PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**TIVICAY**

dolutegravir tablets

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

dolutegravir dispersible tablets

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

Antiretroviral Agent

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

Date of Initial Authorization:
NOV 08, 2013

Date of Revision:
FEB 4, 2025

Submission Control Number: 281488

RECENT MAJOR LABEL CHANGES

Section	Date
4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations	11/2023
7 WARNINGS AND PRECAUTIONS, General	06/2023
7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women	08/2024
7 WARNINGS AND PRECAUTIONS, 7.1.2 Breast-feeding	10/2022

TABLE OF CONTENTS

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

1.1 Pediatrics

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

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

1.2 Geriatrics

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

2 CONTRAINDICATIONS

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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

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

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

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

Dolutegravir is available as tablets or as dispersible tablets for patients in whom tablets are not appropriate. For dosing recommendations using tablets and dispersible tablets see Table 1 for the recommended dose for adults, and Table 2 for pediatric patients.

Dispersible tablets may be swallowed whole with drinking water or dispersed in drinking water. When dispersed, the amount of water will depend on the number of tablets prescribed. The tablet(s) should be fully dispersed before swallowing, and the dose should be administered orally within 30 minutes. Do not chew, cut or crush the tablets (see Instructions For Use).

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

4.2 Recommended Dose and Dosage Adjustment

Adult Patients

Table 1 Recommended Dosing Regimen in Adults

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

* QD – once daily

** BID – twice daily

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

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

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

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

Geriatrics

There are limited data available on the use of TIVICAY in patients aged 65 years and older. In general, caution should be exercised in the administration of TIVICAY in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatric

Treatment-naive or Treatment-experienced INSTI-naive

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

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

Table 2 Recommended Dosing Regimen in pediatric patients

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

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

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

Hepatic Insufficiency

No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied. Therefore, dolutegravir is not recommended for use in patients with severe hepatic impairment (Child-Pugh Score C) (see 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

Renal Insufficiency

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

4.5 Missed Dose

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

5 OVERDOSAGE

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

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

Treatment

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

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

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

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

Dosage Forms

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

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

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

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

Packaging

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

TIVICAY 10 mg tablets contain a silica gel desiccant.

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

7 WARNINGS AND PRECAUTIONS

General

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

TIVICAY tablets and TIVICAY dispersible tablets are not bioequivalent and are not interchangeable on a milligram-per-milligram basis (see 10 CLINICAL PHARMACOLOGY). If a patient switches from one formulation to the other, the dose must be adjusted for the new dosage formulation (see 4 DOSAGE AND ADMINISTRATION). Incorrect dosing of a given formulation may result in underdosing and loss of therapeutic effect and possible development of resistance or possible clinically significant adverse reactions from greater exposure of dolutegravir.

Driving and Operating Machinery

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

Hepatic/Biliary/Pancreatic

Hepatoxicity

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

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

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

Hypersensitivity Reactions

Hypersensitivity reactions have been reported with integrase inhibitors, including TIVICAY, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. Discontinue TIVICAY and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general

malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with TIVICAY or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

Immune

Immune Reconstitution Inflammatory Syndrome (IRIS)

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

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

7.1 Special Populations

7.1.1 Pregnant Women

TIVICAY should not be used in pregnant women unless the potential benefits outweigh the potential risks to the fetus.

There are insufficient human data on the use of dolutegravir during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. However, available human data from the Antiretroviral Pregnancy Registry (APR) do not indicate an increased risk of birth defects. In the Canadian general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 3% to 5% and 15% to 25%, respectively.

Two large birth outcome surveillance studies in Botswana (Tsepamo) and Eswatini, which together include over 19,000 individuals taking dolutegravir-containing regimens at conception, show no significant difference in neural tube defect prevalence in infants born to individuals taking dolutegravir at conception compared to those born to individuals taking non-dolutegravir containing antiretroviral regimens at conception, or infants born to HIV-negative individuals.

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

The Eswatini birth outcome surveillance study includes 9,743 individuals exposed to dolutegravir at conception, 1,838 individuals exposed to non-dolutegravir-containing regimens, and 32,259 HIV-

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

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

Based on prospective reports to the APR of 1,378 exposures to dolutegravir during pregnancy resulting in live births (including 874 exposed in the first trimester), there was no difference between the overall risk of birth defects for dolutegravir when compared to the background birth defect rate from two population based surveillance systems (Metropolitan Atlanta Congenital Defects Program (MACDP) with defects of 2.72 per 100 live births and the Texas Birth Defects Registry (TBDR) with 4.17 per 100 live births). The prevalence of defects in live births was 3.3% (95% CI: 2.2% to 4.7%) following first trimester exposure to dolutegravir-containing regimens and 5.0% (95% CI: 3.2% to 7.3%) following second/third trimester exposure to dolutegravir-containing regimens.

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

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

In reproductive toxicity studies in animals, no evidence of teratogenicity, reproductive function, relevant embryonic or fetal toxicity, including neural tube defects, was identified in rats and rabbits at ≥30 and 0.55 times human clinical exposure based on AUC, respectively (see 16 NON-CLINICAL TOXICOLOGY).

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

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

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

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

8.2 Clinical Trial Adverse Reactions

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

Treatment-Naïve Patients

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

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

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

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

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

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

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

Antiretroviral-Experienced and Integrase Inhibitor-Naïve Patients

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

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

Integrase Inhibitor-Resistant Patients

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

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

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

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

Co-infection with Hepatitis B or C

In Phase III studies, patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C co-infection for all treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected patients compared with HIV mono-infected patients receiving TIVICAY were observed in 18% vs. 3% with the 50 mg once-daily dose and 13% vs. 9% with the 50 mg twice-daily dose. Liver chemistry elevations consistent with immune reconstitution inflammatory syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Liver chemistry changes in patients with hepatitis B or C co-infection).

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

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

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

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

Through Week 24, Grade 3 or 4 laboratory abnormalities reported in more than one subject were decreased neutrophil count (n=11), decreased blood bicarbonate (n=4), decreased haemoglobin (n=3), increased lipase (n=2), and increased blood potassium (n=2). These laboratory events were not considered to be drug related. The change in median serum creatinine was similar to that observed in adults.

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

8.3 Less Common Clinical Trial Adverse Reactions

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

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

General Disorders: Fatigue

Hepatobiliary Disorders: Hepatitis

Immune System Disorders: Hypersensitivity, immune reconstitution inflammatory syndrome

Skin and Subcutaneous Tissue Disorders: Pruritus

Musculoskeletal and Connective Tissue Disorders: Myalgia, myositis

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

Renal and Urinary Disorders: Renal impairment

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

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

Treatment-Naïve Patients

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

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

Laboratory Parameter Preferred Term (Unit)	SPRING-2		SINGLE	
	TIVICAY 50 mg QD+ 2 NRTIs (N = 411)	ISENTRESS 400 mg BID + 2 NRTIs (N = 411)	TIVICAY 50 mg + KIVEXA QD (N = 414)	ATRIPLA QD (N = 419)
ALT (IU/L)				
Grade 2 (>2.5-5.0 x ULN)	8 (2%)	14 (3%)	9 (2%)	20 (5%)
Grade 3 to 4 (>5.0 x ULN)	9 (2%)	7 (2%)	1 (<1%)	2 (<1%)
AST (IU/L)				
Grade 2 (>2.5-5.0 x ULN)	15 (4%)	14 (3%)	7 (2%)	13 (3%)
Grade 3 to 4 (>5.0 x ULN)	11 (2%)	9 (2%)	0	10 (2%)

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)
Total Bilirubin (µmol/L)				
Grade 2 (1.6-2.5 x ULN)	8 (2%)	8 (2%)	2 (<1%)	1 (<1%)
Grade 3 to 4 (>2.5 x ULN)	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Creatine kinase (IU/L)				
Grade 2 (6.0-9.9 x ULN)	8 (2%)	14 (3%)	15 (4%)	7 (2%)
Grade 3 to 4 (≥10.0 x ULN)	20 (5%)	14 (3%)	11 (3%)	19 (5%)
Hyperglycemia (mmol/L)				
Grade 2 (6.95-13.88 mmol/L)	24 (6%)	23 (6%)	28 (7%)	19 (5%)
Grade 3 to 4 (>13.88 mmol/L)	2 (<1%)	6 (1%)	6 (1%)	1 (<1%)
Lipase (U/L)				
Grade 2 (>1.5-3.0 x ULN)	23 (6%)	25 (6%)	33 (8%)	30 (7%)
Grade 3 to 4 (>3.0 x ULN)	7 (2%)	14 (3%)	11 (3%)	8 (2%)
Phosphorus, inorganic (mmol/L)				
Grade 2 (0.65-0.80 mmol/L)	34 (8%)	48 (12%)	37 (9%)	52 (12%)
Grade 3 to 4 (<0.65mmol/L)	5 (1%)	7 (2%)	5 (1%)	12 (3%)
Total neutrophils (10^3/µL)				
Grade 2 (0.75-0.99 x 10^9)	15 (4%)	11 (3%)	10 (2%)	15 (4%)
Grade 3 to 4 (<0.75 x 10^9)	8 (2%)	7 (2%)	7 (2%)	12 (3%)

ULN = Upper limit of normal

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

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

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

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

Treatment-experienced and Integrase Inhibitor-Naïve Patients

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

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

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

[a] Background Regimen

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

Treatment-experienced and Integrase Inhibitor-Resistant Patients

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

Changes in Clinical Laboratory Values

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

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

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

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

8.5 Post-Market Adverse Reactions

Hepatobiliary disorders: acute hepatic failure

Musculoskeletal and connective tissue disorders: arthralgia, myalgia

Psychiatric disorders: anxiety*

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

Investigations: weight increased

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Effect of Dolutegravir on the Pharmacokinetics of Other Agents

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

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

In vitro, dolutegravir did not inhibit (IC50 >50 µM) the enzymes: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or transporters: P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, or multidrug resistance protein (MRP)2 or MRP4. In vitro, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4. Based on these data, TIVICAY is not expected to affect the pharmacokinetics of drugs that are

substrates of these enzymes or transporters.

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

Effect of Other Agents on the Pharmacokinetics of Dolutegravir

Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP in vitro; therefore drugs that induce those enzymes and transporters, may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir.

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

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

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

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

9.4 Drug-Drug Interactions

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

Table 9 Established or Potential Drug-Drug Interactions

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

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

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

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

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

9.5 Drug-Food Interactions

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

9.6 Drug-Herb Interactions

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

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration, which is essential for the HIV replication cycle. *In vitro*, dolutegravir dissociates slowly from the active site of the wild-type integrase-DNA complex (t ½ 71 hours). Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

10.2 Pharmacodynamics

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

Effects on Electrocardiogram: In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single-dose oral administrations of placebo, dolutegravir 250 mg suspension (exposures approximately 3-fold of the 50 mg once-daily dose at steady state), and moxifloxacin (400 mg, active control) in random sequence. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) was 1.99 msec (1-sided 95% upper CI: 4.53 msec). TIVICAY did not prolong the QTc interval for 24 hours post-dose**.**

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

10.3 Pharmacokinetics

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

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

Parameter	50 mg QD Geometric mean (% CV)[a]	50 mg BID Geometric mean (% CV)[b]
$AUC_{(0-24)}$ (mcg.hr/mL)	53.6 (27)	75.1 (35)
C_{max} (mcg/mL)	3.67 (20)	4.15 (29)
C_{min} (mcg/mL)	1.11 (46)	2.12 (47)

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

[b] Based on population pharmacokinetic analyses using data from VIKING and VIKING-3

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

Absorption

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

Distribution

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

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

Metabolism

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

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

Elimination

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

Effects of Food on Oral Absorption

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

Drug interactions

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

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

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

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

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

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

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

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

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

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

Special Populations and Conditions

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

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

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

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

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

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

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

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

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

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

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

11 STORAGE, STABILITY AND DISPOSAL

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

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

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

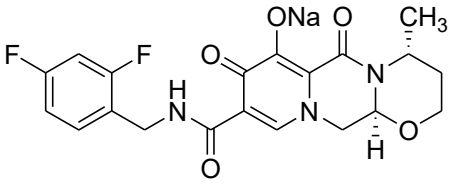
Drug Substance

Proper name: dolutegravir sodium

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

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

Structural formula:



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

14 CLINICAL TRIALS

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

14.1 Clinical Trials by Indication

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

Trial Design and Study Demographics

Treatment-Naïve Patients

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

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

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

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

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

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

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

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

Treatment-Experienced (and Integrase Inhibitor-Naïve) Patients

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

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

Table 15 Baseline Population Characteristics (SAILING)

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

Integrase Inhibitor-Resistant Patients

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

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

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

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

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

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

Pediatric

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

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

Study Results

Treatment-Naïve Patients

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

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

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

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

* Adjusted for baseline stratification factors

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Treatment-Experienced (and Integrase Inhibitor-Naïve) Patients

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

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

	SAILING	
	TIVICAY 50 mg QD + BR N=354§ n/N (%)	ISENTRESS 400 mg BID + BR N=361§ n/N (%)
HIV-1 RNA <50 copies/mL	251/354 (71)	230/361 (64)
Adjusted Treatment Difference‡	7.4% (95% CI: 0.7%, 14.2%), p=0.030	
Virologic non-response†	71/354 (20)	100/361 (28)
No virologic data	32/354 (9)	31/361 (9)
Reasons		
Discontinued study/study drug due to adverse event or death‡	9 (3)	13 (4)
Discontinued study/study drug for other reasons§	16 (5)	14 (4)
Missing data during window but on study	7 (2)	4 (1)
HIV-1 RNA <50 copies/mL by baseline covariates		
Baseline Plasma Viral Load (copies/mL)		
≤50,000 copies/mL	186 / 249 (75)	180 / 254 (71)
>50,000 copies/mL	65 / 105 (62)	50 / 107 (47)
Baseline CD4+ (cells/ 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)

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

Adjusted for pre-specified stratification factors

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

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

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

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

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

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

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

Integrase Inhibitor-Resistant Patients

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

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

	Week 24	Week 48
	TIVICAY 50 mg BID + OBT (N = 183)	TIVICAY 50 mg BID + OBT (N = 183)
HIV-1 RNA <50 copies/mL	126 (69%)	116 (63%)
Virologic non-response	50 (27%)	58 (32%)
No virologic data		
Reasons		
Discontinued study/study drug due to adverse event or death	5 (3%)	5 (3%)
Discontinued study/study drug for other reasons	2 (1%)	4 (2%)
Missing data during window but on study	0 (0%)	0 (0%)
Proportion (%) with HIV-1 RNA < 50 c/mL by Baseline Category		
Gender		
Male	96/141 (68)	89/141 (63)
Female	30/42 (71)	27/42 (64)
Race		
White	91/130 (70)	82/130 (63)
African-American/African Heritage/Other	35/53 (66)	34/53 (64)
Median change from baseline in CD4+ cell count (range) in cells/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 20 Virologic Response (HIV-1 RNA <50 copies/mL) by Derived Integrase-Resistance Substitution Group at Week 24 and Week 48 (Intent-to-Treat Exposed Population: Snapshot Algorithm)

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

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

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

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

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

Pediatric

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

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

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

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

[b] Snapshot algorithm was used in the RNA analysis

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

15 MICROBIOLOGY

Antiviral Activity in cell culture

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

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

Antiviral Activity in combination with other antiviral agents

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

Effect of Human Serum and Serum Proteins

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

Resistance *in vitro*

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

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

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

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

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

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

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

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

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

Resistance *in vivo*: integrase inhibitor-resistant patients

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

16 NON-CLINICAL TOXICOLOGY

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

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

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

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

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

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

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]TIVICAY

dolutegravir tablets
dolutegravir dispersible tablets

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

What is TIVICAY used for?

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

TIVICAY is a type of anti-HIV medicine called an integrase inhibitor. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

TIVICAY is used in combination with other anti-HIV medicines. To control your HIV infection, and to stop your illness from getting worse, you must keep taking all your medicines, unless your healthcare professional tells you otherwise.

How does TIVICAY work?

TIVICAY blocks an enzyme which the virus (HIV) needs in order to make more virus. The enzyme that TIVICAY blocks is called HIV integrase. This helps control HIV infection.

When used with other anti-HIV medicines, TIVICAY may do two things:

1. It may reduce the amount of HIV in your blood. This is called your "viral load".
   -Reducing the amount of HIV in the blood may keep your immune system healthy.
   -This in turn, can help your immune system to fight infection.
2. It may also increase the number of white blood cells, called CD4 (T) cells, that help fight the virus (HIV).

What are the ingredients in TIVICAY?

Medicinal ingredients: dolutegravir (as dolutegravir sodium)

Non-medicinal ingredients:

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

TIVICAY dispersible tablets: Calcium sulfate dihydrate, crospovidone, hypromellose, mannitol, microcrystalline cellulose, polyethylene glycol, povidone K29/32, silicified microcrystalline cellulose, sodium starch glycolate, sodium stearyl fumarate, strawberry cream flavor, sucralose, titanium dioxide.

TIVICAY comes in the following dosage forms:

dispersible tablets: 5 mg

film-coated tablets: 10 mg, 25 mg, 50 mg

Do not use TIVICAY if:

- you are allergic to dolutegravir or any of the other ingredients in TIVICAY (see **What are the ingredients in TIVICAY?**)
- you are taking dofetilide to treat heart conditions, or fampridine (also known as dalfampridine) to treat multiple sclerosis.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TIVICAY. Talk about any health conditions or problems you may have, including if you:

- have liver problems, including hepatitis B or C
- have a history of depression or other mental health problems
- have any other medical condition

Other warnings you should know about:

Serious Liver Problems: Serious liver problems including liver injury and liver failure have been seen in patients taking medicines containing dolutegravir. In some cases the liver injury has led to a liver transplant. While you are being treated with TIVICAY your healthcare professional will monitor you closely for any signs of liver problems. See the **Serious Side Effects and What To Do About Them** table, below for information on this and other serious side effects.

Pregnancy and Breastfeeding:

- Tell your healthcare professional if you are pregnant or plan to become pregnant. Your healthcare professional will consider the benefit to you and the risk to your baby when taking TIVICAY while you are pregnant.
- If you take TIVICAY while you are pregnant, talk to your healthcare professional about enrolling in the Antiretroviral Pregnancy Registry.
- Talk to your healthcare professional if you are breastfeeding or plan to breastfeed. Women who are HIV positive should not breastfeed because HIV infection can pass into breastmilk. A small amount of the ingredients in TIVICAY can also pass into your breast milk. You should not breastfeed while you are taking TIVICAY**.**

Immune System Changes:

- Changes to your immune system, called **Immune Reconstitution Inflammatory Syndrome**, can happen when you start taking medicines for HIV infection. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time.
- Autoimmune disorders, when the immune system attacks healthy body tissue, can also happen after you start taking medicines for HIV infection. Examples of this include: Grave's disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the nervous system), polymyositis (which affects the muscles), or autoimmune hepatitis (which affects the liver). Autoimmune disorders can happen many months after you start taking TIVICAY.
- See the **Serious side effects and what to do about them** table, below for more information on these and other serious side effects.

Blood Tests: TIVICAY can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Diving and Using Machines: Use caution when driving and using machines until you know how you respond to TIVICAY.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TIVICAY:

- metformin, to treat diabetes
- medicines called antacids, to treat indigestion and heartburn. Do not take an antacid during the 6 hours before you take TIVICAY, or for at least 2 hours after you take it.
- calcium and iron supplements. Do not take a calcium or iron supplement during the 6 hours before you take TIVICAY, or for at least 2 hours after you take it. If you take TIVICAY with food, you can take a calcium or iron supplement at the same time as TIVICAY.
- etravirine, efavirenz, fosamprenavir/ritonavir, nevirapine or tipranavir/ritonavir, to treat HIV infection
- rifampin, to treat tuberculosis (TB) and other bacterial infections
- phenytoin and phenobarbital, to treat epilepsy
- oxcarbazepine and carbamazepine, to treat epilepsy and bipolar disorder
- St. John's wort, (*Hypericum perforatum*), a herbal remedy to treat depression

How to take TIVICAY:

Always take TIVICAY exactly as your healthcare professional has told you to. Check with your healthcare professional if you're not sure. Do not change your dose, switch from one tablet type to another, or stop taking TIVICAY without talking with your healthcare professional.

TIVICAY tablets and TIVICAY dispersible tablets can be taken with or without food.

TIVICAY tablets and TIVICAY dispersible tablets are not the same and cannot be substituted for each other. Your healthcare professional will decide which type of tablet is right for you.

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

Usual dose:

Adults:
TIVICAY tablets:

- The usual dose is one 50 mg tablet, once a day.
- For adults with HIV infection that is resistant to other HIV medicines similar to TIVICAY, the usual dose is one 50 mg tablet, twice a day.

TIVICAY dispersible tablets:

- The usual dose is 30 mg, taken as 6 dispersible tablets, once a day.
- For adults with HIV infection that is resistant to other HIV medicines similar to TIVICAY, the usual dose is 30 mg, taken as 6 dispersible tablets, twice a day.

Children 4 weeks of age and older and weighing at least 3 kg: Your healthcare professional will decide on the correct dose of TIVICAY for your child, depending on the age and weight of the child.

The tablet(s) should be swallowed whole with some liquid. To reduce the risk of choking, do not let your child swallow more than one tablet at a time. If your child is unable to swallow the tablet(s), dispersible tablets should be used.

The dispersible tablets may be swallowed whole with drinking water or dispersed (dissolved) in

drinking water. When swallowed whole, children should not swallow more than one dispersible tablet at a time to reduce the risk of choking. When dispersed, the amount of water will depend on the number of tablets to be taken. The tablet(s) should be fully dispersed before swallowing. Do not chew, cut or crush the tablet(s). Refer to the Instructions for Use.

Children should see their healthcare professional regularly because their TIVICAY dose may change as they get older or gain weight.

Antacid medicines

Antacids, to treat indigestion and heartburn, can stop TIVICAY from being absorbed into your body and make it less effective.

Do not take an antacid during the 6 hours before you take TIVICAY, or for at least 2 hours after you take it. Other acid-lowering medicines like ranitidine and omeprazole can be taken at the same time as TIVICAY. Talk to your healthcare professional for further advice on taking acid-lowering medicines with TIVICAY.

Calcium or iron supplements

Calcium or iron supplements can stop TIVICAY from being absorbed into your body and make it less effective.

Do not take a calcium or iron supplement during the 6 hours before you take TIVICAY, or for at least 2 hours after you take it. If you take TIVICAY with food, then you can take calcium and iron supplements at the same time as TIVICAY.

Overdose:

If you think you, or a person you are caring for, have taken too much TIVICAY, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember, but if your next dose is due within 4 hours, skip the dose you missed and take the next one at the usual time. Then continue your treatment as before. DO NOT take a double dose of your medicine to make up for a missed dose.

What are possible side effects from using TIVICAY?

These are not all the possible side effects you may have when taking TIVICAY. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- diarrhea
- headache
- trouble sleeping (insomnia), abnormal dreams
- nausea, vomiting
- stomach pain, stomach discomfort
- gas
- lack of energy (fatigue)
- rash
- itching
- joint pain, muscle pain

- weight gain
- dizziness

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Allergic reaction: skin rash, fever, lack of energy, swelling of the mouth or face causing difficulty in breathing, muscle or joint aches			✓
Liver problems (Hepatitis): nausea/vomiting, loss of appetite, pain, aching or tenderness on the right side below the ribs, yellowing of the skin or whites of the eyes, dark or tea coloured urine, pale coloured stools/ bowel movements			✓
Mental health problems: depression (feelings of deep sadness and unworthiness, lack of interest in activities, fatigue, loss of appetite), anxiety, suicidal thoughts and behaviours		✓	
RARE			
Liver failure: nausea/vomiting, loss of appetite, pain, aching or tenderness on the right side below the ribs, yellowing of the skin and the whites of the eyes, dark or tea coloured urine, pale coloured stools/bowel movements.			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
FREQUENCY NOT KNOWN			
Immune Reconstitution Inflammatory Syndrome: fever, redness, rash or swelling**,** fatigue**,** joint or muscle pain, numbness, tingling, or weakness beginning in the hands and feet and moving up towards the trunk of the body**,** palpitations, chest pain or rapid heartbeat**,** yellowing of the skin or eyes**,** anxiety and irritability accompanied by tremor of your hands or fingers**,** muscle weakness in your hips, thighs, shoulders, upper arms and neck		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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

Store TIVICAY 5mg dispersible tablets and 10 mg tablets in the original package (HDPE bottle) in order to protect from moisture. Keep the bottle tightly closed. Do not remove the silica gel desiccant. The 5mg dispersible tablet package contains a dosing cup, an oral syringe and instructions for use.

Keep out of reach and sight of children.

If you want more information about TIVICAY:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this

Patient Medication Information by visiting the Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.viivhealthcare.ca or by calling 1-877-393-8448.

This leaflet was prepared by ViiV Healthcare ULC

Last Revised FEB4, 2025