral Suspension	
Body Weight	Daily Dose[a]	Number of 5-mg Tablets
14 kg to less than 20 kg	25 mg once daily	5
20 kg and greater	30 mg once daily	6

[a] If certain UGT1A or CYP3A inducers are coadministered, then administer TIVICAY PD twice daily *[see Drug Interactions (7.2, 7.3)]*.

Table 4. Recommended Dosage of TIVICAY Tablets in Pediatric Patients Weighing 14 kg or Greater

	TIVICAY Tablets	
Body Weight	Daily Dose[a]	Number of Tablets
14 kg to less than 20 kg	40 mg once daily	4 x 10-mg
20 kg and greater	50 mg once daily	1 x 50-mg

[a] If certain UGT1A or CYP3A inducers are coadministered, then administer TIVICAY twice daily *[see Drug Interactions (7.2, 7.3)]*.

2.6 Additional Administration Instructions

Administer TIVICAY tablets and TIVICAY PD tablets for oral suspension with or without food.

Administration Instructions for TIVICAY PD

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

FLSIP 804

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TIVICAY 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) aged at least 4 weeks and weighing at least 3 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 per 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 Pregnancy Testing before Initiation

Pregnancy testing is recommended before initiation of TIVICAY in adolescents and adults of childbearing potential *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

2.2 Recommended Dosage in Adults

TIVICAY tablets may be taken with or without food.

2.5 Recommended Dosage in Pediatric Patients Weighing 14 kg or Greater

For **pediatric patients weighing 14 kg or greater** (4 weeks and older, treatment-naïve, or treatment-experienced but naïve to INSTI treatment) administer:

- The 10 mg, 25 mg, 50 mg tablets and 5 mg tablets for oral suspension are not being imported by LifeScience Logistics.
- TIVICAY tablets for oral use (Table 4)

Table 3. Recommended Dosage of TIVICAY PD Tablets for Oral Suspension in Pediatric Patients Weighing 14 kg or Greater

	TIVICAY PD Tablets for Oral Suspension	
Body Weight	Daily Dose[a]	Number of 5-mg Tablets
14 kg to less than 20 kg	25 mg once daily	5
20 kg and greater	30 mg once daily	6

[a] If certain UGT1A or CYP3A inducers are coadministered, then administer TIVICAY PD twice daily *[see Drug Interactions (7.2, 7.3)]*. The 10 mg, 25 mg, 50 mg tablets and 5 mg tablets for oral suspension are not being imported by LifeScience Logistics.

Table 4. Recommended Dosage of TIVICAY Tablets in Pediatric Patients Weighing 14 kg or Greater

	TIVICAY Tablets	
Body Weight	Daily Dose[a]	Number of Tablets
14 kg to less than 20 kg	40 mg once daily	4 x 10-mg
20 kg and greater	50 mg once daily	1 x 50-mg

[a] If certain UGT1A or CYP3A inducers are coadministered, then administer TIVICAY twice daily *[see Drug Interactions (7.2, 7.3)]*.

2.6 Additional Administration Instructions

Administer TIVICAY tablets with or without food.

The 10 mg tablets 25 mg tablets and 5 mg tablets for oral suspension (Tivicay PD) are not being imported by LifeScience Logistics.

FDA

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)]*.

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 subjects receiving TIVICAY in Phase 3 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.

14.3 Pediatric Subjects

IMPAACT P1093 is an ongoing Phase 1/2, multicenter, open-label trial to evaluate the pharmacokinetic parameters, safety, tolerability, and efficacy of TIVICAY or TIVICAY PD in combination treatment regimens in HIV-1–infected infants, children, and adolescents aged at least 4 weeks to 18 years. Subjects were stratified by 5 age cohorts: Cohort 1, aged 12 to less than 18 years; Cohort 2A, aged 6 to less than 12 years; Cohort 3, aged 2 to less than 6 years; Cohort 4, aged 6 months to less than 2 years; and Cohort 5, aged 4 weeks to less than 6 months. Seventy-five subjects received the recommended dose (determined by weight and age) of TIVICAY or TIVICAY PD *[see Dosage and Administration (2.3, 2.4, 2.5)]*.

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

Virologic outcomes from IMPAACT P1093 include subjects who received either TIVICAY tablets or TIVICAY PD tablets for oral suspension as per the dosing recommendations for their weight band and who had reached Week 24 (n = 58) or Week 48 (n = 42). At Week 24, 62% of

FLSIP 804

3 DOSAGE FORMS AND STRENGTHS

TIVICAY Tablets:

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.

The 10 mg tablets 25 mg tablets and 5 mg tablets for oral suspension (Tivicay PD) are not being imported by LifeScience Logistics.

4 CONTRAINDICATIONS

TIVICAY 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)]*.

5.1 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 subjects receiving TIVICAY in Phase 3 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

are contraindicated in patients who have experienced a previous hypersensitivity reaction to dolutegravir.

14.3 Pediatric Subjects

IMPAACT P1093 is an ongoing Phase 1/2, multicenter, open-label trial to evaluate the pharmacokinetic parameters, safety, tolerability, and efficacy of TIVICAY in combination treatment regimens in HIV-1–infected infants, children, and adolescents aged at least 4 weeks to 18 years. Subjects were stratified by 5 age cohorts: Cohort 1, aged 12 to less than 18 years; Cohort 2A, aged 6 to less than 12 years; Cohort 3, aged 2 to less than 6 years; Cohort 4, aged 6 months to less than 2 years; and Cohort 5, aged 4 weeks to less than 6 months. Seventy-five subjects received the recommended dose (determined by weight and age) of TIVICAY or TIVICAY PD *[see Dosage and Administration (2.3, 2.4, 2.5)]*.

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

Virologic outcomes from IMPAACT P1093 include subjects who received either TIVICAY tablets 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

FDA

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

Hypersensitivity Reactions

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

Hepatotoxicity

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

Embryo-Fetal Toxicity

Advise adolescents and adults of childbearing potential, including those actively trying to become pregnant, to discuss the risks and benefits of TIVICAY and TIVICAY PD with their healthcare provider to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy. If pregnancy is confirmed in the first trimester, advise patients to contact their healthcare provider *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

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

Immune Reconstitution Syndrome

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

Different Formulations Are Not Bioequivalent

Advise patients that TIVICAY and TIVICAY PD are not bioequivalent and are not interchangeable on a milligram-per-milligram basis. Advise patients or their care provider that

FLSIP 804

16 HOW SUPPLIED/STORAGE AND HANDLING

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 42067-280-30.

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

The 10 mg tablets 25 mg tablets and 5 mg tablets for oral suspension (Tivicay PD) are not being imported by LifeScience Logistics.

This drug was imported from Canada without the authorization of ViiV Healthcare or GlaxoSmithKline under the State of Florida Section 804 Importation Program.
Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

17 PATIENT COUNSELING INFORMATION

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

Drug Interactions

TIVICAY may interact with other drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or

Hypersensitivity Reactions

Advise patients to immediately contact their healthcare provider if they develop rash. Instruct patients to immediately stop taking TIVICAY 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 is recommended, especially for patients with liver disease, such as hepatitis B or C.

Embryo-Fetal Toxicity

Advise adolescents and adults of childbearing potential, including those actively trying to become pregnant, to discuss the risks and benefits of TIVICAY with their healthcare provider to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy. If pregnancy is confirmed in the first trimester, advise patients to contact their healthcare provider *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

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

Immune Reconstitution Syndrome

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

Different Formulations Are Not Bioequivalent

Advise patients or their care provider that

FDA

Pregnancy Registry

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

Lactation

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

Administration Instructions

To avoid a dosing error from using the wrong formulation of dolutegravir, strongly advise patients and caregivers to visually inspect the tablets to verify the correct formulation each time the prescription is filled *[see Dosage and Administration (2), Warnings and Precautions (5.6), How Supplied/Storage and Handling (16)]*.

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

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

Storage

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

Manufactured for:

ViiV Healthcare

FLSIP 804

Pregnancy Registry

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

Lactation

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

Administration Instructions

To avoid a dosing error from using the wrong formulation of dolutegravir, strongly advise patients and caregivers to visually inspect the tablets to verify the correct formulation each time the prescription is filled *[see Dosage and Administration (2), Warnings and Precautions (5.6), How Supplied/Storage and Handling (16)]*.

Instruct patients and caregivers that if a dose of TIVICAY 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

Do not remove desiccant *[see How Supplied/Storage and Handling (16)]*.

Manufactured for:

ViiV Healthcare

FDA

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

TIVICAY (TIV-eh-kay)
(dolutegravir)
tablets

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

What is TIVICAY and TIVICAY PD?

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

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

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

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

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

Do not take TIVICAY or TIVICAY PD if you:

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

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

- have or have had liver problems, including hepatitis B or C infection.
- are pregnant or plan to become pregnant. TIVICAY or TIVICAY PD may harm your unborn baby.
  - Your healthcare provider may prescribe a different medicine than TIVICAY or TIVICAY PD if you are planning to become pregnant or if pregnancy is confirmed during the first 12 weeks of pregnancy
  - If you can become pregnant, your healthcare provider may perform a pregnancy test before you start treatment with TIVICAY or TIVICAY PD.
  - If you can become pregnant, you and your healthcare provider should talk about the use of effective birth control (contraception) during treatment with TIVICAY or TIVICAY PD.
  - Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with TIVICAY or TIVICAY PD.

Pregnancy Registry. There is a pregnancy registry for individuals who take antiretroviral medicines, including TIVICAY and TIVICAY PD, during pregnancy. The purpose of this registry is to collect

FLSIP 804

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

TIVICAY (TIV-eh-kay)
(dolutegravir)
tablets

What is TIVICAY? The 10 mg tablets 25 mg tablets and 5 mg tablets for oral suspension (Tivicay PD) are not being imported by LifeScience Logistics.

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

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

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

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

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

Do not take TIVICAY if you:

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

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

- have or have had liver problems, including hepatitis B or C infection.
- are pregnant or plan to become pregnant. TIVICAY may harm your unborn baby.
  - Your healthcare provider may prescribe a different medicine than TIVICAY if you are planning to become pregnant or if pregnancy is confirmed during the first 12 weeks of pregnancy
  - If you can become pregnant, your healthcare provider may perform a pregnancy test before you start treatment with TIVICAY.
  - If you can become pregnant, you and your healthcare provider should talk about the use of effective birth control (contraception) during treatment with TIVICAY.
  - Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with TIVICAY.

Pregnancy Registry. There is a pregnancy registry for individuals who take antiretroviral medicines, including TIVICAY, during pregnancy. The purpose of this registry is to collect

FDA

information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.

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

  Talk with your healthcare provider about the best way to feed your baby.

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

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

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

How should I take TIVICAY or TIVICAY PD?

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

FLSIP 804

information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.

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

  Talk with your healthcare provider about the best way to feed your baby.

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

Some medicines interact with TIVICAY. 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.
- **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 with other medicines.

How should I take TIVICAY?

- **Take TIVICAY exactly as your healthcare provider tells you to take it.**
- Take TIVICAY with or without food.
- **TIVICAY tablets cannot be substituted. Check to make sure you receive the correct form of TIVICAY each time you or your child's prescription is filled to avoid using the wrong medicine.**
- Do not change your dose, switch medicines or stop taking TIVICAY without talking with your healthcare provider first.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, TIVICAY should be taken at least 2 hours before or 6 hours after you take these medicines.
- If you need to take iron or calcium supplements by mouth during treatment with TIVICAY:
  - If you take TIVICAY with food, you may take these supplements at the same time that you take TIVICAY.
  - If you do not take TIVICAY with food, take TIVICAY at least 2 hours before or 6 hours after you take these supplements.
- Do not miss a dose of TIVICAY.
- If you miss a dose of TIVICAY, take it as soon as you remember. Do not take 2 doses at the same time or take more than your prescribed dose.

FDA

- Stay under the care of a healthcare provider during treatment with TIVICAY or TIVICAY PD.
- Do not run out of TIVICAY or TIVICAY PD. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too much TIVICAY or TIVICAY PD, call your healthcare provider or go to the nearest hospital emergency room right away.

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

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

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

How should I store TIVICAY or TIVICAY PD?

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

FLSIP 804

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

What are the possible side effects of TIVICAY?

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

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

How should I store TIVICAY?

- Store TIVICAY 50-mg tablets at room temperature between 68°F to 77°F (20°C to 25°C). The 10 mg tablets 25 mg tablets and 5 mg tablets for oral suspension (Tivicay PD) are not being imported by LifeScience Logistics.

FDA

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

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

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

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

What are the ingredients in TIVICAY and TIVICAY PD?

Active ingredient: dolutegravir.

Inactive ingredients:

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

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

Manufactured for:

ViiV Healthcare

ViiV Healthcare
Durham, NC 27701

by:

GlaxoSmithKline
Durham, NC 27701

TVC:13PIL

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 10/2022

FLSIP 804

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

General information about the safe and effective use of TIVICAY.

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

What are the ingredients in TIVICAY?

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.

The 10 mg, 25 mg, 50 mg tablets and 5 mg tablets for oral suspension are not being imported by LifeScience Logistics.

Manufactured for:

ViiV Healthcare

ViiV Healthcare
Durham, NC 27701

by:

GlaxoSmithKline
Durham, NC 27701

TVC:13PIL

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 10/2022

This drug was imported from Canada without the authorization of ViiV healthcare or GlaxoSmithKline under the State of Florida Section 804 Importation Program. Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

FDA

INSTRUCTIONS FOR USE

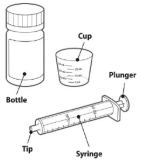
TIVICAY PD (TIV-eh-kay Pe De)
(dolutegravir) tablets for oral suspension
5 mg

Read this Instructions for Use before giving a dose of medicine.
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

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

- Pour clean drinking water into the cup.

Figure A

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

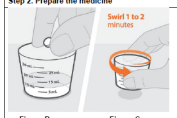


Figure B Figure C

- Add the prescribed number of tablet(s) to the water. **See Figure B.**
- Swirl the cup gently for 1 to 2 minutes to disperse the tablet(s). The medicine will become 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 tablet, 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

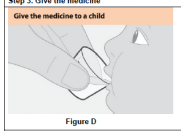


Figure D

- 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.**

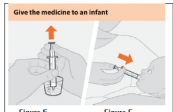


Figure E Figure F

- 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

Step 4. Clean the dosing items

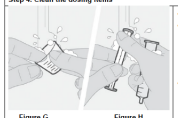


Figure G Figure H

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

Storage Information

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

Disposal Information

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

Manufactured for:
ViiV Healthcare
ViiV Healthcare
Durham, NC 27701

by:
GlaxoSmithKline
Durham, NC 27701

TVC: 2IFU

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: 10/2022

FLSIP 804

Manufactured for:
ViiV Healthcare
ViiV Healthcare
Durham, NC 27701

by:
GlaxoSmithKline
Durham, NC 27701

TVC: 2IFU

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: 10/2022

This drug was imported from Canada without the authorization of ViiV healthcare or GlaxoSmithKline under the State of Florida Section 804 Importation Program. Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

Proposed Package Label

Label Comparisons FDA VS. FLCPDIP
Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Label SIZE due to production process & adding SIP804 language
Importer Name & Address
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.

Comparisons
FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	FLSIP Proprietary Name	FLSIP Generic Name	FLSIP Strength	LSL NDC	Relabeler Name	Applicant Holder Name	Applicant Holder Address	Active Ingredients	FDA Comments
Oct-22	Tivicay	DOLUTEGRAVIR SODIUM	50 mg	49702-228-13	204790	VIIV HEALTHCARE CO	406 Blackwell St Durham NC 27701	DOLUTEGRAVIR SODIUM	Aug-23	Tivicay	DOLUTEGRAVIR SODIUM	50 mg	42067-280-30	LifeScience Logistics, LLC	VIIV HEALTHCARE CO	406 Blackwell St Durham NC 27701	DOLUTEGRAVIR SODIUM	n/a

Canadian to FDA Drug Comparison

Comparisons

Canada to FDA

Active Ingredient	Canadian Submission Number	Canadian Proprietary Name	Canadian Generic Name	DIN	Date Labeling Approved	Company Name	Address	Canadian Strength	Dosage Form	# of active Ingred.	Canadian Ingredients	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	US Active Ingredients
DOLUTEGRAVIR SODIUM	264438	Tivicay	DOLUTEGRAVIR	02414345	October-22	ViiV Healthcare ULC	75 Rue Queen, Suite 1400 Montreal, Quebec Canada H3C 2N6	50 mg	tablet, oral	1	dolutegravir	Tivicay	DOLUTEGRAVIR	50 mg	49702-228-13	204790	VIIV HEALTHCARE CO	DOLUTEGRAVIR SODIUM

Canadian Monograph

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTIVICAY

dolutegravir tablets

Tablets, 10, 25 and 50 mg dolutegravir (as dolutegravir sodium), oral

dolutegravir dispersible tablets

Dispersible tablets, 5 mg dolutegravir (as dolutegravir sodium), oral

Antiretroviral Agent

ViiV Healthcare ULC
75 Queen, Street Suite 1400
Montreal, Quebec
Canada
H3C 2N6

Date of Initial Authorization:
NOV 08, 2013

Date of Revision:
JUN 27, 2023

Submission Control Number: 272507

RECENT MAJOR LABEL CHANGES

Section	Date
1 INDICATIONS	01/2021
4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations	01/2021
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	12/2021
7 WARNINGS AND PRECAUTIONS, General	01/2021
7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics	01/2021
7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women	10/2022
7 WARNINGS AND PRECAUTIONS, 7.1.2 Breast-feeding	10/2022
7 WARNINGS AND PRECAUTIONS, General	06/2023

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TIVICAY, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adults and in INSTI-naïve pediatric patients aged 4 weeks and older and weighing at least 3 kg.

1.1 Pediatrics

Pediatrics (aged less than 4 weeks or weighing less than 3 kg or INSTI-experienced):

Safety and efficacy of TIVICAY have not been established in children aged less than 4 weeks or weighing less than 3 kg or who are INSTI-experienced with documented or clinical suspected resistance to other INSTIs.

1.2 Geriatrics

Geriatrics (> 65 years of age): Clinical studies of TIVICAY did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from adult patients < 65 years of age.

2 CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- TIVICAY is contraindicated in combination with drugs with narrow therapeutic windows, that are substrates of organic cation transporter 2 (OCT2), including but not limited to dofetilide, or fampridine (also known as dalfampridine) (see 9 DRUG INTERACTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

As with all antiretroviral drugs, dolutegravir therapy should be initiated by a healthcare practitioner experienced in the management of HIV infection.

Perform pregnancy testing before initiation of TIVICAY in individuals of childbearing potential.

The following should be considered prior to initiating treatment with TIVICAY:

- Poor virologic response was observed in subjects treated with TIVICAY 50mg twice daily with an integrase strand transfer inhibitor (INSTI)-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions, including, but not limited to T66A, L74I/M, E138A/K/T, G140A/C/S, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R.

Dolutegravir tablets and dispersible tablets may be taken with or without food.

Dolutegravir is available as tablets or as dispersible tablets for patients in whom tablets are not appropriate. For dosing recommendations using tablets and dispersible tablets see the recommended dose for adults, and Table 2 for pediatric patients.

Dispersible tablets may be swallowed whole with drinking water or dispersed in drinking water. When dispersed, the amount of water will depend on the number of tablets prescribed. The tablet(s) should

be fully dispersed before swallowing, and the dose should be administered orally within 30 minutes. Do not chew, cut or crush the tablets (see Instructions For Use).

Do not interchange TIVICAY tablets and TIVICAY dispersible tablets for oral suspension on a milligram-per-milligram basis due to differing pharmacokinetic profiles (see 7 WARNINGS AND PRECAUTIONS, General and **4.2 Recommended Dose and Dosage Adjustment** and **10.3 Pharmacokinetics).**

4.2 Recommended Dose and Dosage Adjustment

Adult Patients

Table 1 Recommended Dosing Regimen in Adults

Patient Population	Tablet Dose	Regimen
Treatment-naïve[a]	50 mg	QD*
Treatment-experienced, INSTI-naïve[a]	50 mg	QD
Treatment-experienced, INSTI-resistant[b]	50 mg	BID**

* QD – once daily

** BID – twice daily

[a] The dose of TIVICAY is 50 mg twice daily when co-administered with potent UGT1A/CYP3A inducers, including efavirenz, tipranavir/ritonavir, fosamprenavir/ritonaviror rifampin (see 9 DRUG INTERACTIONS).

[b] Alternative combinations that do not include metabolic inducers should be used where possible for INSTI-resistant patients. The safety and efficacy of doses above 50 mg twice daily have not been evaluated (see 9 DRUG INTERACTIONS).

The recommended QD adult dose of the dispersible tablets is 30 mg (taken as 6 x 5mg).

Patients that are treatment-experienced, INSTI-resistant, the recommended adult dose of the dispersible tablets is 30 mg, BID.

Geriatrics

There are limited data available on the use of TIVICAY in patients aged 65 years and older. 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.

Pediatric

Treatment-naive or Treatment-experienced INSTI-naive

The recommended dose of TIVICAY in pediatric patients aged at least 4 weeks and weighing at least 3 kg is provided in Table 2.

Safety and efficacy of TIVICAY have not been established in pediatric patients aged less than 4 weeks or weighing less than 3 kg, or who are INSTI-experienced with suspected or confirmed INSTI-resistant HIV-1.

Table 2 Recommended Dosing Regimen in pediatric patients

Body Weight (kg)	TIVICAY Dispersible Tablets		TIVICAY Tablets	
	Daily Dose (QD)[a]	Number of Dispersible Tablets	Daily Dose (QD)	Number of Tablets
3 to less than 6	5 mg	1 x 5mg	NA	NA
6 to less than 10 less than 6 months of age	10 mg	2 x 5 mg	NA	NA
6 months of age and older	15 mg	3 x 5 mg		
10 to less than 14	20 mg	4 x 5 mg	NA	NA
14 to less than 20	25 mg	5 x 5 mg	40 mg	4 x 10 mg tablets
20 and greater	30 mg	6 x 5 mg	50 mg	One 50 mg tablet

[a] If certain UGT1A or CYP3A inducers including efavirenz, tipranavir/ritonavir, fosamprenavir/ritonavir or rifampin are coadministered, then increase the weight-based dose of TIVICAY to twice daily (see 9 DRUG INTERACTIONS)

To reduce the risk of choking, do not swallow more than one tablet at a time When possible, children weighing less than 20 kg should use dispersible tablets.

Hepatic Insufficiency

No dosage adjustment is required in patients with mild or 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, dolutegravir is not recommended for use in patients with severe hepatic impairment (Child-Pugh Score C) (see 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

Renal Insufficiency

Dolutegravir plasma concentrations were decreased in subjects with severe renal impairment compared with those in matched healthy controls. No dosage adjustment is required in INSTI-naïve patients with mild, moderate or severe (CrCl<30 mL /min, not on dialysis) renal impairment. Caution is advised for INSTI-resistant patients with severe renal impairment as the decreased dolutegravir exposure may result in loss of therapeutic effect and development of resistance to dolutegravir. There is limited information on dolutegravir in patients receiving dialysis (see 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

4.5 Missed Dose

If a dose is missed, patients should take the missed dose as soon as possible unless it is within 4 hours of their next scheduled dose. If a dose is skipped, the patient should not double the next dose.

5 OVERDOSAGE

Symptoms and signs
There is currently limited experience with overdosage in dolutegravir.

Limited experience of single higher doses (up to 250 mg in healthy subjects) revealed no specific symptoms or signs, apart from those listed as adverse reactions.

Treatment

There is no specific treatment for an overdose of dolutegravir. If overdose occurs, the patient should be closely monitored and treated supportively as necessary. As TIVICAY is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 Route of Administration, Dosage Form, Strength and Non-medicinal Ingredients

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Film-coated tablets / 10, 25 and 50 mg dolutegravir (as dolutegravir sodium)	D-mannitol, iron oxide yellow (25 mg and 50 mg tablets only), macrogol/PEG, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, sodium stearyl fumarate, polyvinyl alcohol – part hydrolyzed, talc, titanium dioxide
Oral	Film-coated dispersible tablets / 5 mg dolutegravir (as dolutegravir sodium)	Calcium sulfate dihydrate, crospovidone, hypromellose, mannitol, microcrystalline cellulose, polyethylene glycol, povidone K29/32, silicified microcrystalline cellulose, sodium starch glycolate, strawberry cream flavor, sucralose, sodium stearyl fumarate, titanium dioxide

Dosage Forms

TIVICAY 5 mg dispersible tablets are white, round, film-coated, biconvex tablets debossed with “SV H7S” on one side and “5” on the other side.

TIVICAY 10 mg tablets are white, round, film-coated, biconvex tablets debossed with ‘SV 572’ on one side and ‘10’ on the other side. Each tablet contains 10 mg dolutegravir (as dolutegravir sodium).

TIVICAY 25 mg tablets are pale yellow, round, film-coated, biconvex tablets debossed with ‘SV 572’ on one side and ‘25’ on the other side. Each tablet contains 25 mg dolutegravir (as dolutegravir sodium).

TIVICAY 50 mg tablets are yellow, round, film-coated, biconvex tablets debossed with ‘SV 572’ on one side and ‘50’ on the other side. Each tablet contains 50 mg dolutegravir (as dolutegravir sodium).

Packaging

TIVICAY 10, 25 and 50 mg are available in 60 cc bottles containing 30 tablets.

TIVICAY 10 mg tablets contain a silica gel desiccant.

TIVICAY 5 mg dispersible tablets are packaged in a kit with one 60 cc bottle containing 60 tablets, one 30 mL dosing cup and one 10 mL oral dosing syringe. The 5 mg dispersible tablets contain a silica gel desiccant.

7 WARNINGS AND PRECAUTIONS

General

Patients receiving TIVICAY or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

TIVICAY tablets and TIVICAY dispersible tablets are not bioequivalent and are not interchangeable on a milligram-per-milligram basis (see 10 CLINICAL PHARMACOLOGY). If a patient switches from one formulation to the other, the dose must be adjusted for the new dosage formulation (see 4 DOSAGE AND ADMINISTRATION). 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.

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Hepatic/Biliary/Pancreatic

Hepatoxicity

Cases of hepatic toxicity including elevated serum liver biochemistries, hepatitis, and acute liver failure have been reported in patients receiving a dolutegravir-containing regimen who had no pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with TRIUMEQ (dolutegravir/abacavir/lamivudine). Monitoring for hepatotoxicity is recommended.

Liver chemistry changes in patients with hepatitis B or C co-infection

Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TIVICAY. Liver chemistry elevations consistent with immune reconstitution inflammatory syndrome were observed in some hepatitis B and/or C co-infected patients at the start of TIVICAY therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B co-infected patients (see 8.2 Clinical Trial Adverse Reactions, Co-infection with Hepatitis B or C).

Hypersensitivity Reactions

Hypersensitivity reactions have been reported with integrase inhibitors, including TIVICAY, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. Discontinue TIVICAY 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, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with TIVICAY or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

Immune

Immune Reconstitution Inflammatory Syndrome (IRIS)

Immune reconstitution inflammatory syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including TIVICAY. During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium-complex* (MAC), cytomegalovirus (CMV), *Pneumocystis jirovecii pneumonia* (PCP), and *tuberculosis* (TB)], which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, autoimmune hepatitis and Guillain-Barre 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 and sometimes can be an atypical presentation.

7.1 Special Populations

7.1.1 Pregnant Women

TIVICAY has not been studied in pregnant women. TIVICAY should not be used in pregnant women unless the potential benefits outweigh the potential risks to the fetus (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). Women of childbearing potential (WOCBP) should be informed about the potential risk of neural tube defects with dolutegravir and counselled about the use of effective contraception. It is recommended that pregnancy testing is conducted prior to initiation of TIVICAY. If there are plans to become pregnant, or if pregnancy is confirmed within the first trimester while on TIVICAY, the risks and benefits of continuing TIVICAY versus switching to another antiretroviral regimen should be discussed with the patient. Factors to consider should include feasibility of switching, tolerability, ability to maintain viral suppression, actual gestational age, risk of transmission to the infant and the available data around the potential risk of neural tube defects and other pregnancy outcomes for dolutegravir and alternative antiretroviral drugs.

In a birth outcome surveillance study in Botswana, a numerically higher rate of neural tube defects was identified with exposure to dolutegravir compared to non-dolutegravir-containing antiretroviral regimens at the time of conception, however, the difference was not statistically significant. Seven cases of neural tube defects were reported in 3,591 deliveries (0.19%) to mothers taking dolutegravir-containing regimens at the time of conception, compared with 21 cases in 19,361 deliveries (0.11%) to mothers taking non-dolutegravir-containing regimens at the time of conception (Prevalence Difference 0.09%; 95% CI -0.03, 0.30). In the same study, an increased risk of neural tube defects was not identified in women who started dolutegravir during pregnancy. Two out of 4,448 deliveries (0.04%) to mothers who started dolutegravir during pregnancy had a neural tube defect, compared with five out of 6,748 deliveries (0.07%) to mothers who started non dolutegravir-containing regimens during pregnancy. A causal relationship of these events to the use of dolutegravir has not been established. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births. As most neural tube defects occur within the first 4 weeks of foetal development (approximately

6 weeks after the last menstrual period) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy.

Data analysed to date from other sources including the Antiretroviral Pregnancy Registry, clinical trials, and post-marketing data are insufficient to address the risk of neural tube defects with dolutegravir. From the APR, one NTD has been identified in 312 (0.32%) live births with periconceptual exposures to DTG. More than 1000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes and the APR continues to monitor for DTG safety in pregnancy.

Dolutegravir use during pregnancy have been evaluated in the Antiretroviral Pregnancy Registry (APR) in over 700 women. Available human data from the APR do not show an increased risk of major birth defects for dolutegravir compared to the background rate.

Dolutegravir readily crosses the placenta in humans. In HIV-infected pregnant women, the median (range) foetal umbilical cord concentrations of dolutegravir were 1.28 (1.21 to 1.28) fold greater compared with maternal peripheral plasma concentrations.

There is insufficient information on the effects of dolutegravir on neonates.

Based on prospective reports to the APR of over 700 exposures to dolutegravir during pregnancy resulting in live births (including over 450 exposed in the first trimester), there was no difference between the overall risk of birth defects for dolutegravir when compared to the background birth defect rate of 2.7% and 4.17% from two population based surveillance systems (Metropolitan Atlanta Congenital Defects Program (MACDP) with defects of 2.72 per 100 live births and the Texas Birth Defects Registry (TBDR) with 4.17 per 100 live births). The prevalence of defects in live births was 3.5% (95% CI: 2.0% to 5.6%) following first trimester exposure to dolutegravir-containing regimens and 4.2% (95% CI: 2.2% to 7.2%) following second/third trimester exposure to dolutegravir-containing regimens.

In reproductive toxicity studies in animals, no evidence of teratogenicity, reproductive function, relevant embryonic or fetal toxicity, including neural tube defects, was identified (see 16 NON-CLINICAL TOXICOLOGY).

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women with HIV exposed to TIVICAY and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients:
http://www.apregistry.com
Telephone: (800) 258-4263
Fax: (800) 800-1052

7.1.2 Breast-feeding

HIV-1-infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. Dolutegravir is excreted in human milk in small amounts. In an open-label randomised study in which HIV- infected treatment-naïve pregnant women were administered a dolutegravir based regimen until two weeks post-partum, the median (range) dolutegravir breast milk to maternal plasma ratio was 0.033 (0.021 to 0.050). Nursing mothers should be instructed not to breast-feed if they are receiving TIVICAY.

7.1.3 Pediatrics

Pediatrics (aged less than 4 weeks or weighing less than 3 kg or INSTI-experienced): Safety and efficacy of TIVICAY have not been established in children aged less than 4 weeks or weighing less than 3 kg or who are INSTI-experienced with documented or clinical suspected resistance to other INSTIs.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Clinical studies of TIVICAY did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from adult patients less than 65 years of age. In general, caution should be exercised in dose selection for the elderly patients due to the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The overall safety profile of TIVICAY is based on over 1500 HIV-infected patients treated with a TIVICAY-based regimen in Phase 2 and 3 clinical studies. The overall safety profile was similar across the treatment-naïve, treatment-experienced (and integrase-naïve) and integrase-resistant patient populations. The most common adverse reactions of moderate to severe intensity and incidence ≥ 2% (in those receiving TIVICAY in any one study) are insomnia, headache, fatigue, nausea, and diarrhea.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Treatment-Naïve Patients

The safety assessment of TIVICAY in HIV-1-infected treatment-naïve patients is based on the analyses of 48-week data from two randomized, ongoing, international, multicentre, double-blind studies, SPRING-2 (ING113086) and SINGLE (ING114467).

In SPRING-2, 822 adult patients were randomized and received at least one dose of either TIVICAY 50 mg once daily (QD) or ISENTRESS 400 mg twice daily (BID), both in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) treatment (either abacavir sulfate and lamivudine [KIVEXA] or emtricitabine/tenofovir [TRUVADA]). The rate of adverse events leading to discontinuation was 2% in both treatment arms.

In SINGLE, 833 adult patients were randomized to receive at least one dose of either TIVICAY 50 mg with fixed-dose abacavir and lamivudine (KIVEXA) once daily or fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA) once daily. The rate of adverse events leading to discontinuation were 2% in patients receiving TIVICAY 50 mg once daily + KIVEXA and 10% in patients receiving ATRIPLA once daily.

Treatment-emergent adverse reactions (adverse events assessed as causally related by the investigators) of moderate to severe intensity with a ≥ 2% frequency in either treatment arm in SPRING-2 and SINGLE studies are provided in Table 4.

The adverse drug reactions and laboratory abnormalities observed at 96 weeks in SPRING-2 and at 144 weeks in SINGLE were generally consistent with those seen at 48 weeks.

Table 4 Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2-4) and ≥ 2% Frequency in Treatment-Naïve Patients in SPRING-2 and SINGLE Trials (Through 48 weeks)

Body System/ Preferred Term	SPRING-2		SINGLE	
	TIVICAY 50 mg QD + 2 NRTIs (N = 411)	ISENTRESS 400 mg BID + 2 NRTIs (N = 411)	TIVICAY 50 mg + KIVEXA QD (N = 414)	ATRIPLA QD (N = 419)
Psychiatric				
Insomnia	1 (<1%)	1 (<1%)	13 (3%)	9 (2%)
Abnormal dreams	1 (<1%)	1 (<1%)	2 (<1%)	8 (2%)
Nervous System				
Dizziness	1 (<1%)	1 (<1%)	2 (<1%)	19 (5%)
Headache	3 (<1%)	4 (<1%)	7 (2%)	9 (2%)
Gastrointestinal				
Nausea	6 (1%)	5 (1%)	3 (<1%)	12 (3%)
Diarrhea	2 (<1%)	2 (<1%)	4 (<1%)	7 (2%)
Skin and Subcutaneous Tissue				
Rash	0	2 (<1%)	1 (<1%)	14 (3%)
Ear and Labyrinth				
Vertigo	0	1 (<1%)	0	7 (2%)

Antiretroviral-Experienced and Integrase Inhibitor-Naïve Patients

In an international, multicentre, double-blind study (ING111762, SAILING), 719 HIV-1-infected, antiretroviral treatment-experienced adults were randomized to receive either TIVICAY 50 mg once daily or ISENTRESS 400 mg twice daily with investigator-selected background regimen (BR) consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rates of adverse events leading to discontinuation were 2% (7/357) in patients receiving TIVICAY 50 mg once daily + BR and 4% (13/362) in patients receiving ISENTRESS 400 mg twice daily + BR.

Through 48 wks, the only treatment-emergent adverse reaction of moderate to severe intensity with a ≥ 2% frequency in either treatment group was diarrhea, 2% (6/357) in subjects receiving TIVICAY 50 mg once daily + BR and 1% (5/362) in subjects receiving ISENTRESS 400 mg twice daily + BR.

Integrase Inhibitor-Resistant Patients

In a multicentre, open-label, single-arm study (ING112574, VIKING-3), 183 HIV-1-infected, antiretroviral treatment-experienced adults with virologic failure with current or historical evidence of raltegravir and/or elvitegravir resistance received TIVICAY 50 mg twice daily with the current failing background regimen for 7 days and with Optimized Background Therapy (OBT) from Day 8. The rate of discontinuation due to adverse events was 4% of patients at the Week 48 analysis.

Treatment-emergent adverse reactions (adverse events assessed as causally related by the investigator) of moderate to severe intensity with a ≥ 2% frequency are listed in Table 5.

Table 5 Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4) and ≥ 2% Frequency in Integrase Inhibitor-Resistant Patients in the VIKING-3 Study (Week 24 and Week 48 Analyses)

Body System/ Preferred Term	Week 24	Week 48
	TIVICAY 50 mg BID + OBT (N = 183)	TIVICAY 50 mg BID + OBT (N = 183)
Gastrointestinal		
Diarrhea	4 (2%)	4 (2%)
Nausea	3 (2%)	3 (2%)
Nervous System		
Headache	3 (2%)	2 (1%)

Co-infection with Hepatitis B or C

In Phase III studies, patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients 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 co-infection for all treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected patients compared with HIV mono-infected patients receiving TIVICAY were observed in 18% vs. 3% with the 50 mg once-daily dose and 13% vs. 9% with the 50 mg twice-daily dose. Liver chemistry elevations consistent with immune reconstitution inflammatory syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Liver chemistry changes in patients with hepatitis B or C co-infection).

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The safety of TIVICAY in HIV-1–infected pediatric subjects (n=172) aged at least 4 weeks and weighing at least 3 kg was evaluated in the IMPAACT P1093 study (n=75) and 2 weight-band-based pharmacokinetic sub-studies of the ODYSSEY study (n=97). Overall, in pediatric patients who received the recommended doses of either tablets or dispersible tablets once daily showed no additional safety concerns as compared to adults.

IMPAACT P1093 is an ongoing Phase I/II, multicentre, open-label non-comparative study to evaluate the pharmacokinetic parameters, safety, tolerability, and efficacy of dolutegravir in combination regimens in HIV-1 infected INSTI-naive infants, children, and adolescents.

Through Week 24, Grade 1 to 2 ADRs reported by more than one subject were decreased neutrophil count (n = 4), decreased blood bicarbonate (n=3), decreased haemoglobin (n=2), and immune reconstitution inflammatory syndrome (IRIS) (n=2). There were no Grade 3 or 4 drug-related ADRs reported. No ADRs led to discontinuation.

Through Week 24, Grade 3 or 4 laboratory abnormalities reported in more than one subject were decreased neutrophil count (n=11), decreased blood bicarbonate (n=4), decreased haemoglobin (n=3), increased lipase (n=2), and increased blood potassium (n=2). These laboratory events were not

considered to be drug related. The change in median serum creatinine was similar to that observed in adults.

The ODYSSEY study is an ongoing, multicentre, open-label, randomized, non-inferiority study to evaluate the safety, efficacy, and pharmacokinetic parameters of TIVICAY plus 2 NRTIs compared with standard of care in HIV-1-infected paediatric patients younger than 18 years of age. No new ADRs or laboratory abnormalities were identified in the ODYSSEY weight-band-based pharmacokinetic sub-studies compared to those observed in the IMPAACT P1093 study and no ADRs led to discontinuation.

8.3 Less Common Clinical Trial Adverse Reactions

The following treatment-emergent adverse reactions occurred in < 2% of treatment-naïve or treatment-experienced adult patients in any one study receiving TIVICAY in a combination regimen. These events have been included because of their assessment of potential causal relationship and/or severity:

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

General Disorders: Fatigue

Hepatobiliary Disorders: Hepatitis

Immune System Disorders: Hypersensitivity, immune reconstitution inflammatory syndrome

Skin and Subcutaneous Tissue Disorders: Pruritus

Musculoskeletal and Connective Tissue Disorders: Myalgia, myositis

Psychiatric Disorders: Depression, suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)

Renal and Urinary Disorders: Renal impairment

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

A summary of laboratory abnormalities is presented below by the treatment population.

Treatment-Naïve Patients

Selected laboratory abnormalities, with a worsening grade from baseline in ≥ 2% (Grades 2 to 4) of patients in SPRING-2 and SINGLE studies are presented in Table 6.

Table 6 Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Patients in SPRING-2 and SINGLE Studies (Analysis through 48 Weeks)

Laboratory Parameter Preferred Term (Unit)	SPRING-2		SINGLE	
	TIVICAY 50 mg QD+ 2 NRTIs (N = 411)	ISENTRESS 400 mg BID + 2 NRTIs (N = 411)	TIVICAY 50 mg + KIVEXA QD (N = 414)	ATRIPLA QD (N = 419)
ALT (IU/L)				
Grade 2 (>2.5-5.0 x ULN)	8 (2%)	14 (3%)	9 (2%)	20 (5%)
Grade 3 to 4 (>5.0 x ULN)	9 (2%)	7 (2%)	1 (<1%)	2 (<1%)
AST (IU/L)				
Grade 2 (>2.5-5.0 x ULN)	15 (4%)	14 (3%)	7 (2%)	13 (3%)

Laboratory Parameter Preferred Term (Unit)	SPRING-2		SINGLE	
	TIVICAY 50 mg QD+ 2 NRTIs (N = 411)	ISENTRESS 400 mg BID + 2 NRTIs (N = 411)	TIVICAY 50 mg + KIVEXA QD (N = 414)	ATRIPLA QD (N = 419)
Grade 3 to 4 (>5.0 x ULN)	11 (2%)	9 (2%)	0	10 (2%)
Total Bilirubin (μmMol/L)				
Grade 2 (1.6-2.5 x ULN)	8 (2%)	8 (2%)	2 (<1%)	1 (<1%)
Grade 3 to 4 (>2.5 x ULN)	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Creatine kinase (IU/L)				
Grade 2 (6.0-9.9 x ULN)	8 (2%)	14 (3%)	15 (4%)	7 (2%)
Grade 3 to 4 (≥10.0 x ULN)	20 (5%)	14 (3%)	11 (3%)	19 (5%)
Hyperglycemia (mmol/L)				
Grade 2 (6.95-13.88 mmol/L)	24 (6%)	23 (6%)	28 (7%)	19 (5%)
Grade 3 to 4 (>13.88 mmol/L)	2 (<1%)	6 (1%)	6 (1%)	1 (<1%)
Lipase (U/L)				
Grade 2 (>1.5-3.0 x ULN)	23 (6%)	25 (6%)	33 (8%)	30 (7%)
Grade 3 to 4 (>3.0 x ULN)	7 (2%)	14 (3%)	11 (3%)	8 (2%)
Phosphorus, inorganic (mmol/L)				
Grade 2 (0.65-0.80 mmol/L)	34 (8%)	48 (12%)	37 (9%)	52 (12%)
Grade 3 to 4 (<0.65mmol/L)	5 (1%)	7 (2%)	5 (1%)	12 (3%)
Total neutrophils (10^3/μL)				
Grade 2 (0.75-0.99 x 10^9)	15 (4%)	11 (3%)	10 (2%)	15 (4%)
Grade 3 to 4 (<0.75 x 10^9)	8 (2%)	7 (2%)	7 (2%)	12 (3%)

ULN = Upper limit of normal

The mean change from baseline observed for selected lipid values is presented in Table 7.

Table 7 Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SPRING-2 and SINGLE Studies (Week 48 Analysis)

Laboratory Parameter Preferred Term (Unit)	SPRING-2		SINGLE	
	TIVICAY 50 mg QD + 2 NRTIs (N = 411)	ISENTRESS 400 mg BID + 2 NRTIs (N = 411)	TIVICAY 50 mg + KIVEXA QD (N = 414)	ATRIPLA QD (N = 419)
Cholesterol (mmol/L)*	0.18	0.23	0.44	0.62
HDL cholesterol (mmol/L)	0.07	0.07	0.14	0.21
LDL cholesterol** (mmol/L)	0.08	0.09	0.22	0.34
Total cholesterol/HDL (ratio)	-0.04	-0.05	-0.09	-0.10
Triglycerides (mmol/L)	0.10	0.10	0.20	0.21

SINGLE Study: p-value versus ATRIPLA at Week 48; p-value adjusted for baseline value and stratification factors: *p=0.005, **p=0.032

Treatment-experienced and Integrase Inhibitor-Naïve Patients

Selected laboratory abnormalities, with a worsening grade from baseline, in ≥ 2% (Grades 2 to 4) of patients are presented in Table 8. The mean change from baseline observed for lipid values was similar across both treatment groups at Week 48.

Table 8 Selected Laboratory Abnormalities (Grades 2 to 4) in Antiretroviral Treatment-Experienced and Integrase Inhibitor-Naïve Patients in the SAILING Trial (Week 48 Analysis)

Laboratory Parameter Preferred Term (Unit)	TIVICAY 50 mg QD + BR[a] (N = 357)	ISENTRESS 400 mg BID + BR[a] (N = 362)
ALT (IU/L)		
Grade 2 (>2.5-5.0 x ULN)	13 (4%)	9 (2%)
Grade 3 to 4 (>5.0 x ULN)	9 (3%)	7 (2%)
AST (IU/L)		
Grade 2 (>2.5-5.0 x ULN)	7 (2%)	16 (4%)
Grade 3 to 4 (>5.0 x ULN)	12 (3%)	5 (1%)
Bilirubin (μmol/L)		
Grade 2 (1.6-2.5 x ULN)	23 (6%)[b]	26 (7%)[b]
Grade 3 to 4 (>2.5 x ULN)	21 (6%)[b]	14 (4%)[b]
Creatine kinase (IU/L)		
Grade 2 (6.0-9.9 x ULN)	4 (1%)	8 (2%)
Grade 3 to 4 (≥10.0 x ULN)	7 (2%)	4 (1%)
Hyperglycemia (mmol/L)		
Grade 2 (6.95-13.88 mmol/L)	32 (9%)	25 (7%)
Grade 3 to 4 (>13.88 mmol/L)	4 (1%)	7 (2%)
Lipase (U/L)		
Grade 2 (>1.5-3.0 x ULN)	26 (7%)	30 (8%)
Grade 3 to 4 (>3.0 x ULN)	4 (1%)	7 (2%)
Total neutrophils (10^3/μL)		
Grade 2 (0.75-0.99 x 10^9)	12 (3%)	10 (3%)
Grade 3 to 4 (<0.75 x 10^9)	12 (3%)	10 (3%)

[a] Background Regimen

[b] Grade 2: 20/23 on dolutegravir and 23/26 on raltegravir received atazanavir.
Grade 3 to 4: 16/21 on dolutegravir and 11/14 on raltegravir received atazanavir.
ULN = Upper limit of normal.

Treatment-experienced and Integrase Inhibitor-Resistant Patients

In VIKING-3 at Week 48, treatment-emergent changes in clinical chemistry to Grade 3 events occurred in 21% (39/183) of patients and 5% (10/183) had a Grade 4 event. The most common laboratory abnormality was Grade 3 to 4 elevated creatine kinase (5%, 9/183). Two percent (4/183) of patients had a Grade 3 to 4, treatment-emergent hematology laboratory abnormality, with neutropenia (2%, 3/183) being the most frequently reported.

Changes in Clinical Laboratory Values

Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. Increases in serum creatinine occurred within the first 4 weeks of treatment with TIVICAY and remained stable through 48 weeks. In treatment-naïve

patients a mean change from baseline of 9.96 μmol/L (range: -53 μmol/L to 54.8 μmol/L) was observed after 48 weeks of treatment. Creatinine increases were comparable by background NRTIs, and were similar in treatment-experienced patients (see 10.2 Pharmacodynamics, Effects on Renal Function).

Increases in total bilirubin (without clinical jaundice) were observed on TIVICAY and ISENTRESS (but not efavirenz) arms in the programme. These changes of -0.04 μmol/L (range -24 μmol/L to 14 μmol/L) are not considered clinically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1) (see 10.3 Pharmacokinetics, Metabolism).

In Phase III studies, Grade 3 to 4 creatine phosphokinase (CPK) abnormalities were reported 3% to 5% in treatment-naïve patients, 2% in treatment-experienced INSTI-naïve subjects, and 4% in INSTI-resistant patients with TIVICAY therapy. Cases of myalgia or myositis with concurrent CPK elevations have been reported and relationship with the use of TIVICAY could not be excluded.

8.5 Post-Market Adverse Reactions

Hepatobiliary disorders: acute hepatic failure

Musculoskeletal and connective tissue disorders: arthralgia, myalgia

Psychiatric disorders: anxiety*

*In a post marketing analysis of clinical trial data, the total number of anxiety cases seen with TIVICAY therapy was 4% (n=1672), versus the total number of anxiety cases seen with comparator arms of 5% (n=1681).

Investigations: weight increased

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, dolutegravir inhibited the renal organic cation transporter, OCT2 (IC50 = 1.93 micromolar), multidrug and toxin extrusion transporter (MATE) 1 (IC50 = 6.34 micromolar) and MATE2-K (IC50 = 24.8 micromolar). Dolutegravir has a low potential to affect the transport of MATE2-K substrates. *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2. Based on this observation, TIVICAY may increase plasma concentrations of drugs in which excretion is dependent upon OCT2 (for example dofetilide, fampridine (also known as dalfampridine) [see 2 CONTRAINDICATIONS], metformin) or MATE1 (see Table 9).

In vitro, dolutegravir inhibited the basolateral renal transporters: organic anion transporter (OAT) 1 (IC50 = 2.12 micromolar) and OAT3 (IC50 = 1.97 micromolar). Based upon the dolutegravir unbound plasma concentration, in silico modelling and no notable effect on the in vivo pharmacokinetics of the OAT substrates tenofovir and para aminohippurate, dolutegravir thus has a low propensity to cause drug interactions via inhibition of OAT transporters.

In vitro, dolutegravir did not inhibit (IC50 >50 μM) the enzymes: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or transporters: P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, or multidrug resistance protein (MRP)2 or MRP4. In vitro, dolutegravir did not induce CYP1A2, CYP2B6, or

CYP3A4. Based on these data, TIVICAY is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

In drug interaction studies, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following: midazolam, tenofovir, methadone, rilpivirine, daclatasvir and oral contraceptives containing norgestimate and ethinyl estradiol. Using cross-study comparisons to historical pharmacokinetic data for each interacting drug, dolutegavir did not appear to affect the pharmacokinetics of the following drugs: atazanavir, darunavir, efavirenz, etravirine, fosamprenavir, lopinavir, ritonavir, boceprevir, and telapravir.

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, CYP3A4, Pgp, and BCRP in vitro; therefore drugs that induce those enzymes and transporters, may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir.

Co-administration of dolutegravir and other drugs that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration (see Table 9).

In vitro, dolutegravir is not a substrate of human OATP1B1, OATP1B3, or OCT1, therefore drugs that solely modulate these transporters are not expected to affect dolutegravir plasma concentration.

Etravirine significantly reduced plasma concentrations of dolutegravir but the effect of etravirine was mitigated by co-administration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir.

Tenofovir, nelfinavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin, daclatasvir and omeprazole had no clinically significant effect on dolutegravir pharmacokinetics.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 9 Established or Potential Drug-Drug Interactions

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 (ETR)	Dolutegravir↓ ETR↔	The recommended QD dose of TIVICAY (see Table 1) should be given twice daily when co-administered with etravirine without boosted protease inhibitors. In pediatric patients, increase the weight-based dose to twice daily (Table 2). No dose adjustment is needed in these patients if etravirine is taken with atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir. TIVICAY should only be used with etravirine when co-administered with atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in INSTI resistant patients.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)[a]	Dolutegravir↓ EFV ↔	The recommended QD dose of TIVICAY (see Table 1) should be given twice daily when co-administered with efavirenz in ART-naïve and ART-experienced, INSTI-naïve patients. Alternative combinations that do not include efavirenz should be used where possible in INSTI-resistant patients[b]. In pediatric patients, increase the weight-based dose to twice daily (Table 2).
Non-nucleoside Reverse Transcriptase Inhibitor: Nevirapine	Dolutegravir↓	Co-administration with nevirapine should be avoided because there are insufficient data to make a dosing recommendation.
Protease Inhibitor: Atazanavir (ATV)	Dolutegravir↑ ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV/RTV)	Dolutegravir↑ ATV↔ RTV↔	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Tipranavir/ritonavir[a] (TPV+RTV)	Dolutegravir↓ TPV ↔	The recommended QD dose of TIVICAY (see Table 1) should be given twice daily when co-administered with tipranavir/ritonavir in ART-

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir and/or Concomitant Drug	Clinical Comment
		naïve and ART-experienced, INSTI-naïve patients. In pediatric patients, increase the weight-based dose to twice daily (Table 2). Alternative combinations that do not include tipranavir/ritonavir should be used where possible in INSTI-resistant patients[b].
Protease Inhibitor: Fosamprenavir/ritonavir[a] (FPV/RTV)	Dolutegravir↓ FPV ↔ RTV ↔	A dose adjustment to the recommended QD dose twice daily should be given in ART-naive and ART-experienced, INSTI-naive adult patients (see Table 1). In pediatric patients, increase the weight-based dose to twice daily (Table 2). Alternative combinations that do not include fosamprenavir/ritonavir should be used where possible in INSTI-resistant patients[b].
Other Agents		
Antiarrhythmic: Dofetilide	Dofetilide ↑	Co-administration of dolutegravir has the potential to increase dofetilide plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. TIVICAY and dofetilide co-administration is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration.
Potassium channel blocker: Fampridine (also known as dalfampridine)	Fampridine/dalfampridine↑	Co-administration is contraindicated with TIVICAY due to potential for seizures associated with fampridine/dalfampridine.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir and/or Concomitant Drug	Clinical Comment
Anticonvulsants: Oxcarbazepine Phenytoin Phenobarbital Carbamazepine	Dolutegravir↓	The recommended QD dose of TIVICAY (see Table 1) should be given twice daily in adults when co-administered with these metabolic inducers. In pediatric patients, increase the weight-based dose to twice daily (Table 2). Co-administration with these metabolic inducers should be avoided in INSTI-resistant patients.
Medications containing polyvalent cations (e.g. Mg or Al) Cation-containing antacids[a] or laxative, sucralfate, buffered medications	Dolutegravir↓	TIVICAY is recommended to be administered 2 hours before or 6 hours after taking medications containing polyvalent cations.
Calcium and iron supplements[a]	Dolutegravir ↓	When taken with food, TIVICAY and calcium and/or iron supplements or multivitamins containing calcium and/or iron can be taken at the same time. Under fasting conditions, TIVICAY should be taken 2 hours before or 6 hours after taking supplements containing calcium and/or iron.
Metformin	Metformin ↑	Consider metformin dose adjustments when starting or stopping concomitant treatment to maintain glycemic control.
Rifampin[a]	Dolutegravir ↓	The recommended QD dose of TIVICAY (see Table 1) should be given twice daily when co-administered with rifampin in ART-naïve and ART-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily (Table 2). Alternatives to rifampin should be used where possible for INSTI-resistant patients[b].

[a] See 10.3 Pharmacokinetics for magnitude of interaction (Table 11 and Table 12).

[b] The lower dolutegravir exposure when co-administered with potential metabolic inducers may result in loss of therapeutic effect and development of resistance to dolutegravir or other co-administered antiretroviral agents in patients with suspected or confirmed INSTI-resistance.

9.5 Drug-Food Interactions

The rate and extent of absorption of dolutegravir increased while the time to reach maximum concentrations was prolonged when TIVICAY tablets were administered with food. The impact of food on the bioavailability of the TIVICAY dispersible tablets was not evaluated (see, 4.1 Dosing Considerations and 10.3 Pharmacokinetics, Effects of Food on Oral Absorption).

9.6 Drug-Herb Interactions

No interaction study has been conducted, however, St. John's Wort is a potent CYP3A inducer and may potentially decrease dolutegravir plasma concentration. In adults, the recommended QD dose of TIVICAY twice daily (see Table 1) may be considered when taken together with St. John's Wort. St. John's Wort should be avoided in INSTI-resistant patients. In pediatric patients the weight-based, once-daily dose should be administered twice-daily (see Table 2).

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration, which is essential for the HIV replication cycle. *In vitro*, dolutegravir dissociates slowly from the active site of the wild-type integrase-DNA complex (t ½ 71 hours). 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.

10.2 Pharmacodynamics

In a randomized, dose-ranging trial, HIV-1-infected subjects treated with dolutegravir monotherapy (ING111521) demonstrated rapid and dose-dependent antiviral activity, with mean declines from baseline to Day 11 in HIV-1 RNA of 1.5, 2.0, and 2.5 $\log_{10}$ for dolutegravir 2 mg, 10 mg, and 50 mg once daily, respectively. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

Effects on Electrocardiogram: In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects 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) was 1.99 msec (1-sided 95% upper CI: 4.53 msec). TIVICAY did not prolong the QTc interval for 24 hours post-dose**.**

Effects on Renal Function: The effect of dolutegravir on serum creatinine clearance (CrCl), glomerular filtration rate (GFR) using iohexol as the probe and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled study in 37 healthy subjects, who were administered dolutegravir 50 mg once daily (n=12), 50 mg twice daily (n=13) or placebo once daily (n=12) for 14 days. A decrease in CrCl, as determined by 24-hour urine collection, was observed with both doses of dolutegravir (9% and 13%, for dolutegravir 50 mg once daily and twice daily, respectively). Dolutegravir had no significant effect on GFR or ERPF at either dose level.

10.3 Pharmacokinetics

The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult patients and HIV-1-infected adult patients. Dolutegravir pharmacokinetics are generally similar between healthy subjects and HIV-infected patients. The non-linear exposure of dolutegravir following 50 mg twice daily compared with 50 mg once daily in HIV-1-infected patients (Table 10) was attributed to the use of metabolic inducers in their background antiretroviral regimens (e.g. darunavir/ritonavir) of subjects receiving dolutegravir 50 mg twice daily. Dolutegravir was administered without regard to food in these trials.

Table 10 Steady-State Dolutegravir Pharmacokinetic Parameter Estimates in HIV-1-Infected Adults

Parameter	50 mg QD Geometric mean (% CV)[a]	50 mg BID Geometric mean (% CV)[b]
$AUC_{(0-24)}$ (mcg.hr/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 and VIKING-3

Following administration of a 25 mg dose of a dispersion of the 5 mg dispersible tablets there was an increase in AUC_T and C_{max} by approximately 63% and 79%, respectively when compared to administration of a 25 mg dose of the 25 mg tablets under fasting conditions. Similarly, when a 25 mg dose of the 5 mg dispersible tablets were administered whole with water, there was an increase in AUC_T and C_{max} by approximately 55% and 80% when compared to administration of the same dose of the 25 mg tablets under fasting conditions.

Absorption

Following oral administration peak plasma concentrations were observed 2 to 3 hours post-dose for the tablet formulation. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days of dosing with average accumulation ratios for AUC, C_{max}, $C_{24\ hr}$ ranging from 1.2 to 1.5. Dolutegravir plasma concentration increased in a less than dose proportional manner above 50 mg. The absolute bioavailability of dolutegravir has not been established.

Distribution

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

Cerebrospinal Fluid (CSF): In 12 treatment-naïve subjects on dolutegravir plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 18 ng/mL (ranging from 4 to 23 ng/mL) 2 to 6 hours post-dose after 2 weeks of treatment. The clinical relevance of this finding has not been established.

Metabolism

Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A. Renal elimination of unchanged drug was low (< 1% of the dose). After a single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose was excreted unchanged in the faeces. Thirty-one percent of the total oral

dose was excreted in the urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), N-dealkylation metabolite (3.6% of total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose).

Elimination

Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 0.9-1.05 L/hr based on population pharmacokinetic analyses.

Effects of Food on Oral Absorption

The rate and extent of absorption of dolutegravir increased while the time to reach maximum concentrations was prolonged when TIVICAY tablets were administered with food. When compared to administration under fasting conditions, low, moderate and high fat meals increased AUC_T by 34%, 42% and 67%, respectively, $AUC_{(0-\infty)}$ by 33%, 41%, and 66%, respectively, C_{max} by 46%, 52%, and 67%, respectively and prolonged T_{max} to 3, 4, and 5 hours, respectively. The impact of food on the bioavailability of the TIVICAY dispersible tablets was not evaluated.

Drug interactions

Drug interaction studies were performed with TIVICAY and other drugs likely to be co-administered or commonly used as probes for pharmacokinetic interactions. As there is low propensity of dolutegravir to alter the pharmacokinetics of other drugs dependent on hepatic metabolism (Table 11), the primary focus of these drug interaction studies was to evaluate the effect of co-administered drug on dolutegravir (Table 12).

Dosing recommendations as a result of established and other potentially significant drug-drug interactions with TIVICAY are provided in Table 9.

Table 11 Summary of Effect of Dolutegravir on the Pharmacokinetics of Co-administered Drugs

Co-administered Drug(s) and Dose(s)	Dose of TIVICAY	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Co-administered Drug With/Without Dolutegravir No Effect = 1.00		
			C_τ or C_{24}	AUC	C_{max}
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	1.02 (0.93, 1.11)	1.03 (0.96, 1.11)	0.99 (0.91, 1.08)
Methadone 20 to 150 mg	50 mg twice daily	12	0.99 (0.91, 1.07)	0.98 (0.91, 1.06)	1.00 (0.94, 1.06)
Midazolam 3 mg	25 mg once daily	10	_	0.95 (0.79, 1.15)	_
Norgestimate 0.25 mg	50 mg twice daily	15	0.93 (0.85, 1.03)	0.98 (0.91, 1.04)	0.89 (0.82, 0.97)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.21 (1.07, 1.38)	1.06 (0.98, 1.16)	1.10 (0.99, 1.22)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	16	1.19 (1.04, 1.35)	1.12 (1.01, 1.24)	1.09 (0.97, 1.23)
Metformin 500 mg twice daily	50 mg once daily	14	_	1.79 (1.65, 1.93)	1.66 (1.53, 1.81)
Metformin 500 mg twice daily	50 mg twice daily	14	_	2.45 (2.25, 2.66)	2.11 (1.91, 2.33)

Table 12 Summary of Effect of Co-administered Drugs on the Pharmacokinetics of Dolutegravir

Co-administered Drug(s) and Dose(s)	Dose of TIVICAY	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters With/Without Co-administered Drugs No Effect = 1.00		
			C_τ or C_{24}	AUC	C_{max}
Atazanavir 400 mg once daily	30 mg once daily	12	2.80 (2.52, 3.11)	1.91 (1.80, 2.03)	1.50 (1.40, 1.59)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	2.21 (1.97, 2.47)	1.62 (1.50, 1.74)	1.34 (1.25, 1.42)
Tenofovir 300 mg once daily	50 mg once daily	15	0.92 (0.82, 1.04)	1.01 (0.91, 1.11)	0.97 (0.87, 1.08)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.62 (0.56, 0.69)	0.78 (0.72, 0.85)	0.89 (0.83, 0.97)
Efavirenz 600 mg once daily	50 mg once daily	12	0.25 (0.18, 0.34)	0.43 (0.35, 0.54)	0.61 (0.51, 0.73)

Co-administered Drug(s) and Dose(s)	Dose of TIVICAY	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters With/Without Co-administered Drugs No Effect = 1.00		
			C_τ or C_{24}	AUC	C_{max}
Etravirine 200 mg twice daily	50 mg once daily	15	0.12 (0.09, 0.16)	0.29 (0.26, 0.34)	0.48 (0.43, 0.54)
Etravirine + darunavir/ritonavir 200 mg + 600/100 mg twice daily	50 mg once daily	9	0.63 (0.52, 0.76)	0.75 (0.69, 0.81)	0.88 (0.78, 1.00)
Etravirine + lopinavir/ritonavir 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.28 (1.13, 1.45)	1.11 (1.02, 1.20)	1.07 (1.02, 1.13)
Fosamprenavir/ritonavir 700 mg + 100 mg twice daily	50 mg once daily	12	0.51 (0.41, 0.63)	0.65 (0.54, 0.78)	0.76 (0.63, 0.92)
Lopinavir/ritonavir 400/100 mg twice daily	30 mg once daily	15	0.94 (0.85, 1.05)	0.97 (0.91, 1.04)	1.00 (0.94, 1.07)
Maalox	50 mg single dose	16	0.26 (0.21, 0.31)	0.26 (0.22, 0.32)	0.28 (0.23, 0.33)
Maalox 2 hrs after dolutegravir	50 mg single dose	16	0.70 (0.58, 0.85)	0.74 (0.62, 0.90)	0.82 (0.69, 0.98)
Calcium Carbonate 1200 mg simultaneous administration (fasted)	50 mg single dose	12	0.61 (0.47, 0.80)	0.61 (0.47, 0.80)	0.63 (0.50, 0.81)
Calcium Carbonate 1200 mg simultaneous administration (fed)	50 mg single dose	11	1.08 (0.81, 1.42)	1.09 (0.84, 1.43)	1.07 (0.83, 1.38)
Calcium Carbonate 1200 mg 2 hrs after dolutegravir	50 mg single dose	11	0.90 (0.68, 1.19)	0.94 (0.72, 1.23)	1.00 (0.78, 1.29)
Ferrous Fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.44 (0.36, 0.54)	0.46 (0.38, 0.56)	0.43 (0.35, 0.52)
Ferrous Fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.00 (0.81, 1.23)	0.98 (0.81, 1.20)	1.03 (0.84, 1.26)

Co-administered Drug(s) and Dose(s)	Dose of TIVICAY	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters With/Without Co-administered Drugs No Effect = 1.00		
			C_τ or C_{24}	AUC	C_{max}
Ferrous Fumarate 324 mg 2 hrs after dolutegravir	50 mg single dose	10	0.92 (0.74, 1.13)	0.95 (0.77, 1.15)	0.99 (0.81, 1.21)
Multivitamin One tablet once daily	50 mg single dose	16	0.68 (0.56, 0.82)	0.67 (0.55, 0.81)	0.65 (0.54, 0.77)
Omeprazole 40 mg once daily	50 mg single dose	12	0.95 (0.75, 1.21)	0.97 (0.78, 1.20)	0.92 (0.75, 1.11)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.17 (1.06, 1.28)	1.11 (1.03, 1.20)	1.06 (0.99, 1.14)
Rifampin[a] 600 mg once daily	50 mg twice daily[a]	11	0.28 (0.23, 0.34)	0.46 (0.38, 0.55)	0.57 (0.49, 0.65)
Rifampin[b] 600 mg once daily	50 mg twice daily[b]	11	1.22 (1.01, 1.48)	1.33 (1.15, 1.53)	1.18 (1.03, 1.37)
Rifabutin 300 mg once daily	50 mg once daily	9	0.70 (0.57, 0.87)	0.95 (0.82, 1.10)	1.16 (0.98, 1.37)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.22 (1.15, 1.30)	1.12 (1.05, 1.19)	1.13 (1.06, 1.21)
Tipranavir/ritonavir 500/200 mg twice daily	50 mg once daily	14	0.24 (0.21, 0.27)	0.41 (0.38, 0.44)	0.54 (0.50, 0.57)
Telaprevir 750 mg every 8 hours	50 mg once daily	15	1.37 (1.29, 1.45)	1.25 (1.20, 1.31)	1.18 (1.11, 1.26)
Boceprevir 800 mg every 8 hours	50 mg once daily	13	1.08 (0.91, 1.28)	1.07 (0.95, 1.20)	1.05 (0.96, 1.15)
Carbamazepine 300 mg twice daily	50 mg once daily	14	0.27 (0.24, 0.31)	0.51 (0.48, 0.55)	0.67 (0.61, 0.73)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.06 (0.88, 1.29)	0.98 (0.83, 1.15)	1.03 (0.84, 1.25)

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

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

Special Populations and Conditions

Pediatrics: The pharmacokinetics, safety, virologic and immunologic responses were evaluated in HIV-1 infected pediatric patients aged 4 weeks to <18 years (weighing ≥ 3 kg), who received TIVICAY in an ongoing open-label, multicentre, dose-finding non-comparative clinical trial; IMPAACT P1093. Additional safety and pharmacokinetics data were also evaluated from 2 weight-band-based

pharmacokinetic substudies in ODYSSEY, an ongoing open-label, randomized, non-inferiority trial. The pharmacokinetic parameters of TIVICAY in pediatric patients weighing at least 3 kg from these studies were comparable to those of HIV-1-infected adults receiving 50 mg once daily (Table 13). See 4.2 Recommended Dose and Dosage Adjustment, Pediatric.

Table 13 Summary of Pharmacokinetic Parameters in Pediatric HIV-1 Infected Subjects (Pooled Analyses for IMPAACT P1093 and ODYSSEY[a] Trials)

Weight (n)	Dosage Form of TIVICAY[b]	Dose of TIVICAY	Pharmacokinetic Parameter Estimates Geometric Mean (%CV)		
			C_{max} (mcg/mL)	$AUC_{(0-24)}$ (mcg.h/mL)	C_{24} (ng/mL)
3 kg to <6 kg (n = 8)	Dispersible Tablets	5 mg once daily	3.80 (34)	49.37 (49)	962 (98)
6 to <10 kg [<6 months of age] (n = 4)	Dispersible Tablets	10 mg once daily	5.68 (38)	85.49 (32)	1,821 (41)
[≥6 months of age] (n=17)		15 mg once daily	5.27 (50)	57.17 (76)	706 (177)
10 to <14 kg (n = 13)	Dispersible Tablets	20 mg once daily	5.99 (33)	68.75 (48)	977 (100)
14 to <20 kg (n=19)	Dispersible Tablets	25 mg once daily	5.97 (42)	58.97 (44)	725 (75)
	Tablets	40[c] mg once daily			
20 kg to <25 kg (n=9)	Dispersible Tablets	30 mg once daily	7.16 (26)	71.53 (26)	759 (73)
≥20 kg (n=49)	Tablet	50 mg once daily	4.92 (40)	54.98 (43)	778 (62)

[a] Data from 2 weight-band-based pharmacokinetic sub-studies in the ODYSSEY trial

[b] The bioavailability of TIVICAY 25 mg (taken as 5 x 5mg) dispersible tablets is ~1.6-fold that of TIVICAY 25 mg tablets. The Population PK analysis based on clinical data in pediatric subjects with different formulations and dose strengths demonstrated that DTG bioavailability was approximately 53% higher on a mg per mg basis with the dispersible tablet formulation as compared to the film coated tablet.

[c] No observed data for tablet 40 mg in 14 to <20 kg weight band; dose is recommended based on PopPK model based simulations and the relative bioavailability of dispersible tablet vs. tablet.

See also 8.2.1 Clinical Trial Adverse Reactions-Pediatrics; and 14.1 Clinical Trials by Indication, Pediatric.

- **Geriatrics:** Population pharmacokinetic analysis using pooled pharmacokinetic data from adult studies indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir.
- **Gender:** Population PK analyses using pooled pharmacokinetic data from adult studies revealed

no clinically relevant effect of gender on the exposure of dolutegravir.

- **Ethnic Origin:** Population PK analyses using pooled pharmacokinetic data from Phase IIb and Phase III adult studies revealed no clinically relevant effect of race on the exposure of dolutegravir.
- **Hepatic Insufficiency:** Dolutegravir is primarily metabolized and eliminated by the liver. In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh Score B) to 8 matched healthy adult controls, exposure of dolutegravir from a single 50 mg dose was similar between the two groups. 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, dolutegravir is not recommended for use in patients with severe hepatic impairment.
- **Renal Insufficiency:** Renal clearance of unchanged drug is a minor pathway of elimination for dolutegravir. In a study evaluating the pharmacokinetics of a single 50 mg tablet of dolutegravir comparing 8 subjects with severe renal impairment (CrCL<30 mL/min) to 8 matched healthy controls, the mean AUC, C_{max} and C_{24} of dolutegravir in renally impaired subjects were decreased by 40%, 23% and 43%, respectively. No dosage adjustment is necessary for INSTI-naïve patients with renal impairment or INSTI-experienced patients with mild to moderate renal impairment. Caution is advised for INSTI-experienced patients with severe renal impairment, as the reduced dolutegravir plasma concentrations may result in loss of therapeutic effect and development of resistance. There is limited information on dolutegravir in patients on dialysis.
- **Polymorphisms in Drug Metabolizing Enzymes:** In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n=7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n=41).
- **Hepatitis B/Hepatitis C Co-infection:** Population analyses using pooled pharmacokinetic data from adult studies indicated no clinically relevant effect of hepatitis C co-infection on the pharmacokinetics of dolutegravir. There were limited data on hepatitis B co-infection.

11 STORAGE, STABILITY AND DISPOSAL

TIVICAY 5 mg dispersible tablets store up to 25 ˚C. TIVICAY 10, 25 and 50 mg tablets store up to 30 ˚C.

Store TIVICAY 5 mg dispersible tablets and 10 mg tablets in the original package in order to protect from moisture. Keep the bottle tightly closed. Do not remove the silica gel desiccant.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special requirements for use or handling of this product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

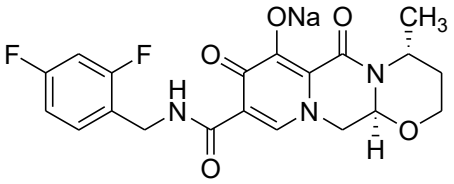
Drug Substance

Proper name: dolutegravir sodium

Chemical name: sodium (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazin-7-olate

Molecular formula and molecular mass: $C_{20}H_{18}F_2N_3NaO_5$, 441.36 g/mol

Structural formula:



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

14 CLINICAL TRIALS

The efficacy of TIVICAY in treatment-naïve, HIV-1-infected patients (n=1,655), is based on analyses of data from two studies, SPRING-2 (ING113086) and SINGLE (ING114467). The efficacy of TIVICAY in treatment-experienced, INSTI-naïve (n=715) and INSTI-resistant (n=183), HIV-1-infected patients is based on analyses of data from one study, SAILING (ING111762) and one study, VIKING-3 (ING112574), respectively. The SPRING-2, SINGLE, SAILING and VIKING-3 studies were conducted using the 50 mg tablet dose. The use of TIVICAY in pediatric patients aged 4 weeks and older is based on the ongoing evaluation of safety, pharmacokinetics and efficacy through 24 weeks in a multicentre, open-label trial in patients without INSTI-resistance. The IMPAACT and ODYSSEY studies were conducted with both the tablet and dispersible tablet formulations.

14.1 Clinical Trials by Indication

Treatment of human immunodeficiency virus (HIV-1) infection in adults and in INSTI-naïve pediatric patients aged 4 weeks and older and weighing at least 3 kg

Trial Design and Study Demographics

Treatment-Naïve Patients

The efficacy of dolutegravir in HIV-infected, therapy-naïve subjects is based on the analyses of 48-week data from two randomized, international, double-blind, active-controlled trials, SPRING-2 (ING113086) and SINGLE (ING114467).

In SPRING-2, 822 adults were randomized and received at least one dose of either TIVICAY 50 mg once daily or ISENTRESS 400 mg twice daily, both administered with fixed-dose dual NRTI therapy (either KIVEXA [ABC/3TC] or TRUVADA [TDF/FTC]).

In SINGLE, 833 patients were randomized and received at least one dose of either TIVICAY 50 mg once daily with fixed-dose abacavir-lamivudine (KIVEXA) or fixed-dose efavirenz-tenofovir-emtricitabine

(EFV/TDF/FTC, ATRIPLA). Table 14 shows baseline characteristics of patients in the SPRING-2 study and SINGLE study. The baseline characteristics were similar between treatment groups. Side-by-side tabulation is to simplify presentation; direct comparisons across studies should not be made due to differing study designs.

Table 14 Baseline Population Characteristics in ART-Naïve, HIV-1-Infected Adult Patients (SPRING-2 and SINGLE)

Demographic Characteristics	SPRING-2		SINGLE	
	TIVICAY 50 mg QD N=411 n (%)	ISENTRESS 400 mg BID N=411 n (%)	TIVICAY 50 mg + ABC/3TC QD N=414 n (%)	ATRIPLA QD N=419 n (%)
Age in Years, median (range)	37 (18-68)	35 (18-75)	36 (18-68)	35 (18-85)
Sex				
Male	348 (85)	355 (86)	347 (84)	356 (85)
Female	63 (15)	56 (14)	67 (16)	63 (15)
Race				
African American/African Heritage	49 (12)	39 (9)	98 (24)	99 (24)
American Indian or Alaska Native	7 (2)	9 (2)	13 (3)	17 (4)
White – White/Caucasian/European Heritage	346 (84)	352 (86)	284 (69)	285 (68)
Median Baseline HIV-1 RNA (log_{10} c/mL)	4.52	4.58	4.67	4.70
≤100,000	297 (72)	295 (72)	280 (68)	288 (69)
>100,000	114 (28)	116 (28)	134 (32)	131 (31)
Median Baseline CD4+ (cells/mm^3)	359.0	362.0	334.5	339.0
<200	55 (13)	50 (12)	57 (14)	62 (15)
200 to <350	144 (35)	139 (34)	163 (39)	159 (38)
≥350	212 (52)	222 (54)	194 (47)	198 (47)
Hepatitis B and/or C co-infection[a]				
B only*	7 (2)	8 (2)	-	-
C only	41 (10)	35 (9)	27 (7)	29 (7)
B and C*	1 (<1)	0	-	-
Neither	359 (87)	363 (89)	385 (93)	385 (92)
CDC Category				
A: Asymptomatic or lymphadenopathy or acute HIV	359 (87)	347 (84)	343 (83)	350 (84)
B: Symptomatic, not AIDS	43 (10)	55 (13)	53 (13)	52 (12)
C: AIDS	9 (2)	9 (2)	18 (4)	17 (4)

a. Denominator reflects subjects with result for hepatitis B or hepatitis C; for ISENTRESS arm, N=410

* Hepatitis B co-infection is one of the exclusion criteria in the SINGLE study

Treatment-Experienced (and Integrase Inhibitor-Naïve) Patients

In the international, multicentre, double-blind SAILING study (ING111762), 719 HIV-1-infected, treatment-experienced adults were randomized and received either TIVICAY 50 mg once daily or ISENTRESS 400 mg twice daily with investigator selected background regimen consisting of up to 2

agents (including at least one fully active agent). All patients had at least two-class ART resistance, and 49% of subjects had at least 3-class ART resistance at baseline. The baseline characteristics were similar between treatment groups. The baseline characteristics for patients in the SAILING study are shown in Table 15.

Table 15 Baseline Population Characteristics (SAILING)

Demographic Characteristics	TIVICAY 50 mg QD N=354 n (%)	ISENTRESS 400 mg BID N = 361 n (%)
Age (years)		
Median (Range)	42 (21-69)	43 (18-73)
Sex		
Female	107 (30)	123 (34)
Male	247 (70)	238 (66)
Race		
African American/African heritage	143 (41)	160 (44)
American Indian or Alaska native	10 (3)	17 (5)
White – White/Caucasian/European Heritage	175 (50)	172 (48)
CDC Classification		
A: Asymptomatic or lymphadenopathy or acute HIV	111 (31)	114 (32)
B: Symptomatic, not AIDS	70 (20)	89 (25)
C: AIDS	173 (49)	158 (44)
Hepatitis B and/or C co-infection	49 (14)	65 (18)
B only	17 (5)	16 (4)
C only	31 (9)	48 (13)
B and C	1 (<1)	1 (<1)
Neither	288 (81)	271 (75)
Clade		
B	241 (68)	245 (68)
C	55 (16)	48 (13)
Other	57 (16)	68 (19)
Baseline HIV-1 RNA copies/mL		
<50,000	249 (70)	254 (70)
≥50,000	105 (30)	107 (30)
Baseline CD4+ cells/mm^3		
<50	62 (18)	59 (16)
50 to <200	111 (31)	125 (35)
200 to <350	82 (23)	79 (22)
≥ 350	99 (28)	98 (27)

Integrase Inhibitor-Resistant Patients

VIKING-3 examined the effect of dolutegravir 50 mg twice daily over 7 days of functional monotherapy, followed by optimized background therapy and continued dolutegravir twice daily treatment.

In the multicentre, open-label, single arm VIKING-3 study (ING112574), 183 HIV-1-infected, treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or

elvitegravir resistance received TIVICAY 50 mg twice daily with the current failing background regimen for 7 days, and then received TIVICAY with optimized background therapy from Day 8. Of the 183 patients enrolled, 133 showed INSTI-resistance (genotypic or phenotypic) at Screening and 50 had only historical evidence of resistance (and not at Screening). Table 16 shows baseline characteristics of patients in the VIKING-3 trial.

Table 16 Baseline Characteristics for all 183 patients enrolled that reached Week 24 (VIKING-3)

Demographic Characteristics	ITT-E TIVICAY 50 mg BID N=183 n (%)
Age (years)	
Median (Range)	48 (19-67)
Sex	
Female	42 (23)
Male	141 (77)
Race	
African American/African heritage	49 (27)
American Indian or Alaska native & White	1 (<1)
White	130 (71)
CDC Classification	
A: Asymptomatic or lymphadenopathy or acute HIV	44 (24)
B: Symptomatic, not AIDS	37 (20)
C: AIDS	102 (56)
Hepatitis B and/or C co-infection	
B only	10 (5)
C only	26 (14)
B and C	2 (1)
Baseline CD4+ cell counts cells/mm^3	
Median CD4+ (range)	140.0 (19, 1100)
Prior Antiretroviral Therapy (ART)	
Etravirine	103 (56)
Darunavir-ritonavir	133 (73)
Enfuvirtide	89 (49)
Maraviroc	58 (32)
Median Number of prior ART (range)	14 (3-22)
Median Duration (years) of prior ART (range)	14 (4 months, 27 years)
Number (%) of Major ART Associated Mutations at Baseline	
≥2 NRTI	145 (79)
≥1 NNRTI	137 (75)
≥2 PI	129 (70)
Prevalence of CCR5 and/or CXCR4 Tropism at Baseline	
CCR5	61 (33)
Non-CCR5	113 (62)

Mean reduction from baseline in HIV RNA at Day 8 (primary endpoint) was 1.4 $\log_{10}$ (95% CI 1.3 – 1.5 $\log_{10}$, $p < 0.001$). More than 90% of subjects achieved full response (>1 $\log_{10}$ c/mL decline or <50 c/mL plasma HIV-1 RNA) at Day 8 in the group of subjects without detectable Q148 primary mutations. In subjects with Q148 mutations, virologic response at Day 8 decreased with increasing number of secondary mutations (i.e. viral response rate was dropped to 71% and to 45% in Q148 plus 1 or ≥ 2 secondary substitutions, respectively).

Pediatric

In the ongoing Phase I/II multicentre, non-comparative, open-label study (IMPAACT P1093/ING112578), the pharmacokinetic parameters, safety, tolerability and efficacy of dolutegravir were evaluated in combination regimens in HIV-1-infected treatment-naïve or treatment experienced INSTI-naïve infants, children and adolescents aged ≥4 weeks to <18 years. Subjects were stratified by 5 age cohorts, enrolling adolescents first (Cohort I: aged 12 to <18 years) and then younger children (Cohort IIA: aged 6 to <12 years; Cohort III: aged 2 to <6 years; Cohort IV: aged 6 months to <2 years; and Cohort V, aged 4 weeks to <6 months). Seventy-five subjects received the recommended dose (determined by weight and age) of TIVICAY (see 4.2 Recommended Dose and Dosage Adjustment, Pediatric).

These 75 patients 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 ≥ 50,000 copies/mL and 12% had a CDC HIV clinical classification of category C. Most patients had previously used at least 1 NNRTI (44%) or 1 PI (76%).

Study Results

Treatment-Naïve Patients

Week 48 outcomes (including outcomes by key baseline covariates) for SPRING-2 and SINGLE are shown in Table 17 .

Table 17 Virologic Outcomes of SPRING-2 and SINGLE at 48 Weeks (Snapshot algorithm)

	SPRING-2		SINGLE	
	TIVICAY 50 mg QD + 2 NRTI N=411 n (%)	**ISENTRESS 400 mg BID + 2 NRTI N=411 n (%)**	**TIVICAY 50 mg + KIVEXA QD N=414 n (%)**	**ATRIPLA QD N=419 n (%)**
HIV-1 RNA <50 copies/mL	361 (88)	351 (85)	364 (88)	338 (81)
Treatment Difference*	2.5% (95% CI: -2.2%, 7.1%)		7.4% (95% CI: 2.5%, 12.3%), p = 0.003	
Virologic non-response†	20 (5)	31 (8)	21 (5)	26 (6)
No virologic data at Week 48 window	30 (7)	29 (7)	29 (7)	55 (13)
Reasons: Discontinued study/study drug due to adverse event or death‡	9 (2)	6 (1)	9 (2)	40 (10)
Discontinued study/study drug for other reasons§	21 (5)	23 (6)	20 (5)	14 (3)

	SPRING-2		SINGLE	
	TIVICAY 50 mg QD + 2 NRTI N=411 n (%)	**ISENTRESS 400 mg BID + 2 NRTI N=411 n (%)**	**TIVICAY 50 mg + KIVEXA QD N=414 n (%)**	**ATRIPLA QD N=419 n (%)**
Missing data during window but on study	0	0	0	1 (<1)
HIV-1 RNA <50 copies/mL by Baseline Plasma Viral Load (copies/mL)	n / N (%)	n / N (%)	n / N (%)	n / N (%)
≤100,000	267 / 297 (90)	264 / 295 (89)	253 / 280 (90)	238 / 288 (83)
>100,000	94 / 114 (82)	87 / 116 (75)	111 / 134 (83)	100 / 131 (76)
HIV-1 RNA <50 copies/mL by Baseline CD4+ (cells/ mm^3)				
<200	43 / 55 (78)	34 / 50 (68)	45 / 57 (79)	48 / 62 (77)
200 to <350	128 / 144 (89)	118 / 139 (85)	143 / 163 (88)	126 / 159 (79)
≥350	190 / 212 (90)	199 / 222 (90)	176 / 194 (91)	164 / 198 (83)
HIV RNA <50 copies/mL by NRTI backbone				
KIVEXA [ABC/3TC]	145 / 169 (86)	142 / 164 (87)	364 / 414 (88)	N/A
TRUVADA [TDF/FTC]	216 / 242 (89)	209 / 247 (85)	N/A	338 / 419 (81)
HIV RNA <50 copies/mL by baseline HIV-RNA and NRTI backbone				
≤100,000 c/mL, ABC/3TC	115/132 (87)	110/125 (88)	253 / 280 (90)	N/A
≤100,000 c/mL, TDF/FTC	152/165 (92)	154/170 (91)	N/A	238 / 288 (83)
>100,000 c/mL, ABC/3TC	30/37 (81)	32/39 (82)	111 / 134 (83)	N/A
>100,000 c/mL, TDF/FTC	64/77 (83)	55/77 (71)	N/A	100 / 131 (76)
Gender				
Male	308 / 348 (88)	305 / 355 (86)	307 / 347 (88)	291 / 356 (82)
Female	53 / 63 (84)	46 / 56 (82)	57 / 67 (85)	47 / 63 (75)
Race				
White	306 / 346 (88)	301 / 352 (86)	255 / 284 (90)	238 /285 (84)
Non white	55 / 65 (85)	50 / 59 (85)	109 / 130 (84)	99 / 133 (74)
Age (years)				
<50	324 / 370 (88)	312 / 365 (85)	319 / 361 (88)	302 / 375 (81)
≥50	37 / 41 (90)	39 / 46 (85)	45 / 53 (85)	36 / 44 (82)

* Adjusted for baseline stratification factors

† Includes patients who changed BR to new class or changed BR not permitted per protocol or due to lack of efficacy prior to Week 48 (for SPRING-2 only), patients who discontinued prior to Week 48 for lack or loss of efficacy and patients who are ≥50 copies in the 48 week window.

‡ Includes patients who discontinued due to an adverse event or death at any time point from Day 1 through the Week 48 window if this resulted in no virologic data on treatment during the Week 48 window.

§ Includes reasons such as withdrew consent, loss to follow-up, moved, protocol deviation.

Notes: ABC/3TC = abacavir 600 mg, lamivudine 300 mg in the form of Kivexa/Epzicom fixed dose combination (FDC)
EFV/TDF/FTC = efavirenz 600 mg, tenofovir 300 mg, emtricitabine 200 mg in the form of Atripla FDC.
N = Number of patients in each treatment group

Snapshot algorithm: Subjects whose last HIV-1 RNA result was <50 c/mL in the analysis window (ie, 48 ± 6 weeks) were counted as responders; subjects who were not suppressed or did not have data at the analysis time point were counted as non-responders. The SPRING-2 protocol allowed one switch in backbone NRTI for management of toxic effects; patients who switched NRTI after week 4 were regarded as non-responders according to the Snapshot algorithm.

In the SPRING-2 study, at 48 weeks, virologic suppression (HIV-1 RNA < 50 copies/mL) in the dolutegravir group (88%) was non-inferior to the raltegravir group (85%) (non-inferiority margin – 10%; treatment difference 2.5% 95 CI: -2.2%, 7.1%). Virologic suppression treatment differences were comparable across baseline characteristics (gender, race, age, ART backbone, and baseline viral load) at 48 weeks.

The median changes in CD4+ T cell count from baseline were + 230 cells/mm^3 in the group receiving TIVICAY and the ISENTRESS group at 48 weeks.

Virologic suppression was maintained through 96 weeks (the proportion of subjects achieving HIV-1 RNA <50 copies/mL was 81% for the dolutegravir group and 76% for the raltegravir group, treatment difference 4.5% (95CI: -1.1%, 10.0%)). The median change in CD4+ T cell count from baseline to 96 weeks was 276 cell/mm^3 in the dolutegravir group compared to 264 cells/mm^3 in the ISENTRESS group

*In the SINGLE study, t*here was a statistically significant difference in the proportion of subjects achieving viral suppression (HIV-1 RNA <50 copies/mL) between the group receiving TIVICAY + KIVEXA (88%) compared to the ATRIPLA group (81%) based on the primary 48-week analysis (7.4% 95% CI: 2.5%, 12.3% p=0.003). The virologic suppression treatment differences were comparable across baseline characteristics (gender, race, and age) at Week 48.

At Week 48, the adjusted mean change in CD4+ T cell count from baseline were 267 cells/mm^3 in the group receiving TIVICAY + KIVEXA and 208 cells/mm^3 for the ATRIPLA arm. The adjusted difference and 95% CI were statistically significant at Week 48 [58.9 (33.4, 84.4; p<0.001)] (repeated measure model adjusting for the baseline stratification factors: baseline HIV-1 RNA and baseline CD4+ T cell count, among other factors). This analysis was pre-specified and the Week 48 analysis was adjusted for multiplicity.

The median time to viral suppression was 28 days in the group receiving TIVICAY + KIVEXA and 84 days in the ATRIPLA arm in SINGLE at 48 weeks (p<0.0001). At 28 days (Week 4), 63% of patients in the TIVICAY arm reached virologic suppression, compared to 14% in the ATRIPLA arm.

Virologic suppression was maintained through 96 weeks (the proportion of subjects achieving HIV-1 RNA <50 copies/mL was 80% for the dolutegravir + KIVEXA group and 72% for the ATRIPLA group (treatment difference 8.0%, 95CI: 2.3%, 13.8%, p=0.006)). The adjusted mean change in CD4+ T cell count from baseline was 325 cells/mm^3 in the group receiving TIVICAY + KIVEXA, which continued to be statistically significantly different from the ATRIPLA arm (281 cells/mm^3) (treatment difference 44 cells/mm^3 (95% CI: 14.34, 73.55) p=0.004).

Virologic suppression was maintained through 144 weeks (open-label phase week 96 to 144 week). The proportion of subjects achieving HIV-1 RNA<50 copies/mL was 71% for the dolutegravir + KIVEXA group and 63% for the ATRIPLA group (treatment difference 8.3% (95% CI: 2.0%, 14.6%, p=0.010)). The adjusted mean change in CD4+ T cell count from baseline was 378 cells/mm^3 in the group receiving TIVICAY + KIVEXA, which continued to be statistically significantly different from the ATRIPLA arm (332 cells/mm^3) (treatment difference 47 cells/mm^3 (95% CI: 15.61, 78.20) p=0.003).

Through 96 weeks in SPRING-2 and 144 weeks in SINGLE, no INSTI-resistant mutations or treatment-emergent resistance in background therapy were isolated on the dolutegravir-containing arms.

Treatment-Experienced (and Integrase Inhibitor-Naïve) Patients

Week 48 outcomes (including outcomes by key baseline covariates) for SAILING are shown in Table 18.

Table 18 Virologic Outcomes of SAILING at 48 Weeks (Snapshot algorithm)

	SAILING	
	TIVICAY 50 mg QD + BR N=354§ n/N (%)	ISENTRESS 400 mg BID + BR N=361§ n/N (%)
HIV-1 RNA <50 copies/mL	251/354 (71)	230/361 (64)
Adjusted Treatment Difference‡	7.4% (95% CI: 0.7%, 14.2%), p=0.030	
Virologic non-response†	71/354 (20)	100/361 (28)
No virologic data	32/354 (9)	31/361 (9)
Reasons		
Discontinued study/study drug due to adverse event or death‡	9 (3)	13 (4)
Discontinued study/study drug for other reasons§	16 (5)	14 (4)
Missing data during window but on study	7 (2)	4 (1)
HIV-1 RNA <50 copies/mL by baseline covariates		
Baseline Plasma Viral Load (copies/mL)		
≤50,000 copies/mL	186 / 249 (75)	180 / 254 (71)
>50,000 copies/mL	65 / 105 (62)	50 / 107 (47)
Baseline CD4+ (cells/ mm³)		
<50	33 / 62 (53)	30 / 59 (51)
50 to <200	77 / 111 (69)	76 / 125 (61)
200 to <350	64 / 82 (78)	53 / 79 (67)
≥350	77 / 99 (78)	71 / 98 (73)
Background Regimen		
Phenotypic Susceptibility Score * < 2	70 / 104 (67)	61 / 94 (65)
Phenotypic Susceptibility Score * = 2	181 / 250 (72)	169 / 267 (63)
Genotypic Susceptibility Score * < 2	155 / 216 (72)	129 / 192 (67)
Genotypic Susceptibility Score * = 2	96 / 138 (70)	101 / 169 (60)
No darunavir use	143 / 214 (67)	126 / 209 (60)
Darunavir use with primary PI substitutions	58 / 68 (85)	50 / 75 (67)
Darunavir use without primary PI substitutions	50 / 72 (69)	54 / 77 (70)
Gender		
Male	172 / 247 (70)	156 / 238 (66)
Female	79 / 107 (74)	74 / 123 (60)
Race		
White	133 / 178 (75)	125 / 175 (71)
African-American/African Heritage/Other	118 / 175 (67)	105 / 185 (57)
Age (years)		
<50	196 / 269 (73)	172 / 277 (62)
≥50	55 / 85 (65)	58 / 84 (69)

	SAILING	
	TIVICAY 50 mg QD + BR N=354§ n/N (%)	ISENTRESS 400 mg BID + BR N=361§ n/N (%)
HIV sub type		
Clade B	173 / 241 (72)	159 / 246 (65)
Clade C	34 / 55 (62)	29 / 48 (60)
Other†	43 / 57 (75)	42 / 67 (63)

Adjusted for pre-specified stratification factors

§ 4 patients were excluded from the efficacy analysis due to data integrity at one study site

*The Phenotypic Susceptibility Score (PSS) and the Genotypic Susceptibility Score (GSS) were defined as the total number of ARTs in BR to which a subject's viral isolate showed susceptibility at baseline based upon phenotypic or genotypic resistance tests. Background regimen was restricted to ≤2 ARTs with at least one fully active agent, however, n=11 PSS 0, n=2 PSS 3.

†Other clades included: Complex (n = 42), F1 (n = 32), A1 (n = 18), BF (n = 14), all others n = <10.

Notes: BR = background regimen, DTG = dolutegravir, RAL = raltegravir; N = Number of patients in each treatment group

At Week 48, virologic suppression (HIV-1 RNA < 50 copies/mL) in the dolutegravir arm (71%) was statistically significantly greater than the raltegravir arm (64%), (p=0.030) (see Table 19). Virologic suppression (HIV-1 RNA < 50 copies/mL) treatment differences were comparable across the baseline characteristics of gender, race, and HIV sub type.

The median changes in CD4+ T cell count from baseline were 144.0 cells/mm^3 in the group receiving TIVICAY and 137.0 cells/mm^3 for the ISENTRESS group.

Statistically significantly fewer patients failed therapy with treatment-emergent resistance in the IN gene on TIVICAY (4/354, 1%) than on ISENTRESS (17/361, 5%), p=0.003.

Integrase Inhibitor-Resistant Patients

After the monotherapy phase, patients' background regimens were optimized when possible. Week 24 and Week 48 virologic response and outcomes for VIKING-3 are shown in Table 19.

Table 19 Virologic Outcomes of VIKING-3 at Week 24 and Week 48 (Snapshot Algorithm)

	Week 24	Week 48
	TIVICAY 50 mg BID + OBT (N = 183)	TIVICAY 50 mg BID + OBT (N = 183)
HIV-1 RNA <50 copies/mL	126 (69%)	116 (63%)
Virologic non-response	50 (27%)	58 (32%)
No virologic data		
Reasons		
Discontinued study/study drug due to adverse event or death	5 (3%)	5 (3%)
Discontinued study/study drug for other reasons§	2 (1%)	4 (2%)
Missing data during window but on study	0 (0%)	0 (0%)
Proportion (%) with HIV-1 RNA < 50 c/mL by Baseline Category		
Gender		
Male	96/141 (68)	89/141 (63)
Female	30/42 (71)	27/42 (64)
Race		
White	91/130 (70)	82/130 (63)
African-American/African Heritage/Other	35/53 (66)	34/53 (64)
Median change from baseline in CD4+ cell count (range) in cells/mm³	61.0 (20.0, 130.0)	110.0 (40.0, 190.0)

Of the 183 patients who completed 24 weeks on study or discontinued before data cut-off, 126 (69%) had < 50 copies/mL RNA at Week 24 (FDA Snapshot algorithm). Patients harbouring virus with Q148H/K/R with 2 or more additional Q148-associated secondary mutations (L74I, E138A/K/T, or G140A/C/S) had a marked lower response at Week 24. Background overall susceptibility score (OSS) was not associated with Week 24 response.

Table 20 Virologic Response (HIV-1 RNA <50 copies/mL) by Derived Integrase-Resistance Substitution Group at Week 24 and Week 48 (Intent-to-Treat Exposed Population: Snapshot Algorithm)

Derived Integrase-Resistance Substitution Group	TIVICAY 50 mg BID (N = 183) Week 24	TIVICAY 50 mg BID (N = 183) Week 48
No Q148H/K/R substitution[a]	100/126 (79%)	90/126 (71%)
Q148 + 1 secondary substitution[b]	21/36 (58%)	20/36 (56%)
Q148 + ≥2 secondary substitutions[b]	5/21 (24%)	6/21 (29%)

[a] N155H, Y143C/H/R, T66A, E92Q, or historical resistant evidence only

[b] Includes key secondary substitutions G140A/C/S, E138A/K/T, L74I

The response rate at Week 48 was sustained with 116/183 (63%) patients having HIV-1 RNA <50

copies/mL (Snapshot algorithm). Response was also sustained through Week 48 in patients harbouring virus with Q148 with additional Q148-associated secondary mutations (see Table 20). Background overall susceptibility score (OSS) was not associated with Week 48 response.

Pediatric

Virologic outcomes from IMPAACT P1093 are shown in Table 21. These results include patients who received either tablets or dispersible tablets as per the dosing recommendations.

Table 21 Virologic Outcomes of Treatment of HIV-1–Infected Pediatric Patients in IMPAACT P1093 through Week 24 and Week 48

Virologic Outcomes	IMPAACT P1093 Week 24 (N = 58)[a]		IMPAACT P1093 Week 48 (N = 24)[a]	
	n	% (95% CI)	n	% (95% CI)
Proportion of patients with HIV RNA <50 copies/mL[b,c]	36	62.1 (48.4 - 74.5)	16	66.7 (44.7 - 84.4)
Proportion of patients with HIV RNA <400 copies/mL[b]	50	86.2 (74.6 - 93.9)	18	75 (53.3 - 90.2)
	Median (n)		Median (n)	
Change from baseline in CD4+ cell count (cells/mm^3)	105 (57)	(-93, 338)	149 (23)	(-17, 291)
Change from baseline in CD4+ percent	5.1 (57)	(1, 9.3)	8 (23)	(0, 11)

[a] Virologic outcomes through Week 24 (N = 58) and Week 48 (N = 24) in subsets of participants who received the recommended dose as determined by weight and age

[b] Snapshot algorithm was used in the RNA analysis

[c] Results of less than 200 copies/mL from HIV-1 RNA testing using a lower limit of detection of 200 copies/mL were censored to greater than 50 copies/mL in this analysis

15 MICROBIOLOGY

Antiviral Activity in cell culture

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.51 nM to 2.1 nM in peripheral blood mononuclear cells (PBMCs) and MT-4 cells.

In a viral integrase susceptibility assay using the integrase coding region from 13 clinically diverse clade B isolates, dolutegravir demonstrated antiviral potency similar to laboratory strains, with a mean EC_{50} of 0.52 nM. When tested in PBMC assays against a panel consisting of 24 HIV-1 clinical isolates [group M (clade A, B, C, D, E, F and G) and group O] and 3 HIV-2 clinical isolates, the geometric mean EC_{50} was 0.20 nM (0.02 to 2.14 nM) for HIV-1, while the geometric mean EC_{50} was 0.18 nM (0.09 to 0.61 nM) for HIV-2 isolates.

Antiviral Activity in combination with other antiviral agents

The following drugs were not antagonistic with dolutegravir in *in vitro* assessments conducted in checkerboard format: stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide, maraviroc, adefovir and raltegravir. In addition, the anti-HCV drug ribavirin had no apparent effect on dolutegravir activity.

Effect of Human Serum and Serum Proteins

In vitro studies suggested a 75-fold shift in EC_{50} of dolutegravir in the presence of 100% human serum (by method of extrapolation), and the protein adjusted EC_{90} (PA-IC_{90}) in PBMCs was estimated to be 0.064 μg/mL. Dolutegravir trough concentration for a single 50 mg dose in integrase inhibitor naïve patients was 1.20 μg/mL, 19 times higher than the estimated PA-EC_{90}.

Resistance *in vitro*

Isolation from wild-type HIV-1: Viruses highly resistant to dolutegravir were not observed during the 112-day passage of strain IIIB, with a 4.1-fold maximum fold change (FC) observed for the passaged resistant virus populations with substitutions at the conserved IN positions S153Y and S153F.

Passage of the wild-type HIV-1 strain NL432 in the presence of dolutegravir selected for E92Q (passage population virus FC=3.1) and G193E (passage population virus FC=3.2) substitutions on Day 56. Additional passage of wild-type subtype B, C, and A/G viruses in the presence of dolutegravir selected for R263K, G118R, and S153T.

Anti-HIV Activity Against Resistant Strains: Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent antiviral activity against 2 non-nucleoside (NN)-RTI-resistant, 3 nucleoside (N)-RTI-resistant, and 2 PI-resistant HIV-1 mutant clones (1 triple and 1 sextuple) compared to the wild-type strain.

Integrase Inhibitor-Resistant HIV-1 Strains: Sixty integrase inhibitor-resistant mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) were produced from wild-type virus NL-432 using site-directed mutagenesis. Dolutegravir showed anti-HIV activity (susceptibility) with FC < 5 against 27 of 28 integrase inhibitor-resistant mutant viruses with single substitutions including T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R, and N155H, while for raltegravir and elvitegravir there were 17/28 and 11/21 tested mutant viruses with FC < 5, respectively. In addition, of the 32 integrase inhibitor-resistant mutant viruses with 2 or more substitutions, 23 of 32 showed FC < 5 to dolutegravir compared with FC < 5 for 4 of 32 for raltegravir and FC < 5 for 2 of 25 tested for elvitegravir.

Integrase Inhibitor-Resistant HIV-2 Strains: Site-directed mutant HIV-2 viruses were constructed based on patients infected with HIV-2 and treated with raltegravir who showed virologic failure (n=6). Overall the HIV-2 FCs observed were similar to HIV-1 FCs observed for similar pathway mutations. Dolutegravir FC was <5 against 4 HIV-2 viruses (S163D, G140A/Q148R, A153G/N155H/S163G and E92Q/T97A/N155H/S163D); for E92Q/N155H, dolutegravir FC was 8.5, and for G140S/Q148R, dolutegravir FC was 17. Dolutegravir, raltegravir and elvitegravir all had had the same activity against site-directed mutant HIV-2 with S163D as wild-type, and for the remaining mutant HIV-2 virus raltegravir FC ranges were 6.4 to 420 and elvitegravir FC ranges were 22 to 640.

Clinical Isolates From Raltegravir Treatment Virologic Failure Patients: Thirty clinical isolate samples with genotypic and phenotypic resistance to raltegravir (median FC > 81) were examined for susceptibility to dolutegravir (median FC 1.5) using the Monogram Biosciences PhenoSense assay. The median FC to dolutegravir for isolates containing changes at G140S + Q148H was 3.75; G140S + Q148R was 13.3; T97A + Y143R was 1.05 and N155H was 1.37.

Seven hundred and five raltegravir-resistant isolates (based on RAL FC > 1.5) from raltegravir-experienced patients were analyzed for susceptibility to dolutegravir using the Monogram Biosciences PhenoSense assay. Dolutegravir has a less than or equal to 10 FC against 93.9% of the 705 clinical isolates. Sixteen of 184 isolates with Q148+1 IN mutation and 25 of 92 isolates with Q148 +≥ 2 IN mutations had dolutegravir FC>10.

Resistance *in vivo*: integrase inhibitor-naïve patients (ART-naïve and -experienced)

No INSTI-resistant mutations or treatment-emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment-naïve studies (SPRING-2, and/or SINGLE studies). In the SAILING study for treatment-experienced (and integrase-naïve) patients (n=354 in the dolutegravir arm), treatment-emergent integrase substitutions were observed at Week 48 in 4 of 17 subjects receiving dolutegravir with virologic failure. Of these four, 2 patients had a unique R263K integrase substitution, with a maximum FC of 1.93, 1 patient had a polymorphic V151V/I integrase substitution, with maximum FC of 0.92, and 1 subject had pre-existing integrase mutations and is assumed to have been integrase-experienced or infected with integrase-resistant virus by transmission. Treatment emergent N155H and T97A integrase substitutions along with dolutegravir FC of 2.4 and RAL FC of 113 were observed at Week 84 for one patient who was non-compliant with IP and thus a protocol deviator. Significantly fewer subjects failed therapy at Week 48 with treatment-emergent resistance in the integrase gene on TIVICAY (4/354 [1.0%]), than on raltegravir (17/361 [5%]). The treatment difference was statistically significant in favour of dolutegravir (p=0.003) based on a pre-specified analysis of this key secondary endpoint (see 14 CLINICAL TRIALS).

Resistance *in vivo*: integrase inhibitor-resistant patients

The VIKING-3 study examined dolutegravir (plus optimized background therapy) in patients with pre-existing INSTI-resistance. Thirty six patients (36/183) experienced protocol defined virologic failure through to Week 24. Of these, 32 had paired baseline and PDVF resistance data for analysis and 17/32 (53%) had treatment emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were L74L/M (n=1), E92Q (n=2), T97A (n=9), E138K/A/T (n=8), G140S (n=2), Y143H (n=1), S147G (n=1), Q148H/K/R (n=4), N155H (n=1) and E157E/Q (n=1). Fourteen of the 17 patients with virus exhibiting treatment-emergent mutations harboured Q148 pathway virus present at baseline or historically. Five further patients experienced PDVF between Weeks 24 and 48, and 2 of these 5 had treatment-emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were L74I (n=1), N155H (n=2). Post Week 48, 4 additional subjects experienced PDVF at Week 60 (n=2), Week 72 (n=1) and Week 84 (n=1). Three of these 4 subjects had treatment-emergent mutations. Treatment- emergent mutations or mixtures of mutations observed were T97A (n=1), E138K (n=1), Q148H (n=2), G140S (n=2), N155H (n=1). L74M/V (n=1).

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity/mutagenicity: Dolutegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay. Dolutegravir was not carcinogenic in long-term studies in the mouse and rat at exposures ~14 and ~12 times, respectively, above the 50 mg twice-daily human clinical exposure based on AUC.

Reproductive and Developmental Toxicology: There are no data on the effects of dolutegravir on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility. Dolutegravir did not affect male or female fertility in rats at doses up to 1000 mg/kg/day, the highest dose tested (~24 times the 50 mg twice-daily human clinical exposure based on AUC).

Oral administration of dolutegravir to pregnant rats at doses up to 1000 mg/kg daily from Days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (~27 times the 50 mg twice-daily human clinical exposure based on AUC).

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from Days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity (0.4 times the 50 mg twice-daily human clinical exposure based on AUC). In rabbits, maternal toxicity (decreased food consumption, scant/no faeces/urine, suppressed body weight gain) was observed at 1000 mg/kg (0.4 times the 50 mg twice-daily human clinical exposure based on AUC).

In a non-clinical distribution study in animals, dolutegravir was shown to cross the placenta.

Animal toxicology and/or pharmacology: The effect of prolonged daily treatment with high doses of dolutegravir has been evaluated in repeat oral dose toxicity studies in rats (up to 26 weeks) and in monkeys (up to 38 weeks). The primary effect of dolutegravir was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures approximately 21 and 0.8 times the 50 mg twice-daily human clinical exposure based on AUC, respectively. Because gastrointestinal (GI) intolerance is considered to be due to local drug administration, mg/kg or mg/m^2 metrics are appropriate determinates of safety cover for this toxicity. GI intolerance in monkeys occurred at 15 times the human mg/kg equivalent dose (based on 50 kg human), and 5 times the human mg/m^2 equivalent dose for a clinical dose of 50 mg twice-daily. Dolutegravir was slightly to mildly irritating to skin and eyes in the rabbit.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTIVICAY

dolutegravir tablets
dolutegravir dispersible tablets

Read this carefully before you start taking **TIVICAY** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TIVICAY**.

What is TIVICAY used for?

TIVICAY is used for treatment of HIV-1 (Human Immunodeficiency Virus) infection in adults and children 4 weeks and older and weighing at least 3 kg.

TIVICAY is a type of anti-HIV medicine called an integrase inhibitor. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

TIVICAY is used in combination with other anti-HIV medicines. To control your HIV infection, and to stop your illness from getting worse, you must keep taking all your medicines, unless your healthcare professional tells you otherwise.

How does TIVICAY work?

TIVICAY blocks an enzyme which the virus (HIV) needs in order to make more virus. The enzyme that TIVICAY blocks is called HIV integrase. This helps control HIV infection.

When used with other anti-HIV medicines, TIVICAY may do two things:

1. It may reduce the amount of HIV in your blood. This is called your "viral load".
   -Reducing the amount of HIV in the blood may keep your immune system healthy.
   -This in turn, can help your immune system to fight infection.
2. It may also increase the number of white blood cells, called CD4 (T) cells, that help fight the virus (HIV).

What are the ingredients in TIVICAY?

Medicinal ingredients: dolutegravir (as dolutegravir sodium)

Non-medicinal ingredients:

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

TIVICAY dispersible tablets: Calcium sulfate dihydrate, crospovidone, hypromellose, mannitol, microcrystalline cellulose, polyethylene glycol, povidone K29/32, silicified microcrystalline cellulose, sodium starch glycolate, sodium stearyl fumarate, strawberry cream flavor, sucralose, titanium dioxide.

TIVICAY comes in the following dosage forms:

dispersible tablets: 5 mg

film-coated tablets: 10 mg, 25 mg, 50 mg

Do not use TIVICAY if:

- you are allergic to dolutegravir or any of the other ingredients in TIVICAY (see **What are the ingredients in TIVICAY?**)
- you are taking dofetilide to treat heart conditions, or fampridine (also known as dalfampridine) to treat multiple sclerosis.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TIVICAY. Talk about any health conditions or problems you may have, including if you:

- have liver problems, including hepatitis B or C
- have a history of depression or other mental health problems
- have any other medical condition

Other warnings you should know about:

Serious Liver Problems: Serious liver problems including liver injury and liver failure have been seen in patients taking medicines containing dolutegravir. In some cases the liver injury has led to a liver transplant. While you are being treated with TIVICAY your healthcare professional will monitor you closely for any signs of liver problems. See the **Serious Side Effects and What To Do About Them** table, below for information on this and other serious side effects.

Pregnancy and Breastfeeding:

- You should not take TIVICAY if you are pregnant or planning to become pregnant.
- Your healthcare professional will ask you to do a pregnancy test before starting treatment with TIVICAY to make sure you are not pregnant.
- If you are a woman who is able to get pregnant you must use a reliable method of birth control while you are taking TIVICAY. Talk to your healthcare professional about the birth control options that are right for you.
- TIVICAY can harm your unborn baby. If you take TIVICAY during the first 12 weeks of your pregnancy your baby is at risk for a type of birth defect called a neural tube defect, such as spina bifida, where the spinal cord has not formed correctly.
- Tell your healthcare professional immediately if you become pregnant while taking TIVICAY. If you take TIVICAY while you are pregnant, talk to your healthcare professional about enrolling in the Antiretroviral Pregnancy Registry.
- Talk to your healthcare professional if you are breastfeeding or plan to breastfeed. Women who are HIV positive should not breastfeed because HIV infection can pass into breastmilk. A small amount of the ingredients in TIVICAY can also pass into your breast milk. You should not breastfeed while you are taking TIVICAY**.**

Immune System Changes:

- Changes to your immune system, called **Immune Reconstitution Inflammatory Syndrome**, can happen when you start taking medicines for HIV infection. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time.
- Autoimmune disorders, when the immune system attacks healthy body tissue, can also happen after you start taking medicines for HIV infection. Examples of this include: Grave's disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the nervous system), polymyositis (which affects the muscles), or autoimmune hepatitis (which affects the liver). Autoimmune disorders can happen many months after you start taking TIVICAY.
- See the **Serious side effects and what to do about them** table, below for more information on these and other serious side effects.

Blood Tests: TIVICAY can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Diving and Using Machines: Use caution when driving and using machines until you know how you respond to TIVICAY.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TIVICAY:

- metformin, to treat diabetes
- medicines called antacids, to treat indigestion and heartburn. Do not take an antacid during the 6 hours before you take TIVICAY, or for at least 2 hours after you take it.
- calcium and iron supplements. Do not take a calcium or iron supplement during the 6 hours before you take TIVICAY, or for at least 2 hours after you take it. If you take TIVICAY with food, you can take a calcium or iron supplement at the same time as TIVICAY.
- etravirine, efavirenz, fosamprenavir/ritonavir, nevirapine or tipranavir/ritonavir, to treat HIV infection
- rifampin, to treat tuberculosis (TB) and other bacterial infections
- phenytoin and phenobarbital, to treat epilepsy
- oxcarbazepine and carbamazepine, to treat epilepsy and bipolar disorder
- St. John's wort, (*Hypericum perforatum*), a herbal remedy to treat depression

How to take TIVICAY:

Always take TIVICAY exactly as your healthcare professional has told you to. Check with your healthcare professional if you're not sure. Do not change your dose, switch from one tablet type to another, or stop taking TIVICAY without talking with your healthcare professional.

TIVICAY tablets and TIVICAY dispersible tablets can be taken with or without food.

TIVICAY tablets and TIVICAY dispersible tablets are not the same and cannot be substituted for each other. Your healthcare professional will decide which type of tablet is right for you.

Be sure to keep a supply of your anti-HIV medicines. When your TIVICAY supply starts to run low, get more from your healthcare professional or pharmacy. Do not wait until your medicine runs out to get more.

Usual dose:

Adults:
TIVICAY tablets:

- The usual dose is one 50 mg tablet, once a day.
- For adults with HIV infection that is resistant to other HIV medicines similar to TIVICAY, the usual dose is one 50 mg tablet, twice a day.

TIVICAY dispersible tablets:

- The usual dose is 30 mg, taken as 6 dispersible tablets, once a day.
- For adults with HIV infection that is resistant to other HIV medicines similar to TIVICAY, the usual dose is 30 mg, taken as 6 dispersible tablets, twice a day.

Children 4 weeks of age and older and weighing at least 3 kg: Your healthcare professional will decide on the correct dose of TIVICAY for your child, depending on the age and weight of the child.

The tablet(s) should be swallowed whole with some liquid. To reduce the risk of choking, do not let your child swallow more than one tablet at a time. If your child is unable to swallow the tablet(s), dispersible tablets should be used.

The dispersible tablets may be swallowed whole with drinking water or dispersed (dissolved) in drinking water. When swallowed whole, children should not swallow more than one dispersible tablet at a time to reduce the risk of choking. When dispersed, the amount of water will depend on the number of tablets to be taken. The tablet(s) should be fully dispersed before swallowing. Do not chew, cut or crush the tablet(s). Refer to the Instructions for Use.

Children should see their healthcare professional regularly because their TIVICAY dose may change as they get older or gain weight.

Antacid medicines

Antacids, to treat indigestion and heartburn, can stop TIVICAY from being absorbed into your body and make it less effective.

Do not take an antacid during the 6 hours before you take TIVICAY, or for at least 2 hours after you take it. Other acid-lowering medicines like ranitidine and omeprazole can be taken at the same time as TIVICAY. Talk to your healthcare professional for further advice on taking acid-lowering medicines with TIVICAY.

Calcium or iron supplements

Calcium or iron supplements can stop TIVICAY from being absorbed into your body and make it less effective.

Do not take a calcium or iron supplement during the 6 hours before you take TIVICAY, or for at least 2 hours after you take it. If you take TIVICAY with food, then you can take calcium and iron supplements at the same time as TIVICAY.

Overdose:

If you think you, or a person you are caring for, have taken too much TIVICAY, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember, but if your next dose is due within 4 hours, skip the dose you missed and take the next one at the usual time. Then continue your treatment as before. DO NOT take a double dose of your medicine to make up for a missed dose.

What are possible side effects from using TIVICAY?

These are not all the possible side effects you may have when taking TIVICAY. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- diarrhea
- headache
- trouble sleeping (insomnia), abnormal dreams
- nausea, vomiting
- stomach pain, stomach discomfort

- gas
- lack of energy (fatigue)
- rash
- itching
- joint pain, muscle pain
- weight gain
- dizziness

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Allergic reaction: skin rash, fever, lack of energy, swelling of the mouth or face causing difficulty in breathing, muscle or joint aches			✓
Liver problems (Hepatitis): nausea/vomiting, loss of appetite, pain, aching or tenderness on the right side below the ribs, yellowing of the skin or whites of the eyes, dark or tea coloured urine, pale coloured stools/ bowel movements			✓
Mental health problems: depression (feelings of deep sadness and unworthiness, lack of interest in activities, fatigue, loss of appetite), anxiety, suicidal thoughts and behaviours		✓	
RARE			
Liver failure: nausea/vomiting, loss of appetite, pain, aching or tenderness on the right side below the ribs, yellowing of the skin and the whites of the eyes, dark or tea coloured urine, pale coloured stools/bowel movements.			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
FREQUENCY NOT KNOWN			
Immune Reconstitution Inflammatory Syndrome: fever, redness, rash or swelling, fatigue, joint or muscle pain, numbness, tingling, or weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, chest pain or rapid heartbeat, yellowing of the skin or eyes, anxiety and irritability accompanied by tremor of your hands or fingers, muscle weakness in your hips, thighs, shoulders, upper arms and neck		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

TIVICAY 5 mg dispersible tablets store up to 25 ˚C. TIVICAY 10, 25 and 50 mg tablets store up to 30 ˚C.

Store TIVICAY 5mg dispersible tablets and 10 mg tablets in the original package (HDPE bottle) in order to protect from moisture. Keep the bottle tightly closed. Do not remove the silica gel desiccant. The 5mg dispersible tablet package contains a dosing cup, an oral syringe and instructions for use.

Keep out of reach and sight of children.

If you want more information about TIVICAY:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this

Patient Medication Information by visiting the Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.viivhealthcare.ca or by calling 1-877-393-8448.

This leaflet was prepared by ViiV Healthcare ULC

Last Revised JUN 27, 2023

Marketing Status in United States

Drug Databases (https://www.fda.gov/Drugs/InformationOnDrugs/)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Search Results

Product Details for NDA 204790

Collapse All

TIVICAY (DOLUTEGRAVIR SODIUM)
EQ 10MG BASE
Marketing Status: Prescription

Active Ingredient: DOLUTEGRAVIR SODIUM
Proprietary Name: TIVICAY
Dosage Form; Route of Administration: TABLET; ORAL
Strength: EQ 10MG BASE
Reference Listed Drug: Yes
Reference Standard: No
TE Code:
Application Number: N204790
Product Number: 002
Approval Date: Jun 9, 2016
Applicant Holder Full Name: VIIV HEALTHCARE CO
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=002&Appl_No=204790&Appl_type=N)

TIVICAY (DOLUTEGRAVIR SODIUM)
EQ 25MG BASE
Marketing Status: Prescription

Active Ingredient: DOLUTEGRAVIR SODIUM
Proprietary Name: TIVICAY
Dosage Form; Route of Administration: TABLET; ORAL
Strength: EQ 25MG BASE
Reference Listed Drug: Yes

Reference Standard: No
TE Code:
Application Number: N204790
Product Number: 003
Approval Date: Jun 9, 2016
Applicant Holder Full Name: VIIV HEALTHCARE CO
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=003&Appl_No=204790&Appl_type=N)

TIVICAY (DOLUTEGRAVIR SODIUM) EQ 50MG BASE Marketing Status: Prescription

Active Ingredient: DOLUTEGRAVIR SODIUM
Proprietary Name: TIVICAY
Dosage Form; Route of Administration: TABLET; ORAL
Strength: EQ 50MG BASE
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N204790
Product Number: 001
Approval Date: Aug 12, 2013
Applicant Holder Full Name: VIIV HEALTHCARE CO
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=204790&Appl_type=N)