PRODUCT MONOGRAPH

[Pr]TIVICAY

Dolutegravir (as dolutegravir sodium)

10, 25 and 50 mg tablets

Human immunodeficiency virus integrase strand transfer inhibitor

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PrTIVICAY

dolutegravir (as dolutegravir sodium) tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Film-coated tablets / 10, 25 and 50 mg dolutegravir (as dolutegravir sodium)	None *For a complete listing, see* **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

INDICATIONS AND CLINICAL USE

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 children at least 6 years of age and weighing at least 15 kg.

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.

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.

Pediatrics (aged less than 6 years or weighing less than 15 kg or INSTI-experienced):

Safety and efficacy of TIVICAY have not been established in children aged less than 6 years or weighing less than 15 kg or who are INSTI-experienced with documented or clinical suspected resistance to other INSTIs.

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 **DOSAGE FORMS, COMPOSITION AND PACKAGING**.
- TIVICAY is contraindicated in combination with dofetilide.

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.

Patients should be advised that current antiretroviral therapy, including TIVICAY, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

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.

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 **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions**, **Co-infection with Hepatitis B or C**).

Immune

Immune Reconstitution Inflammatory Syndrome (IRIS)
During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP and TB), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis 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.

Special Populations

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 **TOXICOLOGY**, **Reproductive Toxicology**, **Pregnancy**). Women of childbearing potential (WOCBP) should undergo pregnancy testing before initiation of TIVICAY and TIVICAY should be avoided in the first trimester. WOCBP who are taking TIVICAY should use effective contraception throughout treatment.

In a preliminary analysis of an ongoing birth outcome surveillance study in Botswana there have been 4 cases (as of May 2018) of neural tube defects reported in 426 infants born to mothers who were exposed to dolutegravir-containing regimens from the time of conception. In the same study, no infant born to a woman who started dolutegravir during pregnancy had a neural tube defect, out of 2824 women. 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 neural tube defects occur within the first 4 weeks of foetal development (at which time the neural tubes are sealed) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy.

Although there is limited experience with the use of dolutegravir in pregnancy, the available data from other sources including the Antiretroviral Pregnancy Registry (including over 120 completed pregnancies as of May 2018 in mothers exposed to

dolutegravir at the time of conception), clinical trials and post-marketing use has not indicated a similar potential safety issue.

In reproductive toxicity studies in animals, dolutegravir was shown to cross the placenta and no evidence of teratogenicity, reproductive function, relevant embryonic or fetal toxicity, including neural tube defects, was identified (see 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

Nursing Women: HIV-1-infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. It is expected that dolutegravir will be secreted into human milk based on animal data, although this has not been confirmed in humans. Nursing mothers should be instructed not to breast-feed if they are receiving TIVICAY.

Pediatrics (<18 years of age): TIVICAY is not recommended in pediatric patients aged less than 6 years or weighing less than 15 kg. Safety and efficacy of TIVICAY have not been established in children who were infected with suspected or confirmed INSTI-resistant HIV-1 virus.

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.

ADVERSE REACTIONS

Adverse Drug 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.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 1.

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 1 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 2.

Table 2 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 **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic, Liver chemistry changes in patients with hepatitis B or C co-infection**).

Pediatrics
TIVICAY is being studied in an ongoing Phase I/II, 48-week 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 (IMPAACT P1093).

Based on limited data in 46 children and adolescents (6 to 18 years of age and weighing at least 15 kg) over 48 weeks, the ADR profile was similar to that for adults. Grade 2 ADRs reported by more than one subject were decreased neutrophil count (n = 3) and diarrhea (n = 2). There were no Grade 3 or 4 drug-related ADRs reported. No ADRs led to discontinuation.

Grade 3 or 4 laboratory abnormalities reported in more than one subject were elevated total bilirubin (n=3) and decreased neutrophil count (n=2). The change in mean serum creatinine was similar to that observed in adults.

Less Common Clinical Trial Adverse Drug Reactions (< 2%)

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

Abnormal Hematologic and Clinical Chemistry Findings

A summary of laboratory abnormalities are 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 3**.**

Table 3 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%)
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 4.

Table 4 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 5. The mean change from baseline observed for lipid values was similar across both treatment groups at Week 48.

Table 5 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 **ACTION AND CLINICAL PHARMACOLOGY**, **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 **ACTION AND CLINICAL PHARMACOLOGY**, **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.

Post-Market Adverse Drug 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

DRUG INTERACTIONS

Overview

Effect of Dolutegravir on the Pharmacokinetics of Other Agents
In vitro, dolutegravir inhibited the renal organic cation transporter, OCT2 (IC_{50} = 1.93 micromolar), multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 micromolar) and MATE2-K (IC_{50} = 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 (dofetilide [see **CONTRAINDICATIONS**], metformin) or MATE1 (see Table 6).

In vitro, dolutegravir inhibited the basolateral renal transporters: organic anion transporter (OAT) 1 (IC_{50} = 2.12 micromolar) and OAT3 (IC_{50} = 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 (IC_{50} >50 μM) the enzymes: cytochrome P_{450} (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 6).

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.

Established and Other Potentially Significant Drug Interactions

Selected drug interactions are presented in Table 6. Recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 6 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 dose of TIVICAY is 50 mg twice daily when co-administered with etravirine without boosted protease inhibitors. 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 dose of TIVICAY is 50 mg twice daily when co-administered with efavirenz in ART-naïve and ART-experieced, 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 8).
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:	Dolutegravir↓	The recommended dose of TIVICAY is 50 mg

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir and/or Concomitant Drug**	**Clinical Comment**
Tipranavir/ritonavir[a] (TPV+RTV)	TPV ↔	twice daily when co-administered with tipranavir/ritonavir in ART-naïve and ART-experienced, INSTI-naïve patients. In pediatric patients, increase the weight-based dose to twice daily (Table 8). 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 50 mg twice daily is recommended in ART-naive and ART-experienced, INSTI-naive adult patients. In pediatric patients, increase the weight-based dose to twice daily (Table 8). Alternative combinations that do not include fosamprenavir/ritonavir should be used where possible in INSTI-resistant patients.[b]
Other Agents		
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.
Oxcarbazepine Phenytoin Phenobarbital Carbamazepine	Dolutegravir↓	The recommended dose of TIVICAY is 50 mg twice daily in adults when co-administered with these metabolic inducers. In pediatric patients, increase the weight-based dose to twice daily (Table 8). 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	Dolutegravir↓	TIVICAY is recommended to be administered 2 hours before or 6 hours after taking medications containing polyvalent cations.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir and/or Concomitant Drug	Clinical Comment
medications		
Calcium supplements[a]	Dolutegravir ↓	TIVICAY is recommended to be administered 2 hours before or 6 hours after taking products containing calcium. If administered with food, TIVICAY can be taken at the same time as calcium supplements.
Iron supplements[a]	Dolutegravir ↓	TIVICAY is recommended to be administered 2 hours before or 6 hours after taking products containing iron. If administered with food, TIVICAY can be taken at the same time as iron supplements.
Metformin	Metformin ↑	Consider metformin dose adjustments when starting or stopping concomitant treatment to maintain glycemic control.
Rifampin[a]	Dolutegravir ↓	The recommended dose of TIVICAY is 50 mg 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 8). Alternatives to rifampin should be used where possible for INSTI-resistant patients.[b]

[a] See **DETAILED PHARMACOLOGY**, **Pharmacokinetics** for magnitude of interaction (Table 19 and Table 20).

[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.

Drug-Food Interactions

TIVICAY may be administered with or without food (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, **Effects of Food on Oral Absorption**).

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, TIVICAY 50 mg twice daily 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.

Drug-Laboratory Interactions

No Drug-Laboratory interactions have been identified.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Dolutegravir can be taken with or without food. The 10 mg tablet strength is not interchangeable with the 25 mg or the 50 mg tablet strengths.

Recommended Dose

Adult Patients

Table 7 Recommended Dosing Regimen in Adults

Patient Population	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 **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 **DRUG INTERACTIONS**).

Pediatric Patients

Treatment-naive or Treatment-experienced INSTI-naive
The recommended dose of TIVICAY in pediatric patients aged at least 6 years and weighing at least 15 kg is provided in Table 8.

Safety and efficacy of TIVICAY have not been established in pediatric patients aged less than 6 years or weighing less than 15 kg, or who are INSTI-experienced with suspected or confirmed INSTI-resistant HIV-1.

Table 8 Recommended Dosing Regimen in pediatric patients

Body Weight (kg)	Once Daily Dosing Regimen[a]
15 to less than 20	20 mg (Two 10 mg tablets)
20 to less than 30	25 mg
30 to <40	35 mg (one 25 mg tablet and one 10 mg tablet)
≥40	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 **DRUG INTERACTIONS**).

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.

Renal impairment

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. Dolutegravir has not been studied in patients receiving dialysis (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Renal Impairment**).

Hepatic impairment

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 **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Hepatic Impairment**).

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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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.

ACTION AND CLINICAL PHARMACOLOGY

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.

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.

Pharmacokinetics

The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult patients and HIV-1-infected adult patients. Dolutegravir pharmacokinetics is 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 9) 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 9 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]
$AUC_{(0\text{-}24)}$ (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

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.

Effects of Food on Oral Absorption: Dolutegravir may be administered with or without food. Food increased the extent of absorption and slowed the rate of absorption of dolutegravir $AUC_{(0\text{-}\infty)}$ by 33%, 41%, and 66%, increased C_{max} by 46%, 52%, and 67%, 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 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.

Special Populations and Conditions

Pediatrics: The pharmacokinetics, safety, virologic and immunologic responses were evaluated in 46 treatment-experienced, integrase-inhibitor naïve, HIV-1 infected patients aged 6 to <18 years (weighing ≥ 15 kg), who received TIVICAY in an open-label, multicentre, dose-finding non-comparative clinical trial; IMPAACT P1093. The pharmacokinetics results showed that the response to TIVICAY in treatment-experienced, INSTI- naïve HIV-1 infected children and adolescents weighing at least 15 kg was similar to HIV-1-infected adults receiving 50 mg once daily (Table 10). Dosing in the ≥15 to ≤20kg weight band is based on population PK modelling and simulation analysis. See **DOSAGE AND ADMINISTRATION**, **Dosing Considerations**, **Pediatric Patients**.

Table 10 Dolutegravir Steady-State Pharmacokinetic Parameters in Pediatric Subjects

Weight (n)	Dose of TIVICAY	Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (%CV)		
		C_{max} (mcg/mL)	$AUC_{(0-24)}$ (mcg.h/mL)	C_{24} (mcg/mL)
≥40 kg (n = 14)	50 mg once daily	3.89 (43)	50.1 (53)	0.99 (66)
≥30 to <40 kg (n = 3)	35 mg once daily	4.40 (54)	64.6 (64)	1.33 (93)
≥20 to <30 kg (n = 4)	25 mg once daily	2.84 (51)	34.1 (46)	0.52 (44)
≥15 to <20 kg[a]	20 mg once daily	4.29	51.6	1.06

[a] Based on population pharmacokinetic analyses using data from IMPAACT P1093.

Population pharmacokinetic analyses demonstrate comparable exposures in children, at least 15 kg, dosed by weight-bands (20 mg, 25 mg, 35 mg, or 50 mg of dolutegravir) to that observed in adults.

See also **ADVERSE REACTIONS**, **Clinical Trial Adverse Drug Reactions**, **Pediatrics**; and **CLINICAL TRIALS**, **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.

Race: 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 Impairment: 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 Impairment: Renal clearance of unchanged drug is a minor pathway of elimination for dolutegravir. In a study 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. Dolutegravir has not been studied 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.

STORAGE AND STABILITY

Store TIVICAY 10, 25 and 50 mg up to 30˚C.

Store TIVICAY 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.

SPECIAL HANDLING INSTRUCTIONS

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

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).

Composition

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.

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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: dolutegravir sodium

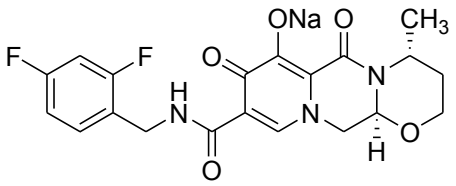
Chemical name:

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

Molecular formula: $C_{20}H_{18}F_2N_3NaO_5$

Molecular mass: 441.36 g/mol

Structural formula:



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

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 use of TIVICAY in pediatric patients aged 6 years and older is based on evaluation of safety, pharmacokinetics and efficacy through 48 weeks in a multicentre, open-label trial in patients without INSTI-resistance (n=46).

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 11 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 11 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

Week 48 outcomes (including outcomes by key baseline covariates) for SPRING-2 and SINGLE are shown in Table 12 .

Table 12 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)
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)

	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 (%)**

* 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, there 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 olutegravir-containing arms.

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 13.

Table 13 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)

Week 48 outcomes (including outcomes by key baseline covariates) for SAILING are shown in Table 14.

Table 14 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/ mm^3)		
<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)
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

	SAILING	
	TIVICAY 50 mg QD + BR N=354§ n/N (%)	**ISENTRESS 400 mg BID + BR N=361§** n/N (%)
≤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 14). 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
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 15 shows baseline characteristics of patients in the VIKING-3 trial.

Table 15 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).

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 16.

Table 16 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 Discontinued study/study drug for other reasons§ Missing data during window but on study	 5 (3%) 2 (1%) 0 (0%)	 5 (3%) 4 (2%) 0 (0%)
Proportion (%) with HIV-1 RNA < 50 c/mL by Baseline Category		
Gender Male Female	 96/141 (68) 30/42 (71)	 89/141 (63) 27/42 (64)
Race White African-American/African Heritage/Other	 91/130 (70) 35/53 (66)	 82/130 (63) 34/53 (64)
Median change from baseline in CD4+ cell count (range) in cells/mm^3	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 17 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 17). Background overall susceptibility score (OSS) was not associated with Week 48 response.

Pediatric
In the ongoing Phase I/II 48-week 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. Subjects were stratified by age into cohorts, enrolling adolescents first (Cohort I: aged 12 to <18 years) and then younger children (Cohort IIA: aged 6 to <12 years). All subjects received the recommended weight-based dose of TIVICAY (see **DOSAGE AND ADMINISTRATION**, **Dosing Considerations**, **Pediatric Patients**).

These 46 patients had a mean age of 12 years (range: 6 to 17), were 54% female, and 52% black. At baseline, mean plasma HIV-1 RNA was 4.6 $\log_{10}$ copies/mL, median CD4+ cell count was 639 cells/mm^3 (range: 9 to 1700), and median CD4% was 23% (range: 1% to 44%). Overall, 39% had baseline plasma HIV-1 RNA ≥ 50,000 copies/mL and 33% had a CDC HIV clinical classification of category C. Most patients had previously used at least 1 NNRTI (50%) or 1 PI (70%). Week 24 and 48 outcomes for IMPAACT P1093/ING112578 are shown in Table 18.

Table 18 Virologic (Snapshot algorithm) and Immunologic Activity of Treatment for Subjects 6 Years and Older in IMPAACT P1093/ING112578

	Dolutegravir ~ 1 mg/kg once daily + OBT	
	Cohort I (12 to <18 years) (n = 23)	Cohort IIA (6 to < 12 years) (n = 23)
HIV-1-RNA < 50 copies/ml at 24 weeks	16 (70%)	14 (61%)
HIV-1-RNA < 50 copies/ml at 48 weeks, n (%)	14 (61%)	-[a]
HIV-1-RNA < 400 copies/ml at 24 weeks, n (%)	19 (83%)	18 (78%)
HIV-1-RNA < 400 copies/ml at 48 weeks, n (%)	17 (74%)	-[a]
Virologic non-response	6	3
CD4+ Cell Count Median Change from Baseline, cells/mm3 Median Percent Change from Baseline	 84[b] 5 %[a]	 209[c] 8 %[b]

[a] Data not yet available
[b] 22 subjects contributed Week 48 CD4+ cell count data
[c] 21 subjects contributed Week 24 CD4+ cell count data

Virologic outcomes were also evaluated based on body weight. Across both cohorts, virologic suppression (HIV-1 RNA less than 50 copies per mL) at Week 24 was achieved in 75% (18/24) of subjects weighing at least 40 kg, 55% (6/11) of subjects in the 30-to-less-than-40-kg weight-band, 50% (4/8) of subjects in the 20-to-less-than-30-kg weight-band, and 67% (2/3) of subjects in the 15-to-less-than-20-kg weight-band. At Week 48, 63% (12/19) of the subjects in Cohort I weighing at least 40 kg were virologically suppressed.

The median CD4+ cell count increase from baseline to Week 48 was 84 cells per mm^3 in Cohort I. For Cohort IIA, the median CD4+ cell count increase from baseline to Week 24 was 209 cells per mm^3.

DETAILED PHARMACOLOGY

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 **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), Week72 (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).

Pharmacokinetics

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 19), the primary focus of these drug interaction studies was to evaluate the effect of co-administered drug on dolutegravir (Table 20).

Dosing recommendations as a result of established and other potentially significant drug-drug interactions with TIVICAY are provided in Table 6.

Table 19 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 20 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)

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}
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)
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)

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 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)
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.

TOXICOLOGY

Carcinogenesis/mutagenesis

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 Toxicology

Fertility: 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).

Pregnancy: 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.

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PART III: CONSUMER INFORMATION

[Pr]TIVICAY
Dolutegravir (as dolutegravir sodium)
10 mg, 25 mg and 50 mg tablets

This leaflet is part III of a three-part "Product Monograph" published when TIVICAY was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TIVICAY. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

TIVICAY is a prescription oral tablet used for treatment of HIV-1 (Human Immunodeficiency Virus) infection in adults and children at least 6 years of age and weighing at least 15 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-retroviral medicines. To control your HIV infection, and to stop your illness from getting worse, you must keep taking all your medicines, unless your doctor tells you otherwise.

What it does:
TIVICAY interferes with viral replication, thereby helping to control HIV infection.

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.

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 that help fight the virus (HIV).
   -physicians call them CD4 (T) cells

When it should not be used:

Do not take TIVICAY if you are allergic to dolutegravir or any of the ingredients in TIVICAY (see **What the important nonmedicinal ingredients are** for a complete list of ingredients in TIVICAY.)

Do not take TIVICAY if you are taking dofetilide to treat heart conditions.

What the medicinal ingredient is:

Each 10 mg, 25 mg and 50 mg tablet of TIVICAY contains 10 mg, 25 mg and 50 mg of dolutegravir, respectively, (as dolutegravir sodium).

What the important nonmedicinal ingredients are:

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.

What dosage forms it comes in:

TIVICAY is available as film-coated 10, 25 and 50 mg tablets.

WARNINGS AND PRECAUTIONS

TIVICAY will not stop you from passing HIV to others through sexual contact or blood contamination. You should use appropriate precautions, such as using condoms when you have oral or penetrative sex, and not reusing or sharing needles.

BEFORE you use TIVICAY talk to your doctor or pharmacist if you:
- have liver problems, including hepatitis B or C;
- are pregnant or planning to become pregnant; do not take TIVICAY without speaking with your doctor. Your doctor will consider the benefit to you and the risk to your baby when taking TIVICAY while pregnant. If you take TIVICAY while you are pregnant, talk to your doctor about enrolling in the Antiretroviral Pregnancy Registry.
- could get pregnant. Use a reliable method of contraception to prevent pregnancy, while taking TIVICAY.
- are breastfeeding or plan to breastfeed. Where possible, women who are HIV positive should not breast feed, because HIV infection can pass into breast milk and harm your baby.

- It is not known if TIVICAY can pass into breast milk and harm your baby. Talk to your doctor immediately, if you are breastfeeding, or thinking about breastfeeding. Do not breastfeed while taking TIVICAY**.**
- have any other medical condition
- are taking any other medications (see Interactions with this medication)

Other special warnings
Serious liver problems including liver injury and liver failure have been seen in people taking medicines containing dolutegravir (see Serious Side Effects box). In some cases the liver injury has led to a liver transplant. While you are being treated with TIVICAY your doctor will monitor you closely for any signs of liver problems.

INTERACTIONS WITH THIS MEDICATION

Tell your healthcare provider about all prescription and non-prescription medications you are taking; including any vitamins, herbal supplements, and dietary supplements. Some drugs may interact with TIVICAY and can affect how TIVICAY works, or make it more likely that you will have side effects. These include:

- 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 food with your medicine, 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

PROPER USE OF THIS MEDICATION

Always take TIVICAY exactly as your doctor has told you to. Check with your doctor or pharmacist if you're not sure. Do not change your dose or stop taking TIVICAY without talking with your doctor.

Usual dose:

Adults: The usual dose of TIVICAY 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 of TIVICAY is one 50 mg tablet, twice a day.

Your doctor will decide on the correct dose of TIVICAY for you.

Children at least 6 years of age and weighing at least 15 kg: Your doctor will decide on the correct dose of TIVICAY for your child, depending on the weight of the child.

Swallow the tablet with some liquid. TIVICAY can be taken with or without food.

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 doctor 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 food with TIVICAY, then you can take calcium and iron supplements at the same time as TIVICAY.

Be sure to keep a supply of your anti-HIV medicines:
- When your TIVICAY supply starts to run low, get more from your physician or pharmacy.
- Do not wait until your medicine runs out to get more.

Overdose:

If you take too many tablets of TIVICAY, contact your doctor or pharmacist for advice. If possible, show them the TIVICAY pack.

In case of drug overdose, contact a health care practitioner, 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of TIVICAY include:
- diarrhea
- headache
- trouble sleeping (insomnia)
- feeling sick (nausea)
- lack of energy (fatigue)

Other side effects include, rash, itching (pruritus), being sick (vomiting), stomach pain (abdominal pain), stomach (abdominal) discomfort, intestinal gas (flatulence), joint pain, muscle pain, weight gain, dizziness, abnormal dreams, depression (feelings of deep sadness and unworthiness), anxiety, and suicidal thoughts and behaviours (mainly in patients who have had depression or mental health problems before). If you have such feelings, talk to your doctor.

Side effects that may show up in blood tests include an increase in bilirubin (a substance produced by the liver), and/or an increase in the level of enzymes produced in the muscles (creatine phosphokinase, creatinine).

Changes in your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time, or you could develop an autoimmune disease in which your immune system reacts against your own body (e.g. Grave's disease (which affects the thyroid gland), Guillain-Barre syndrome (which affects the nervous system) or polymyositis (which affects the muscles) and it may develop at any time, sometimes months later after the start of HIV therapy). Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling, or fatigue or any new symptoms contact your doctor immediately.

Tell your doctor or pharmacist if any of the side effects mentioned becomes severe or troublesome, or if you notice any other side effects not listed in this leaflet.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Only if severe	In all cases	call your doctor or pharmacist
Uncommon	Hypersensitivity (allergic) Skin rash, fever, lack of energy, swelling of the mouth or face causing difficulty in breathing, muscle or joint aches			✓
	Liver problems (Hepatitis): High liver blood test results, nausea/vomiting loss of appetite, pain, aching or tenderness on the right side below the ribs. If hepatitis is severe, the following may occur: yellowing of the skin or whites of the eyes, dark or tea coloured urine, pale coloured stools/ bowel movements.			✓
Rare	Liver failure: Extremely high liver blood test results, 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.			✓

This is not a complete list of side effects. For any unexpected effects while taking TIVICAY*, contact your doctor or pharmacist.*

HOW TO STORE IT

Store TIVICAY 10, 25 and 50 mg up to 30˚C. Store TIVICAY 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

Keep out of reach and sight of young children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.viivhealthcare.ca
or by contacting the sponsor, ViiV Healthcare ULC at:
245, boulevard Armand-Frappier
Laval, Quebec
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