CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204790Orig1s000

LABELING

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

----------INDICATIONS AND USAGE----------

TIVICAY is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg. (1)

The following should be considered prior to initiating TIVICAY:

- Poor virologic response was observed in subjects treated with TIVICAY 50 mg twice daily with an INSTI-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions including L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R. (12.4)

----------DOSAGE AND ADMINISTRATION----------

May be taken without regard to meals. (2)

Adult Population	Recommended Dose
Treatment-naïve or treatment-experienced INSTI-naïve	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[a] (12.4)	50 mg twice daily

[a] Alternative combinations that do not include metabolic inducers should be considered where possible.

Pediatric Patients: (Treatment-naïve or treatment-experienced INSTI-naïve, aged 12 years and older, and weighing at least 40 kg). (2.2)

- The recommended dose is TIVICAY 50 mg once daily.
- If efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin are coadministered, then the dose is TIVICAY 50 mg twice daily.

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

Tablets: 50 mg (3)

----------CONTRAINDICATIONS----------

Coadministration with dofetilide is contraindicated. (4)

---------- WARNINGS and PRECAUTIONS ----------

- Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported. Discontinue TIVICAY 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. TIVICAY should not be used in patients who have experienced a previous hypersensitivity reaction to TIVICAY. (5.1)
- Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TIVICAY. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with TIVICAY is recommended in patients with underlying hepatic disease such as hepatitis B or C. (5.2)
- Redistribution/accumulation of body fat and immune reconstitution syndrome have been reported in patients treated with combination antiretroviral therapy. (5.3, 5.4)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions of moderate to severe intensity and incidence ≥2% (in those receiving TIVICAY in any one adult trial) are insomnia 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----------

- Drugs that are metabolic inducers may decrease the plasma concentrations of dolutegravir. (7 2, 7.3)
- TIVICAY should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications. (7.3)

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

- Pregnancy: TIVICAY should be used during pregnancy only if the potential benefit justifies the potential risk. (8.1)
- Nursing mothers: Breastfeeding is not recommended due to the potential for HIV transmission. (8.3)
- Pediatric patients: Safety and efficacy of TIVICAY have not been established in pediatric patients younger than 12 years or weighing less than 40 kg, or in pediatric patients who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs (raltegravir, elvitegravir). (8.4)

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

Revised: August 2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TIVICAY® is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and children aged 12 years and older and weighing at least 40 kg.

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

- Poor virologic response was observed in subjects treated with TIVICAY 50 mg twice daily with an integrase strand transfer inhibitor (INSTI)-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions, including L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R *[see Microbiology (12.4)]*.

2 DOSAGE AND ADMINISTRATION

TIVICAY tablets may be taken with or without food.

2.1 Adults

Table 1. Dosing Recommendations for TIVICAY in Adult Patients

Population	Recommended Dose
Treatment-naïve or treatment-experienced INSTI-naïve	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[a] *[see Microbiology (12.4)]*	50 mg twice daily

[a] Alternative combinations that do not include metabolic inducers should be considered where possible *[see Drug Interactions (7)]*.

The safety and efficacy of doses above 50 mg twice daily have not been evaluated.

2.2 Pediatric Patients

Treatment-Naïve or Treatment-Experienced INSTI-Naïve: The recommended dose of TIVICAY in pediatric patients aged 12 years and older and weighing at least 40 kg is 50 mg administered orally once daily.

If efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin are coadministered, the recommended dose of TIVICAY is 50 mg twice daily.

Safety and efficacy of TIVICAY have not been established in pediatric patients younger than 12 years or weighing less than 40 kg, or in pediatric patients who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs (raltegravir, elvitegravir).

3 DOSAGE FORMS AND STRENGTHS

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 of dolutegravir (as dolutegravir sodium) *[see Description (11)]*.

4 CONTRAINDICATIONS

Coadministration of TIVICAY with dofetilide is contraindicated 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 1% or fewer subjects receiving TIVICAY in Phase 3 clinical trials. 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 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 other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. TIVICAY should not be used in patients who have experienced a previous hypersensitivity reaction to TIVICAY.

5.2 Effects on Serum Liver Biochemistries 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 *[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. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with TIVICAY are recommended in patients with underlying hepatic disease such as hepatitis B or C.

5.3 Fat Redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.4 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including TIVICAY. 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.

6 ADVERSE REACTIONS

The following adverse drug reactions (adverse events assessed as causally related by the investigator or ADRs) are discussed in other sections of the labeling:

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.
- Effects on serum liver biochemistries in patients with hepatitis B or C co-infection *[see Warnings and Precautions (5.2)]*.
- Fat Redistribution *[see Warnings and Precautions (5.3)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.4)]*.

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.

6.1 Clinical Trials Experience in Adult Subjects

Treatment-Emergent Adverse Drug Reactions (ADRs): *Treatment-Naïve Subjects*: The safety assessment of TIVICAY in HIV-1-infected treatment-naïve subjects is based on the analyses of 48-week data from 2 ongoing, international, multicenter, double-blind trials, SPRING-2 (ING113086) and SINGLE (ING114467).

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. 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. The rates of adverse events leading to discontinuation were 2% in subjects receiving TIVICAY 50 mg once daily + EPZICOM and 10% in subjects receiving ATRIPLA once daily.

Treatment-emergent ADRs of moderate to severe intensity observed in ≥2% of subjects in either treatment arm are provided in Table 2. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 2. Treatment-Emergent Adverse Drug Reactions of at Least Moderate Intensity (Grades 2 to 4) and ≥2% Frequency in Treatment-Naïve Subjects in SPRING-2 and SINGLE Trials (Week 48 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%	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%
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 <1% of subjects receiving TIVICAY and raltegravir, respectively, in SPRING-2; whereas in SINGLE the rates were 7% and 3% for TIVICAY and ATRIPLA, respectively. These events were not treatment limiting.

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 24 weeks, the rates of adverse events leading to discontinuation were 2% 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 ADR of moderate to severe intensity with ≥2% frequency in either treatment group was diarrhea, 1% (5/354) in subjects receiving TIVICAY 50 mg once

daily + background regimen and 2% (6/361) 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 3% of subjects at Week 24.

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

Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials: The following ADRs occurred in <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.

General Disorders: Fatigue.

Hepatobiliary Disorders: Hepatitis.

Musculoskeletal Disorders: Myositis.

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 ≥2% of subjects are presented in Table 3. The mean change from baseline observed for selected lipid values is presented in Table 4. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 3. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in SPRING-2 and SINGLE Trials (Week 48 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)	2%	3%	2%	5%
Grade 3 to 4 (>5.1 x ULN)	2%	1%	<1%	<1%
AST				
Grade 2 (>2.5-5.0 x ULN)	3%	3%	2%	3%
Grade 3 to 4 (>5.1 x ULN)	2%	2%	0	2%
Total Bilirubin				
Grade 2 (1.6-2.5 x ULN)	2%	2%	<1%	0
Grade 3 to 4 (>2.5 x ULN)	<1%	<1%	<1%	0
Creatine kinase				
Grade 2 (6.0-9.9 x ULN)	1%	3%	3%	1%
Grade 3 to 4 (>10.0 x ULN)	4%	3%	3%	4%
Hyperglycemia				
Grade 2 (126-250 mg/dL)	5%	5%	7%	4%
Grade 3 (>251 mg/dL)	<1%	1%	1%	<1%
Lipase				
Grade 2 (>1.5-3.0 x ULN)	5%	6%	8%	7%
Grade 3 to 4 (>3.1 x ULN)	1%	3%	3%	2%
Total neutrophils				
Grade 2 (0.75-0.99 x 10^9)	3%	3%	2%	4%
Grade 3 to 4 (<0.74 x 10^9)	2%	1%	2%	3%

ULN = Upper limit of normal.

Table 4. Mean Change From Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SPRING-2 and SINGLE Trials (Week 48 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)
Cholesterol (mg/dL)	6.7	8.3	17.1	24.0
HDL cholesterol (mg/dL)	2.8	2.6	5.2	7.9
LDL cholesterol (mg/dL)	2.7	2.8	8.5	13.1
Triglycerides (mg/dL)	7.7	9.8	17.7	18.6

[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 n = 27 and ATRIPLA n = 26). Forty-nine subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless if they discontinued the agent (SPRING-2: TIVICAY n = 5, raltegravir n = 8; SINGLE: TIVICAY n = 19 and ATRIPLA: n = 17).

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 (>5% for Grades 2 to 4 combined) were elevated ALT (8%), AST (6%), cholesterol (8%), hyperglycemia (12%), and lipase (8%). Two percent (3/183) of subjects had a Grade 3 to 4, treatment-emergent hematology laboratory abnormality, with neutropenia (1% [2/183]) being the most frequently reported.

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 16% vs. 2% with the 50-mg once-daily dose and 8% vs. 7% 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 24 to 48 weeks. In treatment-naïve subjects, a mean change from baseline of 0.11 mg/dL (range: -0.60 mg/dL to 0.62 mg/dL) was observed after 48 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced subjects.

6.2 Clinical Trials Experience in Pediatric Subjects

IMPAACT P1093 is an ongoing multi-center, open-label, non-comparative trial of approximately 160 HIV-1-infected pediatric subjects aged 6 weeks to less than 18 years, of which 23 treatment-experienced, INSTI-naïve subjects aged 12 to less than 18 years were enrolled *[see Use in Specific Populations (8.4), Clinical Studies (14.2)]*.

The adverse reaction profile was similar to that for adults. Grade 2 ADRs reported in at least 1 subject were rash (n = 1), abdominal pain (n = 1), and diarrhea (n = 1). No Grade 3 or 4 ADRs were reported. The Grade 3 laboratory abnormalities were elevated total bilirubin and lipase reported in 1 subject each. No Grade 4 laboratory abnormalities were reported. The changes in mean serum creatinine were similar to those observed in adults.

7 DRUG INTERACTIONS

Refer to Table 5 for established and other potentially significant drug-drug interactions.

7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, dolutegravir inhibited the renal organic cation transporter, OCT2 (IC_{50} = 1.93 μM). In vivo, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 (dofetilide and metformin, Table 5) *[see Contraindications (4), Drug Interactions (7.3)]*.

In vitro, dolutegravir did not inhibit (IC_{50} >50 μM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1, UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, or multidrug resistance protein (MRP)2. 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.

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

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 5) *[see Drug Interactions (7.3), Clinical Pharmacology (12.3)]*.

Darunavir/ritonavir, lopinavir/ritonavir, rilpivirine, tenofovir, boceprevir, telaprevir, prednisone, rifabutin, and omeprazole had no clinically significant effect on the pharmacokinetics of dolutegravir.

7.3 Established and Other Potentially Significant Drug Interactions

Table 5 provides clinical recommendations as a result of drug interactions with TIVICAY. 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 5. 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	TIVICAY should not be used with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓Dolutegravir	A dose adjustment of TIVICAY to 50 mg twice daily is recommended in treatment-naïve or treatment-experienced, INSTI-naïve patients. Alternative combinations that do not include metabolic inducers should be considered 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	Coadministration with nevirapine should be avoided because there are insufficient data to make dosing recommendations.
Protease Inhibitor: Fosamprenavir/ritonavir[a] Tipranavir/ritonavir[a]	↓Dolutegravir	A dose adjustment of TIVICAY to 50 mg twice daily is recommended in treatment-naïve or treatment-experienced, INSTI-naïve patients. Alternative combinations that do not include metabolic inducers should be considered where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]
Other Agents		
Oxcarbazepine Phenytoin Phenobarbital Carbamazepine St. John's wort (*Hypericum perforatum*)	↓Dolutegravir	Coadministration with these metabolic inducers should be avoided because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg, Al, Fe, or Ca) Cation-containing antacids[a] or laxatives Sucralfate Oral iron supplements Oral calcium supplements Buffered medications	↓Dolutegravir	TIVICAY should be administered 2 hours before or 6 hours after taking medications containing polyvalent cations.
Metformin	↑Metformin	Close monitoring is recommended when starting or stopping TIVICAY and metformin together. A dose adjustment of metformin may be necessary.

Rifampin[a]	↓Dolutegravir	A dose adjustment of TIVICAY to 50 mg twice daily is recommended in treatment-naïve or treatment-experienced, INSTI-naïve patients. Alternatives to rifampin should be used where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]

[a] *See Clinical Pharmacology (12.3) Table 9 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 potent inducers may result in loss of therapeutic effect and development of resistance to TIVICAY or other coadministered antiretroviral agents.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and dolutegravir was shown to cross the placenta in animal studies, this drug should be used during pregnancy only if clearly needed.

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 by calling 1-800-258-4263.

Animal Data: Reproduction studies have been performed in rats and rabbits at doses up to 27 times the human dose of 50 mg twice daily and have revealed no evidence of impaired fertility or harm to the fetus due to TIVICAY.

Oral administration of dolutegravir to pregnant rats at doses up to 1,000 mg/kg daily, approximately 27 times the 50-mg twice-daily human clinical exposure based on AUC, from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity, or teratogenicity.

Oral administration of dolutegravir to pregnant rabbits at doses up to 1,000 mg/kg daily, approximately 0.4 times the 50-mg twice-daily human clinical exposure based on AUC, from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity. In rabbits, maternal toxicity (decreased food consumption, scant/no feces/urine, suppressed body weight gain) was observed at 1,000 mg/kg.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Studies in lactating rats and their offspring indicate that dolutegravir was present in rat milk. It is not known whether dolutegravir is excreted in human milk.

Because of both the potential for HIV transmission and the potential for adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving TIVICAY**.

8.4 Pediatric Use

TIVICAY is not recommended in pediatric patients younger than 12 years or weighing less than 40 kg. Safety and efficacy of TIVICAY have not been established in pediatric patients who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs (raltegravir, elvitegravir).

The safety, virologic, and immunologic responses in subjects who received TIVICAY were evaluated in 23 treatment-experienced, INSTI-naïve, HIV-1–infected subjects aged 12 to less than 18 years in an open-label, multicenter, dose-finding clinical trial, IMPAACT P1093 *[see Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.2)]*. Pharmacokinetic parameters, evaluated in 9 subjects weighing ≥40 kg receiving 50 mg daily and 1 subject (weighing 37 kg) receiving 35 mg once daily, were similar to adults receiving 50 mg once daily. See *Dosage and Administration (2.2)* for dosing recommendations for pediatric patients aged 12 years and older and weighing at least 40 kg. Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults *[see Adverse Reactions (6.2)]*.

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 is 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,

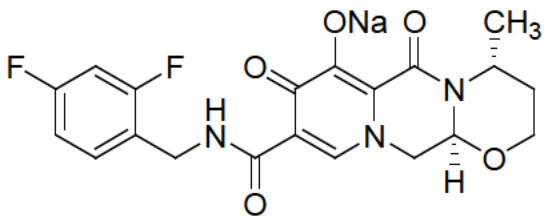
moderate, or severe renal impairment or for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance) with mild or moderate renal impairment. Caution is warranted for INSTI-experienced patients (with certain INSTI-associated resistance 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 or other coadministered antiretroviral agents *[see Clinical Pharmacology (12.3)]*. Dolutegravir has not been studied in patients on dialysis.

10 OVERDOSAGE

Limited experience with single higher doses (up to 250 mg in healthy subjects) revealed no specific symptoms or signs apart from those listed as adverse reactions. There is no known specific treatment for overdose with TIVICAY. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

11 DESCRIPTION

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



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

Each film-coated tablet of TIVICAY for oral administration contains 52.6 mg of dolutegravir sodium, which is equivalent to 50 mg dolutegravir free acid, 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, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

In a randomized, dose-ranging trial, HIV-1-infected subjects treated with dolutegravir monotherapy 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) 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 6) was attributed to the use of metabolic inducers in the background antiretroviral regimens of subjects receiving dolutegravir 50 mg twice daily in clinical trials. TIVICAY was administered without regard to food in these trials.

Table 6. 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.

Absorption: Following oral administration of dolutegravir, peak plasma concentrations were observed 2 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-glycoprotein substrate in vitro. The absolute bioavailability of dolutegravir has not been established.

Effects of Food on Oral Absorption: TIVICAY may be taken with or without food. Food increased the extent of absorption and slowed the rate of absorption of dolutegravir. 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 (≥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 11 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 18 ng/mL (range: 4 ng/mL to 232 ng/mL) 2 to 6 hours postdose after 2 weeks of treatment. The clinical relevance of this finding has not been established.

Metabolism and Elimination: Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A. 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 (<1% of the dose).

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

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).

Specific Populations: *Hepatic Impairment:* Dolutegravir is primarily metabolized and eliminated by the liver. 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. 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 is not recommended for use in patients with severe hepatic impairment.

HBV/HCV Co-infection: 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.

Renal Impairment: Renal clearance of unchanged drug is a minor pathway of elimination for dolutegravir. In a trial comparing 8 subjects with severe renal impairment (CrCl <30 mL/min) with 8 matched healthy controls, AUC, C_{max}, and C_{24} of dolutegravir were decreased by 40%, 23%, and 43%, respectively, compared with those in matched healthy subjects. The cause of this decrease is unknown. 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. 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 or other coadministered antiretroviral agents. Dolutegravir has not been studied in patients requiring dialysis.

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

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

Geriatric Patients: Population analyses using pooled pharmacokinetic data from adult trials indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir.

Pediatric Patients: The pharmacokinetics of dolutegravir in HIV-1–infected children (n = 10) aged 12 to less than 18 years were similar to those observed in HIV-1–infected adults who received dolutegravir 50 mg once daily (Table 7) *[see Clinical Studies (14.2)]*.

Table 7. Dolutegravir Steady-State Pharmacokinetic Parameters in Pediatric Subjects

Age/Weight	Dose of TIVICAY[a]	Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (%CV)		
		C_{max} (mcg/mL) (n = 10)	$AUC_{(0-24)}$ (mcg.h/mL) (n = 10)	C_{24} (mcg/mL) (n = 10)
12 to <18 years and ≥40 kg[a]	50 mg once daily	3.49 (38)	46 (43)	0.90 (59)

[a] One subject weighing 37 kg received TIVICAY 35 mg once daily.

Drug Interactions: Drug interaction trials were performed with TIVICAY and other drugs likely to be coadministered or commonly used as probes for pharmacokinetic interactions. As dolutegravir is not expected to affect the pharmacokinetics of other drugs dependent on hepatic metabolism (Table 8) *[see Drug Interactions (7.1)]*, the primary focus of these drug interaction trials was to evaluate the effect of coadministered drug on dolutegravir (Table 9).

Dosing or regimen recommendations as a result of established and other potentially significant drug-drug interactions with TIVICAY are provided in Table 5 *[see Dosage and Administration (2.1), Drug Interactions (7.3)]*.

Table 8. 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}
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)
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)	–
Norgestromin 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)
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)

Table 9. 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)
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)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/ritonavir 200 mg + 600/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)
Fosamprenavir/ritonavir 700 mg /100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
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 hrs 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)
Multivitamin (One-A-Day®) Simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[a] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)

Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)
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)
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)
Telaprevir 750 mg every 8 hours	50 mg once daily	15	1.18 (1.11 to 1.26)	1.25 (1.19 to 1.31)	1.40 (1.29 to 1.51)
Boceprevir 800 mg every 8 hours	50 mg once daily	13	1.05 (0.96 to 1.15)	1.07 (0.95 to 1.20)	1.08 (0.91 to 1.28)

[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.

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 deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

Antiviral Activity in Cell Culture: Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.5 nM (0.21 ng/mL) to 2.1 nM (0.85 ng/mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} 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 nucleoside reverse transcriptase inhibitors (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 with 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 subjects in the dolutegravir 50-mg once-daily treatment arms of treatment-naïve trials SPRING-2 and SINGLE had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 6 with HIV-1 RNA >400 copies/mL at failure or last visit through Week 48 and having resistance data). One additional subject in SINGLE with 275 copies/mL HIV-1 RNA had a treatment-emergent INSTI-resistance substitution (E157Q/P) detected at Week 24, but no corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to the background regimen was isolated in the dolutegravir arm in either the SPRING-2 or SINGLE trials.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In SAILING, viruses from 5 of 15 subjects in the dolutegravir arm with post-baseline resistance data had evidence of treatment-emergent integrase substitutions (1 subject each with L74I/M, Q95Q/L, or V151V/I, and 2 subjects with R263K). However, none of these subjects' isolates had detectable phenotypic decreases in susceptibility to either dolutegravir or raltegravir. In the comparator raltegravir arm, 9 of 32 subjects with post-baseline resistance data had evidence of emergent INSTI-resistance substitutions (L74M, E92E/Q, Q95Q/R, T97A, G140A/S, Y143C/R, Q148H/R, V151I, N155H, E157E/Q, and G163G/R) and raltegravir phenotypic resistance.

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.

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, Y143C/H/R, Q148H/K/R 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 using a subset of subjects who had reached Week 24, as well as those who discontinued or rebounded before Week 24 (n = 124) (Table 10). The response rate at Week 24 for subjects with only historic evidence of INSTI-resistance at baseline was 75% (33/44). The response rate at Week 24 to dolutegravir-containing regimens was 36% (13/36) when Q148 substitutions were present at baseline; Q148 was always present with additional INSTI-resistance substitutions. Diminished virologic responses (25% [7/28]) were observed when ≥3 of the following INSTI-resistance substitutions were present at baseline: L74I/M, E138A/D/K/T, G140A/S, Y143H/R, Q148H/R, E157Q, G163E/K/Q/R/S, or G193E/R.

Table 10. Response by Baseline Integrase Genotype in Subjects with Prior Experience to an Integrase Strand Transfer Inhibitor in VIKING-3

Baseline Genotype	Response at Week 24 (<50 copies/mL) Subset N = 124
Overall Response	64% (79/124)
N155H without a Q148 substitution	80% (16/20)
Y143C/H/R without a Q148 substitution	56% (10/18)
Q148H/R + G140A/S without additional INSTI-resistance substitutions	56% (10/18)
Q148H/R + ≥2 INSTI-resistance substitutions[a,b]	18% (3/17)

[a] INSTI-resistance substitutions include L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R.

[b] The most common pathway with Q148H/R + ≥2 INSTI-resistance substitutions had Q148+G140+E138 substitutions (n = 12).

Response by Baseline Phenotype: Response rates by baseline phenotype were analyzed using a subset of subjects who had reached Week 24, as well as those who discontinued or rebounded before Week 24 (n = 120) (See Table 11). 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 11. 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 24 (<50 copies/mL) Subset N = 120
Overall Response	63% (75/120)
<3-fold change	72% (63/87)
3- <10-fold change	42% (10/24)
≥10-fold change	22% (2/9)

Integrase Strand Transfer Inhibitor Treatment-Emergent Resistance: There were 40 subjects on the dolutegravir twice-daily regimen in VIKING-3 with HIV-1 RNA >400 copies/mL at Week 24, the failure timepoint, or the last timepoint on trial who were included in the Week 24 resistance analysis set. In the Week 24 resistance analysis set, 45% (18/40) of the subjects 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 E138K or A, G140S or A, or Q148H or R or

K; substitutions at Q148 were detected in subjects with changes documented at or prior to enrollment in the trial. Substitutions L74M, E92Q, Y143H or C, S147G, V151A, M154I, and N155H each emerged in 1 or 2 subjects' isolates. At failure, the median dolutegravir fold-change from reference was 23-fold (range: 0.92 to 209) for isolates with emergent INSTI-resistance substitutions (n = 18).

Resistance to one or more background drugs in the dolutegravir twice-daily regimen also emerged in 30% (12/40) of the subjects in the Week 24 resistance analysis set**.**

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Impairment of Fertility: In a study conducted in rats, there were no effects on mating or fertility with dolutegravir up to 1,000 mg/kg/day. This dose is associated with an exposure that is approximately 24 times higher than the exposure in humans at the recommended dose of 50 mg twice daily.

14 CLINICAL STUDIES

The efficacy of TIVICAY is based on analyses of data from 2 trials, SPRING-2 (ING113086) and SINGLE (ING114467), in treatment-naïve, HIV-1-infected subjects (n = 1,641); one trial, SAILING (ING111762), in treatment-experienced, INSTI-naïve HIV-1-infected subjects (n = 715); and from VIKING-3 (ING112574) trial in INSTI-experienced HIV-1-infected subjects (n = 183). The use of TIVICAY in pediatric patients aged 12 years and older is based on evaluation of safety, pharmacokinetics, and efficacy through 24 weeks in a multi-center, open-label trial in subjects (n = 23) without INSTI resistance.

14.1 Adult Subjects

Treatment-Naïve Subjects: The efficacy of TIVICAY in HIV-1-infected treatment-naïve adults is based on the analyses of 48-week data from 2 randomized, international, multicenter, double-blind, active-controlled trials, SPRING-2 and SINGLE.

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 >100,000 copies/mL, 48% had CD4+ cell count <350 cells/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 >100,000 copies/mL, and 53% had CD4+ cell count <350 cells/mm^3; these characteristics were similar between treatment groups.

Week 48 outcomes for SPRING-2 and SINGLE are provided in Table 12. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 12. Virologic Outcomes of Randomized Treatment in SPRING-2 and SINGLE at Week 48 (Snapshot Algorithm)

	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)
HIV-1 RNA <50 copies/mL	88%	86%	88%	81%
Treatment difference[a]	2.6% (95% CI: -1.9%, 7.2%)		7.4% (95% CI: 2.5%, 12.3%)	
Virologic nonresponse[b]	5%	7%	5%	6%
No virologic data at Week 48 window	7%	7%	7%	13%
Reasons				
Discontinued study/study drug due to adverse event or death[c]	2%	1%	2%	10%
Discontinued study/study drug for other reasons[d]	5%	6%	5%	3%
Missing data during window but on study	0	0	0	<1%
Proportion (%) of Subjects With HIV-1 RNA <50 copies/mL at Week 48 by Baseline Category				
Plasma viral load (copies/mL)				
≤100,000	91%	90%	90%	83%
>100,000	82%	75%	83%	76%
Gender				
Male	89%	86%	88%	82%
Female	84%	82%	85%	75%
Race				
White	88%	86%	90%	84%
Non-white	85%	85%	84%	74%

[a] Adjusted for pre-specified stratification factors.

[b] Includes subjects 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), subjects who discontinued prior to Week 48 for lack or loss of efficacy, and subjects who were HIV-1 RNA ≥50 copies/mL in the Week 48 window.

[c] Includes subjects 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.

[d] 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 for both groups was +230 cells/mm^3 at 48 weeks.

SINGLE: Treatment differences were maintained across baseline characteristics including HIV-1 RNA, CD4+ cell count, age, gender, and race.

The adjusted mean changes in CD4+ cell counts from baseline were 267 cells/mm^3 in the group receiving TIVICAY + EPZICOM and 208 cells/mm^3 for the ATRIPLA group at 48 weeks. The adjusted difference between treatment arms and 95% CI was 58.9 cells/mm^3 (33.4 cells/mm^3, 84.4 cells/mm^3) (adjusted for pre-specified stratification factors: baseline HIV-1 RNA, baseline CD4+ cell count, and multiplicity).

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, 49% non-white, 16% had hepatitis B and/or C virus co-infection, 46% were CDC Class C (AIDS), 20% had HIV-1 RNA >100,000 copies/mL, and 72% had CD4+ cell count <350 cells/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 24 outcomes for SAILING are shown in Table 13.

Table 13. Virologic Outcomes of Randomized Treatment in SAILING at 24 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	79%	70%
Adjusted[b] treatment difference	9.7% (95% CI: 3.4%, 15.9%)	
Virologic nonresponse	15%	24%
No virologic data at Week 24 window	6%	6%
Reasons		
Discontinued study/study drug due to adverse event or death	2%	2%
Discontinued study/study drug for other reasons[c]	3%	3%
Missing data during window but on study	<1%	<1%
Proportion (%) With HIV-1 RNA <50 copies/mL at Week 24 by Baseline Category		
Plasma viral load (copies/mL)		
≤50,000 copies/mL	83%	77%
>50,000 copies/mL	70%	53%
Background regimen		
No darunavir use or use of darunavir with primary PI substitutions	79%	67%
Use of darunavir without primary PI substitutions	80%	81%
Gender		
Male	78%	70%
Female	83%	69%
Race		
White	79%	69%
Non-white	80%	71%

[a] BR = Background regimen. Background regimen was restricted 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 114 cells/mm^3 in the group receiving TIVICAY and 106 cells/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 optimized background therapy 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 optimized background therapy 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/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 ≥2 NRTI, 75% ≥1 NNRTI, and 71% ≥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 24 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 24 virologic outcomes for VIKING-3 are shown in Table 14.

Table 14. Virologic Outcomes of Treatment of VIKING-3 at 24 Weeks (Snapshot Algorithm)

	TIVICAY 50 mg Twice Daily + Optimized Background Therapy (N = 114)
HIV-1 RNA <50 copies/mL	63%
Virologic nonresponse	32%
No virologic data at Week 24 Reasons Discontinued study/study drug due to adverse event or death	4%
Proportion (%) With HIV-1 RNA <50 copies/mL at Week 24 by Baseline Category	
Gender	
Male	64%
Female	60%
Race	
White	67%
Non-white	52%

Subjects harboring virus with Q148 and with additional Q148-associated secondary substitutions also had a reduced response at Week 24 in a stepwise fashion *[see Microbiology (12.4)]*.

The median change in CD4+ cell count from baseline was 65 cells/mm^3 at Week 24.

14.2 Pediatric Subjects

IMPAACT P1093 is a Phase 1/2, 48-week, 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.

The initial dose-finding stage included intensive pharmacokinetic evaluation in 10 INSTI-naïve subjects (aged 12 to 18 years). Dose selection was based upon achieving similar dolutegravir plasma exposure and trough concentration as seen in adults. After dose selection, an additional 13 subjects were enrolled for evaluation of long-term safety, tolerability, and efficacy.

These 23 subjects had a mean age of 14 years (range: 12 to 17), were 78% female and 52% black. At baseline, mean plasma HIV-1 RNA was 4.3 $\log_{10}$ copies/mL, median CD4+ cell count was 466 cells/mm^3 (range: 11 to 1,025), and median CD4+% was 22% (range: 1% to 39%). Overall, 17% had baseline plasma HIV-1 RNA >50,000 copies/mL and 39% had a CDC HIV clinical classification of category C. Most subjects had previously used at least 1 NNRTI (52%) or 1 PI (78%).

At 24 weeks, 70% of subjects treated with TIVICAY once daily (35 mg: n = 4, 50 mg: n = 19) plus optimized background therapy achieved a viral load <50 copies/mL. The median CD4+ cell count (percent) increase from baseline to Week 24 was 63 cells/mm^3 (5%).

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 49702-228-13.

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling (Patient Information).

Drug Interactions: TIVICAY should not be coadministered with dofetilide because interactions between these drugs can result in potentially life-threatening adverse events *[see Contraindications (4)]*.

Hypersensitivity Reactions: Patients should be advised 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). Patients should understand that if hypersensitivity occurs, they will be

closely monitored, laboratory tests will be ordered, and appropriate therapy will be initiated. Patients should also be told that it is very important that they remain under a physician's care during treatment with TIVICAY *[see Warnings and Precautions (5.1)]*.

Effects on Serum Liver Biochemistries 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 and should be advised that they are recommended to have laboratory testing before and during therapy *[see Warnings and Precautions (5.2)]*.

Fat Redistribution: Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.3)]*.

Immune Reconstitution Syndrome: In some patients with advanced HIV infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Patients should be advised to inform their healthcare provider immediately of any symptoms of infection *[see Warnings and Precautions (5.4)]*.

Information About HIV-1 Infection: TIVICAY is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients must remain on continuous HIV therapy to control HIV infection and decrease HIV-related illness. Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician when using TIVICAY.

Patients should be informed to take all HIV medications exactly as prescribed.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not re-use or share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- Continue to practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- Female patients should be advised not to breastfeed because it is not known if TIVICAY can be passed to the baby in your breast milk and whether it could harm the baby. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Physicians should instruct their patients to read the Patient Information before starting TIVICAY and to reread it each time the prescription is renewed. Patients should be instructed to inform their physician or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Physicians should instruct their patients that if they miss a dose, they should take it as soon as they remember. If they do not remember until it is within 4 hours of the time for the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

TIVICAY and EPZICOM are registered trademarks of ViiV Healthcare.

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Manufactured for:

ViiV Healthcare
Research Triangle Park, NC 27709

by:

GlaxoSmithKline
Research Triangle Park, NC 27709

TVC:XPI

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

Patient Information
TIVICAY® (TIV-eh-kay)
(dolutegravir)
Tablets

Read this Patient Information before you start taking TIVICAY and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is TIVICAY?

TIVICAY is a prescription HIV medicine that is used with other antiretroviral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) infections in adults and children 12 years of age and older and weighing at least 88 pounds.

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

It is not known if TIVICAY is safe and effective in children under 12 years of age or who weigh less than 88 pounds.

When used with other HIV-1 medicines to treat HIV-1 infection, TIVICAY may help:

- Reduce the amount of HIV-1 in your blood. This is called “viral load”.
- Increase the number of white blood cells called CD4+ (T) cells in your blood, which help fight off other infections.
- Reduce the amount of HIV-1 and increase the CD4+ (T) cell in your blood which may help improve your immune system. This may reduce your risk of death or getting infections that can happen when your immune system is weak (opportunistic infections).

TIVICAY does not cure HIV-1 infection or AIDS. You must stay on continuous HIV-1 therapy to control HIV-1 infection and decrease HIV-related illnesses.

Avoid doing things that can spread HIV-1 infection to others.

- Do not share or re-use needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.

- Do not have any kind of sex without protection. Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.

Ask your healthcare provider if you have any questions about how to prevent passing HIV to other people.

Who should not take TIVICAY?

Do not take TIVICAY if you take dofetilide. Taking TIVICAY and dofetilide can cause side effects that may be life-threatening.

What should I tell my healthcare provider before taking TIVICAY?

Before you take TIVICAY, tell your healthcare provider if you:

- have ever had an allergic reaction to TIVICAY
- have or had liver problems, including hepatitis B or C infection
- have any other medical condition
- are pregnant or plan to become pregnant. It is not known if TIVICAY will harm your unborn baby. Tell your healthcare provider if you become pregnant while taking TIVICAY.

  Pregnancy Registry. There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. **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.
  - It is not known if TIVICAY passes into your breast milk.
  - Talk to your healthcare provider about the best way to feed your baby.

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

TIVICAY and other medicines may affect each other causing side effects. TIVICAY may affect the way other medicines work, and other medicines may affect how TIVICAY works.

Especially tell your healthcare provider if you take:

- other HIV-1 medicines including: efavirenz (SUSTIVA®), etravirine (INTELENCE®), fosamprenavir (LEXIVA®)/ritonavir (N0RVIR®), nevirapine (VIRAMUNE®), or tipranavir (APTIVUS®)/ritonavir (N0RVIR).
- antacids or laxatives that contain aluminum, magnesium or calcium, sucralfate (CARAFATE®), iron or calcium supplements, or buffered medicines. TIVICAY should be taken at least 2 hours before or 6 hours after you take these medicines.
- anti-seizure medicines:
  - oxcarbazepine (TRILEPTAL®)
  - phenytoin (DILANTIN®, DILANTIN®-125, PHENYTEK®)
  - phenobarbital (LUMINAL®)
  - carbamazepine (CARBATROL®, EQUETRO®, TEGRETOL®, TEGRETOL®-XR, TERIL®, EPITOL®)
- St. John's wort (*Hypericum perforatum*)
- a medicine that contains metformin
- rifampin (RIFATER®, RIFAMATE®, RIMACTANE®, RIFADAN®)

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take TIVICAY?

- Take TIVICAY exactly as your healthcare provider tells you.
- Do not change your dose or stop taking TIVICAY without talking with your healthcare provider.
- Stay under the care of a healthcare provider while taking TIVICAY.
- You can take TIVICAY with or without food.
- If you miss a dose of TIVICAY, take it as soon as you remember. If it is within 4 hours of your next dose, skip the missed dose and take the next dose at your regular time. Do not take 2 doses at the same time. If you are not sure about your dosing, call your healthcare provider.
- If you take too much TIVICAY, call your healthcare provider or go to the nearest hospital emergency room right away.
- Do not run out of TIVICAY. The virus in your blood may become resistant to other HIV-1 medicines if TIVICAY is stopped for even a short time. When your supply starts to run low, get more from your healthcare provider or pharmacy.

What are the possible side effects of TIVICAY?

TIVICAY may 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
    - extreme tiredness
    - muscle or joint aches
    - blisters or sores in mouth
    - blisters or peeling of the skin
    - redness or swelling of the eyes
    - swelling of the mouth, face, lips, or tongue
    - problems breathing
  - **develop any of the following signs or symptoms of liver problems:**
    - yellowing of the skin or whites of the eyes
    - dark or tea-colored urine
    - pale-colored stools or bowel movements
    - nausea or vomiting
    - loss of appetite
    - pain, aching, or tenderness on the right side below the ribs
- **Changes in liver tests**. 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. Your healthcare provider may do tests to check your liver function before and during treatment with TIVICAY.
- **Changes in body fat** can happen in people who take HIV-1 medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these problems are not known.
- **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 starting your HIV-1 medicine.

The most common side effects of TIVICAY include:

- trouble sleeping
- headache

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of TIVICAY. For more information, ask your healthcare provider or pharmacist.

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 at room temperature between 68°F to 77°F (20°C to 25°C).

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

General information about 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 pharmacist or healthcare provider for information about TIVICAY that is written for health professionals.

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

What are the ingredients in TIVICAY?

Active ingredient: dolutegravir sodium
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, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:

ViiV Healthcare

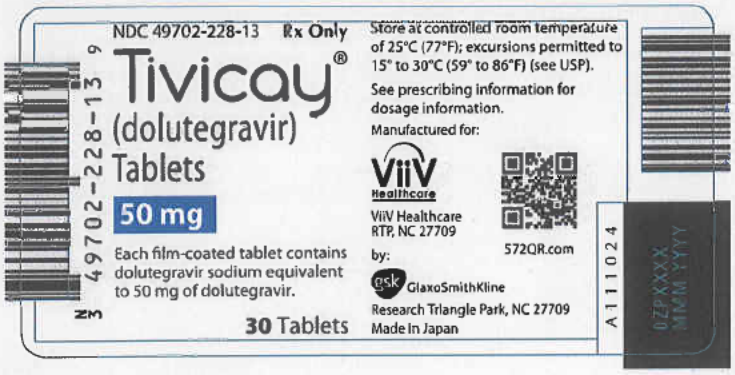
ViiV Healthcare

Research Triangle Park, NC 27709

by:

GlaxoSmithKline
Research Triangle Park, NC 27709

August 2013
TVC:XPIL


NDC 49702-228-13 Rx Only
Tivicay®
(dolutegravir)
Tablets
50 mg
Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg of dolutegravir.
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Store at controlled room temperature of 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP).
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