TIVICAY
Package Insert

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

TIVICAY 50 mg Film-coated tablets

COMPOSITION:

Each tablet contains 50 mg of dolutegravir (as dolutegravir sodium).

Excipients:

Contains sugar (mannitol: up to 145,4 mg/tablet).

Tablet Core: D-mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, sodium stearyl fumarate.

Tablet coating: iron oxide yellow, macrogol/polyethylene glycol, polyvinyl alcohol-part hydrolysed, talc, titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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).

Resistance *in vitro*:

Isolation from wild type HIV-1: Viruses highly resistant to dolutegravir were not observed during HIV-1 passage. During wild type HIV-1 passage in the presence of dolutegravir integrase substitutions observed were S153Y and S153F with FCs ≤ 4,1 for strain IIIB, or E92Q with FC = 3,1, and G193E with FC = 3,2 for strain NL432. Additional passage of wildtype 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 potency 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 wildtype strain.

Integrase Inhibitor-Resistant HIV-1 Strains: 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.

Integrase Inhibitor-Resistant HIV-2 Strains: Site-directed mutant HIV-2 viruses were constructed based on subjects infected with HIV-2 and treated with raltegravir who showed virologic failure. Overall, the HIV-2 FCs observed were similar to HIV-1 FCs observed for similar pathway mutations.

Clinical Isolates From Raltegravir Treatment Virologic Failure Subjects: Seven hundred and five raltegravir-resistant clinical isolates were analyzed for susceptibility to dolutegravir using the Monogram Biosciences PhenoSense assay. Dolutegravir has a < 10 FC against 93,9 % of the 705 clinical isolates.

Resistance *in vivo*: integrase inhibitor naïve patients:

No integrase inhibitor (INI)-resistant mutations or treatment-emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment-naïve studies (SPRING-1, SPRING-2 and SINGLE studies). In the SAILING study for treatment-experienced (and integrase-naïve) patients (n = 354 in the dolutegravir arm), treatment- emergent integrase resistance was observed in 2 of 9 subjects with virologic failure. In both cases, a unique R263K integrase substitution was observed, with a maximum FC of 1,93.

Resistance *in vivo*: integrase inhibitor resistant patients:

The VIKING-3 study examined dolutegravir (plus optimised background therapy) in subjects with pre-existing INI resistance. Twenty-six subjects (26/114) experienced protocol-defined virologic failure through to Week 24. Of these, 25 had paired baseline and PDVF resistance data for analysis and 13/25 (52 %) had treatment-emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were E92Q (n = 2), T97A (n = 6), E138K/A (n = 4), G140S (n=2), Y143H (n = 1), S147G (n=1), Q148H/K/R (n = 3), and N155H (n = 1). Eleven of the 13 subjects with virus exhibiting treatment-emergent mutations harboured Q148 pathway virus present at baseline or historically.

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, randomised, 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 small decrease of 10-14 % in mean serum creatinine clearance (CrCl) was observed with dolutegravir within the first week of treatment. Dolutegravir had no significant effect on glomerular filtration rate (GFR) or the effective renal plasm flow (ERPF). *In vitro* studies suggest that the increases in creatinine observed in clinical studies are due to the nonpathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

Pharmacokinetic properties:

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir ranges between low to moderate. In Phase 1 studies in healthy subjects, between-subject CVb % for AUC and C_{max} ranged from ~20 to 40 % and $C\tau$ from 30 to 65 % across studies. The between-subject PK variability of dolutegravir was higher in HIV-infected subjects than in healthy subjects. Within-subject variability (CVw %) is lower than between-subject variability.

Absorption:

Dolutegravir is absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for the tablet formulation. The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, dolutegravir exhibited nonlinear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 to 100 mg; however, increase in dolutegravir exposure appears dose proportional from 25 mg to 50 mg.

Dolutegravir may be administered with or without food. Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate and high fat meals increased dolutegravir AUC (0-∞) by 34 %, 41 %, and 66 %, increased C_{max} by 46 %, 52 %, and 67 %, and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases are not clinically significant.

The absolute bioavailability of dolutegravir has not been established.

Distribution:

Dolutegravir is highly bound (approximately 99,3 %) to human plasma proteins based on *in vitro* data. The apparent volume of distribution (following oral administration of suspension formulation, Vd/F) is estimated at 12,5 ℓ. Binding of dolutegravir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0,441 to 0,535 indicating minimal association of radioactivity with blood cellular components. Free fraction of dolutegravir in plasma is estimated at approximately 0,2 to 1,1 % in healthy subjects, approximately 0,4 to 0,5 % in subjects with moderate hepatic impairment, and 0,8 to 1,0 % in subjects with severe renal impairment and 0,5 % in HIV-1 infected patients.

Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve subjects on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/ml (comparable to unbound plasma concentration, and above the IC50); CSF:plasma concentration ratio of dolutegravir ranged from 0,11 to 0,66 %. Dolutegravir concentrations in CSF exceeded the IC50, supporting the median reduction from baseline in CSF HIV-1 RNA of 2,1 log after 2 weeks of therapy (see Pharmacodynamic properties).

Metabolism:

Dolutegravir is primarily metabolised via UGT1A1 with a minor CYP3A component (9,7 % of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged medicine is low (< 1 % of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed medicine or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-one percent of the total oral dose is excreted in the urine, represented by 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 ~14 hours and an apparent clearance (CL/F) of 0,56 ℓ/hr.

Special patient populations:

Adolescents:

The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 to < 18 years of age) showed that dolutegravir 50 mg once daily dosage resulted in dolutegravir exposure comparable to that observed in adults who received dolutegravir 50 mg once daily.

Due to lack of clinical data, dolutegravir, as in TIVICAY, is not recommended for use in patients under 18 years of age (see DOSAGE AND DIRECTIONS FOR USE).

Table 1: **Adolescent pharmacokinetic parameters**

Age/weight	Dolutegravir Dose	Dolutegravir Pharmacokinetic Parameter Estimat Geometric Mean (CV %)		
		$AUC_{(0-24)}$ μg.hr/m	C_{max} μg/ml	C_{24} μg/ml
12 to <18 years ≥ 40 kg [a]	50 mg once daily [a]	46 (43)	3,49 (38)	0,90 (59)

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

Elderly:

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure.

Pharmacokinetic data for dolutegravir in subjects of > 65 years old are limited.

Renal impairment:

Renal clearance of unchanged medicine is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CLcr < 30 ml/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CLcr < 30 ml/min) and matching healthy subjects were observed, AUC, C_{max}, and C_{24} of dolutegravir were decreased by 40 %, 23 %, and 43 %, respectively, compared with those in matched healthy subjects. No dosage adjustment is necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Hepatic impairment:

Dolutegravir is primarily metabolised and eliminated by the liver. In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh category B) to 8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the two groups. No dosage adjustment is necessary for patients with mild hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in Metabolising Enzymes:

There is no evidence that common polymorphisms in metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. 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). Polymorphisms in CYP3A4, CYP3A5, and NR1I2 were not associated with differences in the pharmacokinetics of dolutegravir.

Co-infection with Hepatitis B or C:

Population pharmacokinetic analysis indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir. There are limited data on subjects with hepatitis B co-infection.

INDICATIONS:

TIVICAY is indicated for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults aged 18 years and older.

CONTRAINDICATIONS:

TIVICAY is contraindicated in combination with dofetilide and pilsicainide.

TIVICAY is contraindicated in patients with known hypersensitivity to dolutegravir or to any of the excipients of TIVICAY.

TIVICAY is contraindicated in moderate and severe hepatic impairment.

Metformin is contraindicated in patients taking TIVICAY.

TIVICAY is contraindicated in the first trimester of pregnancy.

WARNINGS AND SPECIAL PRECAUTIONS:

Hypersensitivity reactions:

Hypersensitivity reactions have been reported with integrase inhibitors, including TIVICAY and were characterised 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 oedema, 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.

Lipodystrophy and metabolic abnormalities:

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Syndrome:

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are tuberculosis, cytomegalovirus retinitis, generalised and/or focal atypical mycobacterial infections, and *Pneumocystis jirovecii (P. carinii)* pneumonia. Any inflammatory symptoms must be evaluated without delay, and treatment initiated when necessary. Auto-immune disorders (such as Graves' disease, polymyositis and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution: however, the time to onset is more variable and can occur many months after initiation of treatment and can sometimes be an atypical presentation.

Liver chemistry elevations consistent with immune reconstitution 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 SIDE EFFECTS).

Osteonecrosis:

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Hepatic impairment:

The unbound fraction of dolutegravir in the blood is doubled in patients with moderate hepatic impairment. TIVICAY is contraindicated in patients with moderate or severe hepatic impairment (see CONTRAINDICATIONS).

Interactions:

Caution should be exercised in co-administering medicines (prescription and non-prescription) that may change the exposure of TIVICAY or medicines that may have their exposure changed by TIVICAY (see CONTRAINDICATIONS and INTERACTIONS).

The co-administration of TIVICAY with etravirine (ETR) is not recommended unless the patient is also receiving concomitant atazanavir+ritonavir (ATV+RTV), lopinavir+ritonavir (LPV+RTV) or darunavir + ritonavir (DRV+RTV) (see INTERACTIONS).

The recommended dose of TIVICAY is 50 mg twice daily when co-administered with efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin (see INTERACTIONS).

TIVICAY should not be co-administered with polyvalent cation-containing antacids. Recommended administration of TIVICAY is 2 hours before or 6 hours after these agents (see INTERACTIONS).

Metformin concentrations may be increased by TIVICAY. Metformin is contraindicated in patients taking TIVICAY (see CONTRAINDICATIONS).

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. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of TIVICAY therapy, particularly in those whose anti-hepatitis B therapy was withdrawn.

Opportunistic infections:

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 medical practitioners experienced in the treatment of these associated HIV diseases.

Transmission of infection:

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

Effects on ability to drive and use machines:

The clinical status of the patient and the adverse event profile of TIVICAY should be borne in mind when considering the patient's ability to drive or operate machinery.

INTERACTIONS:

Effect of TIVICAY on the Pharmacokinetics of Other Medicines:

In vitro, TIVICAY demonstrated no direct, or weak inhibition (IC50 > 50 µM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, OATP1B1, OATP1B3, OCT1 or MRP2. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. *In vivo*, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on these data, TIVICAY is not expected to affect the pharmacokinetics of medicines that are substrates of these enzymes or transporters (e.g., reverse transcriptase and protease inhibitors, opioid analgesics, antidepressants, statins, azole antifungals (such as fluconazole, itraconazole, clotrimazole), proton pump inhibitors (such as esomeprazole, lansoprazole, omeprazole), anti-erectile dysfunction medicines (such as sildenafil, tadalafil, vardenafil), aciclovir, valaciclovir, sitagliptin, adefovir).

In medicine interaction studies, TIVICAY did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, telaprevir and oral contraceptives containing norgestimate and ethinyl estradiol.

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2). Based on this observation, TIVICAY may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, metformin) (see Table 2: Medicine Interactions – Other Medicines).

Effect of Other Medicines on the Pharmacokinetics of TIVICAY:

TIVICAY is eliminated mainly through metabolism by UGT1A1. TIVICAY is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore, medicines that induce those enzymes may theoretically decrease dolutegravir plasma concentration and reduce the therapeutic effect of TIVICAY.

Co-administration of TIVICAY and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration (see Table 2).

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly and require TIVICAY dose adjustment to 50 mg twice daily.

There is evidence that the concentration of isoniazid is increased by dolutegravir, as contained in TIVICAY.

Etravirine also reduced plasma concentrations, but the effect of etravirine was mitigated by co-administration of the CYP3A4 inhibitors lopinavir/ritonavir, darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir. Therefore, no TIVICAY dose adjustment is necessary when co-administered with etravirine and either lopinavir/ritonavir, darunavir/ritonavir, or atazanavir/ritonavir. Another inducer, fosamprenavir, in combination with ritonavir, decreased plasma concentrations of dolutegravir but does not require a dosage adjustment of TIVICAY. Caution is warranted and clinical monitoring is recommended when these combinations are given in INI-resistant patients (see Table 2: Medicine Interactions – HIV-1 Antiviral Medicines**)**. A medicine interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin, and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no TIVICAY dose adjustment is required when co-administered with these medicines.

Table 2: Medicine Interactions

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of TIVICAY or Concomitant Medicine**	**Clinical Comment**
HIV-1 Antiviral <u>Medicines</u>		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR)	Dolutegravir ↓ AUC ↓ 71 % C_{max} ↓ 52 % Cτ ↓ 88 % ETR ↔	Etravirine decreased plasma dolutegravir concentration, which may result in loss of virologic response and possible resistance to dolutegravir. TIVICAY should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Dolutegravir ↓ AUC ↓ 57 % C_{max} ↓ 39 % Cτ ↓ 75 % EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of TIVICAY is 50 mg twice daily when co-administered with efavirenz. Alternative combinations that do not include efavirenz should be used where possible in INI-resistant patients.
Non-nucleoside Reverse Transcriptase Inhibitor: Nevirapine	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. The recommended dose of TIVICAY is 50 mg twice daily when co-administered with nevirapine. Alternative combinations that do not include nevirapine should be used where possible in INI-resistant patients.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of TIVICAY or Concomitant Medicine**	**Clinical Comment**
Protease Inhibitor: Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91 % C_{max} ↑ 49 % Cτ ↑ 180 % ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV + RTV)	Dolutegravir ↑ AUC ↑ 62 % C_{max} ↑ 33 % Cτ ↑ 121 % ATV ↔ RTV ↔	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Tipranavir/ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47 % Cτ ↓ 76 % TPV ↔ RTV ↔	Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of TIVICAY is 50 mg twice daily when co-administered with tipranavir/ritonavir. Alternative combinations that do not include tipranavir/ritonavir should be used where possible in INI resistant patients.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of TIVICAY or Concomitant Medicine**	**Clinical Comment**
Protease Inhibitor: Fosamprenavir/ ritonavir (FPV+RTV)	Dolutegravir ↓ AUC ↓ 35 % C_{max} ↓ 24 % Cτ ↓ 49 % FPV ↔ RTV ↔	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary in INI-naïve patients. Alternative combinations that do not include fosamprenavir/ritonavir should be used where possible in INI resistant patients.
Protease Inhibitor: Nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir (LPV+RTV)	DTG ↔ AUC ↔ C_{max} ↔ Cτ ↔ LPV ↔ RTV ↔	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir (DRV/RTV)	Dolutegravir ↓ AUC ↓ 32 % C_{max} ↓ 11 % Cτ ↓ 38 % DRV ↔ RTV ↔	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of TIVICAY or Concomitant Medicine**	**Clinical Comment**
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir (TDV)	Dolutegravir ↔ TDV ↔	Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir + Etravirine (LPV/RTV + ETR)	Dolutegravir ↔ AUC ↑ 10 % C_{max} ↑ 7 % Cτ ↑ 28 % LPV ↔ RTV ↔ ETR ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir + Etravirine (DRV/RTV + ETR)	Dolutegravir ↓ AUC ↓ 25 % C_{max} ↓ 12 % Cτ ↓ 36 % DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Other Medicines		

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of TIVICAY or Concomitant Medicine**	**Clinical Comment**
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide ↑	Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Dofetilide or pilsicainide co-administration with TIVICAY is contraindicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see CONTRAINDICATIONS).
Oxcarbazepine Phenytoin Phenobarbitoneone Carbamazepine St. John's wort	Dolutegravir↓	Co-administration may decrease dolutegravir plasma concentration and has not been studied. Co-administration with these metabolic inducers should be avoided.
Antacids containing polyvalent cations (e.g., Mg, Al or Ca)	Dolutegravir ↓ AUC ↓ 74 % C_{max} ↓ 72 % C_{24} ↓ 74 %	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. TIVICAY is recommended to be administered 2 hours before or 6 hours after taking antacid products containing polyvalent cations.
Calcium supplements	Dolutegravir ↓ AUC ↓ 39 % C_{max} ↓ 37 % C_{24} ↓ 39 %	TIVICAY is recommended to be administered 2 hours before or 6 hours after taking products containing calcium, or alternatively, administer with food.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of TIVICAY or Concomitant Medicine**	**Clinical Comment**
Iron supplements	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 57 % C_{24} ↓ 56 %	TIVICAY is recommended to be administered 2 hours before or 6 hours after taking products containing iron, or alternatively, administer with food.
Metformin	Metformin ↑	Co-administration of dolutegravir increased metformin plasma concentration. Metformin is contraindicated in patients taking TIVICAY (see CONTRAINDICATIONS)
Rifampicin	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 43 % $C\tau$ ↓ 72 %	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of TIVICAY is 50 mg twice daily when co-administered with rifampicin. Alternatives to rifampicin should be used where possible for INI resistant patients.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of TIVICAY or Concomitant Medicine**	**Clinical Comment**
Oral contraceptives (Ethinyl estradiol (EE) an Norgestromin (NGMN))	Effect of dolutegravir: EE ↔ AUC ↑ 3 % C_{max} ↓ 1 % Cτ ↑ 2 % Effect of dolutegravir: NGMN ↔ AUC ↓ 2 % C_{max} ↓ 11 % Cτ ↓ 7 %	Dolutegravir did not change ethinyl estradiol and norgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with TIVICAY.
Methadone	Effect of dolutegravir: Methadone ↔ AUC ↓ 2 % C_{max} ↔ 0 % Cτ ↓ 1 %	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when co-administered with TIVICAY.

Concomitant Medicine Class: Medicine Name	Effect on Concentration of TIVICAY or Concomitant Medicine	Clinical Comment

Abbreviations: ↑ = Increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus ti

curve; C_{max}= maximum observed concentration, Cτ= concentration at the end of dosing interval.

PREGNANCY AND LACTATION:

Woman of childbearing potential:

Women of childbearing potential should be counselled about the potential risk of neural tube defects with dolutegravir (see below), including consideration of using effective contraceptive measures.

Perform pregnancy testing before initiation of TIVICAY in women of childbearing potential to exclude inadvertent (unintentional) use of TIVICAY during the first trimester of pregnancy.

If a woman plans pregnancy, the benefits and the risks of starting or continuing treatment with TIVICAY versus using another antiretroviral regimen should be discussed with her.

Pregnancy:

Use of dolutegravir during pregnancy was associated with a small increase in the prevalence of neural tube defects (0,19 %) compared to non-dolutegravir regimens (0,11 %). Most neural tube defects occur within the first 4 weeks of embryonic development after conception (approximately 6 weeks after the last menstrual period).

If a pregnancy is confirmed in the first trimester while on dolutegravir, the benefits and risks of continuing dolutegravir versus switching to another antiretroviral regimen should be discussed with the patient, taking the gestational age and the critical time period of neural tube defect development into account.

Dolutegravir may be used during the second and third trimester of pregnancy when the expected benefit outweighs the potential risk to the foetus. Dolutegravir was shown to cross the placenta in humans, leading to significant exposure to the foetus, but the implications of such exposure are not yet known.

Lactation:

HIV infected women should not breastfeed their infants in order to avoid transmission of HIV or follow appropriate guidelines.

Dolutegravir is excreted in human breast milk, and there is significant exposure to the neonate/infants due to slow elimination; the half-life of dolutegravir in the newborn was 33 hr compared to 14 hr in the adults. There is insufficient information on the effects of dolutegravir in neonates/infants.

Fertility:

There are no data on the effects of dolutegravir on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility.

DOSAGE AND DIRECTIONS FOR USE:

Posology:

TIVICAY therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

TIVICAY can be taken with or without food.

Method of Administration:

Adults:

Treatment-naïve:

For patients initiating antiretroviral therapy for the first time (treatment-naïve) the recommended dose of TIVICAY is 50 mg once daily.

Treatment-experienced, and integrase inhibitor naïve:

For patients who are treatment experienced and have not previously been treated with an integrase inhibitor, the recommended dose of TIVICAY is 50 mg once daily.

Integrase inhibitor resistant:

For patients with integrase inhibitor resistance, the recommended dose of TIVICAY is 50 mg twice daily.

Elderly:

There are limited data available on the use of TIVICAY in patients aged 65 years and over. However, there is no evidence that elderly patients require a different dose than younger adult patients (see Pharmacokinetic properties – Special Patient Populations).

Renal impairment:

No dosage adjustment is required in patients with mild, moderate or severe (CrCl < 30 ml/min, not on dialysis) renal impairment. No data are available in subjects receiving dialysis, although differences in pharmacokinetics are not expected in this population (see Pharmacokinetic properties – Special Patient Populations).

Treatment with TIVICAY resulted in an early small increase of mean serum creatinine levels by 10-14 % which remained stable over time and is not considered clinically relevant (see SIDE EFFECTS).

Hepatic impairment:

No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh grade A or B). TIVICAY is contraindicated in patients with moderate or severe hepatic impairment (see CONTRAINDICATIONS).

SIDE EFFECTS:

Clinical trial data:

Adverse drug reactions (ADRs) identified in an analysis of pooled data from clinical studies are listed below, by system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1 000 and <1/100), rare (≥1/10 000 and <1/1 000) and very rare (<1/10 000), including isolated reports.

Table 3: Adverse reactions

Immune system disorder	Uncommon	Hypersensitivity (see WARNINGS AND SPECIAL PRECAUTIONS)
	Uncommon	Immune Reconstitution Syndrome (see WARNINGS AND SPECIAL PRECAUTIONS)
Psychiatric disorders	Common	Insomnia
Nervous system disorder	Very common	Headache
	Common	Dizziness
	Common	Abnormal dreams
Gastrointestinal disorder	Very common	Nausea
	Very common	Diarrhoea
	Common	Vomiting
	Common	Flatulence
	Common	Upper abdominal pain
	Uncommon	Abdominal pain
	Uncommon	Abdominal discomfort
Hepatobiliary disorders	Uncommon	Hepatitis
Skin and subcutaneous tissue disorders	Common	Rash
	Common	Pruritus
General disorders and administration site conditions	Common	Fatigue

The safety profile was similar across the treatment-naïve, treatment-experienced (and integrase-naïve) and integrase-resistant patient populations.

Changes in laboratory chemistries:

Increases in serum creatinine occurred within the first week 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. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate (see Pharmacodynamic properties - Effects on Renal Function).

Small increases in total bilirubin (without clinical jaundice) were observed on TIVICAY and raltegravir (but not efavirenz) arms in the programme. These changes are not considered clinically relevant as they likely reflect competition between TIVICAY and unconjugated bilirubin for a common clearance pathway (UGT1A1) (see Pharmacokinetic properties - Metabolism).

Asymptomatic creatine phosphokinase (CPK) elevations mainly in association with exercise have also been reported with TIVICAY therapy.

Post-marketing data:

No data available.

Neural tube defects have been reported in post-marketing use in peri/preconception and early pregnancy.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Management should be as clinically indicated or as recommended by the national poisons centre, where available.

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

IDENTIFICATION:

Yellow, round, biconvex film-coated tablets debossed with ‘SV 572’ on one side and ‘50’ on the other side.

PRESENTATION:

TIVICAY Tablets are packed in opaque, white round high density polyethylene (HDPE) bottles with a polypropylene child-resistant closure that includes a polyethylene faced induction seal liner.

The HDPE bottle is packed into an outer cardboard carton. Pack sizes of 30 tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

Keep out of reach of children.

REGISTRATION NUMBER:

48/20.2.8/0403

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of registration: 19 February 2016

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