1. NAME OF THE MEDICINAL PRODUCT

TIVICAY

Dolutegravir

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Yellow, round, biconvex tablets debossed with 'SV 572' on one side and '50' on the other side.

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

3. PHARMACEUTICAL FORM

Film coated tablets.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults and children over 12 years of age.

4.2 Posology and method of administration

Posology

TIVICAY therapy should be initiated by a physician experienced in the management of HIV infection.
TIVICAY can be taken with or without food.

Method of Administration

Adults

Patients infected with HIV-1 without resistance to the integrase class

The recommended dose of *TIVICAY* is 50 mg once daily.

Patients infected with HIV-1 with resistance to the integrase class (documented or clinically suspected)

The recommended dose of *TIVICAY* is 50 mg twice daily. The decision to use *TIVICAY* for such patients should be informed by the integrase resistance pattern (see Clinical studies).

Adolescents

In patients who have not previously been treated with an integrase inhibitor, (12 to less than 18 years of age and weighing greater than or equal to 40 kg) the recommended dose of *TIVICAY* is 50 mg once daily.
There are insufficient data to recommend a dose for *TIVICAY* in integrase inhibitor resistant children and adolescents under 18 years of age.

Children

There are insufficient safety and efficacy data available to recommend a dose for *TIVICAY* in children below age 12 or weighing less than 40 kg.

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 Pharmacokinetics – Special Patient Populations*).

Renal impairment

No dosage adjustment is required in patients with mild, moderate or severe (creatinine clearance (CrCl) <30 mL /min, not on dialysis) renal impairment. Limited data are available in subjects receiving dialysis, although differences in pharmacokinetics are not expected in this population (*see Pharmacokinetics — Special Patient Populations*).

Hepatic impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-

Pugh grade A or B). No data are available in patients with severe hepatic impairment (Child-Pugh grade C) (*see Pharmacokinetics – Special Patient Populations*).

4.3 Contraindications

TIVICAY must not be administered concurrently with medicinal products with narrow therapeutic windows, that are substrates of organic cation transporter 2 (OCT2), including but not limited to dofetilide, pilsicainide or fampridine (also known as dalfampridine; *see Interactions*).

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

4.4 Special warnings and precautions for use

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 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.

Immune Reconstitution Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral 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 cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and Pneumocystis jiroveci (P. carinii) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation.
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 Adverse Reactions*).

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 physicians experienced in the treatment of these associated HIV diseases.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be given to co-administering medications (prescription and non-prescription) that

may change the exposure of *TIVICAY* or medications that may have their exposure changed by *TIVICAY (see Contraindications and Interactions).*
The recommended dose of *TIVICAY* is 50 mg twice daily when co-administered with etravirine (without boosted protease inhibitors), efavirenz, nevirapine, tipranavir/ritonavir, rifampicin, carbamazepine, phenytoin, phenobarbital, and St. John's wort (*see Interactions*).
TIVICAY should not be co-administered with polyvalent cation-containing antacids. *TIVICAY* is recommended to be administered 2 hours before or 6 hours after these agents (*see Interactions*).
TIVICAY is recommended to be administered 2 hours before or 6 hours after taking calcium or iron supplements, or alternatively, administered with food (*see Interactions*).
TIVICAY increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control (*see Interactions*).

Interactions

Effect of Dolutegravir on the Pharmacokinetics of Other Agents
In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC50>50 μM) of the enzymes cytochrome P_{450} (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MRP2 or MRP4. 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 drugs that are substrates of these enzymes or transporters (e.g., reverse transcriptase and protease inhibitors, abacavir, zidovudine, maraviroc, opioid analgesics, antidepressants, statins, azole antifungals, proton pump inhibitors, erectile dysfunction agents, aciclovir, valaciclovir, sitagliptin, adefovir).
In drug interaction studies, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, ritonavir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, boceprevir, telaprevir, daclatasvir, and oral contraceptives containing norgestimate and ethinyl estradiol.
In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) (IC50 = 1.93 μM), multidrug and toxin extrusion transporter (MATE) 1 (IC50 = 6.34 μM) and MATE2-K (IC50 = 24.8 μM). Given dolutegravir's in vivo exposure, it has a low potential to affect the transport of MATE2-K substrates in vivo. In vivo, dolutegravir may increase plasma concentrations of drugs in which excretion is dependent upon OCT2 or MATE1 (for example dofetilide, pilsicainide, fampridine [also known as dalfampridine] or metformin) (see Table 1).
In vitro, dolutegravir inhibited the basolateral renal transporters: organic anion transporter (OAT) 1 (IC50 = 2.12 μM) and OAT3 (IC50 = 1.97 μM). However, dolutegravir had no notable effect on the in vivo pharmacokinetics of the OAT substrates tenofovir and para aminohippurate, and therefore has low propensity to cause drug interactions via inhibition of OAT transporters.
Effect of Other Agents on the Pharmacokinetics of Dolutegravir
Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore drugs that induce those enzymes or transporters may theoretically decrease dolutegravir plasma concentration and reduce the therapeutic effect of *TIVICAY*.
Co-administration of *TIVICAY* and other drugs that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration (see Table 1).
In vitro, dolutegravir is not a substrate of human organic anion transporting polypeptide (OATP)1B1, OATP1B3, or OCT1, therefore drugs that solely modulate these transporter are not expected to affect dolutegravir plasma concentration.
Efavirenz, etravirine, nevirapine, rifampicin, carbamazepine, and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly, and require *TIVICAY* dose adjustment to 50 mg twice daily. 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 dolutegravir 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* (see Table 1). A drug interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin, daclatasvir, and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no *TIVICAY* dose adjustment is required when co-administered with these drugs. Selected drug interactions are presented in Table 1. Recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 1 Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir or Concomitant Drug**	**Clinical Comment**
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR) without boosted protease inhibitors	Dolutegravir↓ AUC ↓ 71% C_{max} ↓ 52% $C\tau$ ↓ 88% ETR ↔	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended dose of *TIVICAY* is 50 mg twice daily when co-administered with etravirine without boosted protease inhibitors. *TIVICAY* should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in INI-resistant patients.
Protease Inhibitor: Lopinavir/ritonavir + Etravirine	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% $C\tau$ ↑ 28% LPV ↔ RTV ↔	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	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% $C\tau$ ↓ 36% DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Dolutegravir↓ AUC ↓ 57% C_{max} ↓ 39% $C\tau$ ↓ 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.
Protease Inhibitor (PI): Atazanavir (ATV)	Dolutegravir↑ AUC ↑ 91% C_{max} ↑ 50% $C\tau$ ↑ 180% ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV/RTV)	Dolutegravir↑ AUC ↑ 62% C_{max} ↑ 34% $C\tau$ ↑ 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% $C\tau$ ↓ 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.
Protease Inhibitor: Fosamprenavir/ritonavir (FPV/RTV)	Dolutegravir↓ AUC ↓ 35% C_{max} ↓ 24% $C\tau$ ↓ 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 ↓ 4% C_{max} ↔ $C\tau$ ↓ 6% LPV ↔ RTV ↔	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir	Dolutegravir ↓ AUC ↓ 22% C_{max} ↓ 11% $C\tau$ ↓ 38%	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir	Dolutegravir ↔ AUC ↔ C_{max} ↓3% $C\tau$ ↓ 8% Tenofovir ↔ AUC ↑ 12 % C_{max} ↑ 9% $C\tau$ ↑ 19 %	Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Other Agents		
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 dolutegravir is contraindicated due to potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration.
Fampridine (also known as dalfampridine)	Fampridine ↑	Co-administration of dolutegravir has the potential to cause seizures due to increased fampridine plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Fampridine co-administration with dolutegravir is contraindicated.
Carbamazepine	Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33% $C\tau$ ↓ 73%	Carbamazepine decreased dolutegravir plasma concentration. The recommended dose of *TIVICAY* is 50 mg twice daily when co-administered with carbamazepine. Alternatives to carbamazepine should be used where possible for INI resistant patients.
Phenytoin Phenobarbital St. John's wort	Dolutegravir↓	Co-administration with these metabolic inducers has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied.

		Effect of these metabolic inducers on dolutegravir exposure is likely similar to carbamazepine. The recommended dose of *TIVICAY* is 50 mg twice daily when co-administered with these metabolic inducers. Alternative combinations that do not include these metabolic inducers should be used where possible in INI-resistant patients.
Oxcarbazepine	Dolutegravir ↓	This interaction has not been studied. Although an inducer of CYP3A4, based on data from other inducers, a clinically significant decrease in dolutegravir is not expected. No dose adjustment is necessary.
Antacids containing polyvalent cations (e.g., Mg, Al)	Dolutegravir↓ AUC ↓ 74% C_{max} ↓ 72% C24 ↓ 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% C24 ↓ 39%	*TIVICAY* is recommended to be administered 2 hours before or 6 hours after taking products containing calcium. If administered with food, *TIVICAY* can be taken at the same time as calcium supplements.
Iron supplements	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% C24 ↓ 56%	*TIVICAY* is recommended to be administered 2 hours before or 6 hours after taking products containing iron. If administered with food, *TIVICAY* can be taken at the same time as iron supplements.
Metformin	Metformin↑ When co-administered with dolutegravir 50mg QD: Metformin AUC ↑ 79% C_{max} ↑ 66% When co-administered with dolutegravir 50mg BID: Metformin AUC ↑ 145 % C_{max} ↑ 111%	Co-administration of *TIVICAY* increased metformin plasma concentration. A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control.
Rifampicin	Dolutegravir↓	Rifampicin decreased dolutegravir

	AUC ↓ 54% C_{max} ↓ 43% Cτ ↓ 72%	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 in INI resistant patients.
Oral contraceptives (Ethinyl estradiol (EE) and Norelgestromin (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 norelgestromin 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*.
Daclatasvir	Dolutegravir ↔ AUC ↑ 33% C_{max} ↑ 29% Cτ ↑ 45% Daclatasvir ↔	Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir did not change daclatasvir plasma concentration. No dose adjustment is necessary.

Abbreviations: ↑ = Increase; ↓ =decrease; ↔ = no significant change; AUC=area under the concentration versus time curve; Cmax=maximum observed concentration, Cτ=concentration at the end of dosing interval

4.6 Pregnancy and Lactation

Fertility

There are no data on the effects of *TIVICAY* on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility (*see Non-Clinical Information*).

Pregnancy

TIVICAY should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus. Women of childbearing potential (WOCBP) should be informed about the potential risk of neural tube defects with dolutegravir and counselled about the use of effective contraception. It is recommended that pregnancy testing is conducted prior to initiation of *TIVICAY*. If there are plans to become pregnant or if pregnancy is confirmed within the first trimester while on *TIVICAY*, the risks and benefits of continuing *TIVICAY* versus switching to another antiretroviral regimen should be discussed with the patient. Factors to consider should include feasibility of switching, tolerability, ability to maintain viral suppression, actual gestational age, risk of transmission to the infant and the available data around the potential risk of neural

tube defects and other pregnancy outcomes for dolutegravir and alternative antiretroviral drugs. In a birth outcome surveillance study in Botswana, a numerically higher rate of neural tube defects was identified with exposure to dolutegravir compared to non-dolutegravir-containing antiretroviral regimens at the time of conception, however, the difference was not statistically significant. Seven cases of neural tube defects were reported in 3,591 deliveries (0.19%) to mothers taking dolutegravir-containing regimens at the time of conception, compared with 21 cases in 19,361 deliveries (0.11%) to mothers taking non-dolutegravir-containing regimens at the time of conception (Prevalence Difference 0.09%; 95% CI -0.03, 0.30).
In the same study, an increased risk of neural tube defects was not identified in women who started dolutegravir during pregnancy. Two out of 4,448 deliveries (0.04%) to mothers who started dolutegravir during pregnancy had a neural tube defect, compared with five out of 6,748 deliveries (0.07%) to mothers who started non-dolutegravir-containing regimens during pregnancy.
A causal relationship of these events to the use of dolutegravir has not been established. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births. As most neural tube defects occur within the first 4 weeks of foetal development (approximately 6 weeks after the last menstrual period) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy.
Data analysed to date from other sources including the Antiretroviral Pregnancy Registry, clinical trials, and post-marketing data are insufficient to address the risk of neural tube defects with dolutegravir.
More than 1,000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes.
In animal reproductive toxicity studies, no adverse development outcomes, including neural tube defects, were identified (*see Non-Clinical Information*).
TIVICAY use during pregnancy has been evaluated in the Antiretroviral Pregnancy Registry (APR) in over 600 women (as of July 2019). Available human data from the APR do not show an increased risk of major birth defects for dolutegravir compared to the background rate (*see Clinical Studies*).
Dolutegravir readily crosses the placenta in humans. In HIV-infected pregnant women, the median (range) foetal umbilical cord concentrations of dolutegravir were 1.28 (1.21 to 1.28) fold greater compared with maternal peripheral plasma concentrations.

There is insufficient information on the effects of *TIVICAY* on neonates.

Lactation

Health experts recommend that where possible HIV infected women do not breast feed their infants in order to avoid transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breast feeding during antiretroviral therapy.
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).

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of *TIVICAY* on driving performance or the ability to operate machinery. 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.

4.8 Undesirable effects

Clinical trial data

Adverse drug reactions (ADRs) identified in an analysis of pooled data from Phase IIb and Phase III clinical studies are listed below by MedDRA 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 2 Adverse reactions

Immune system disorders	Uncommon	Hypersensitivity (see Warnings and Precautions)
	Uncommon	Immune Reconstitution Syndrome (see Warnings and Precautions)
Psychiatric disorders	Common	Insomnia
	Common	Abnormal dreams
	Common	Depression
	Common	Anxiety
	Uncommon	Suicidal ideation*, suicide attempt* *particularly in patients with a pre-existing history of depression or psychiatric illness
Nervous system disorders	Very common	Headache
	Common	Dizziness
Gastrointestinal disorders	Very common	Nausea
	Very common	Diarrhoea
	Common	Vomiting
	Common	Flatulence
	Common	Upper abdominal pain
	Common	Abdominal pain
	Common	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 Pharmacodynamics – Effects on Renal Function*).

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

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

Paediatric population

Based on limited available data in children and adolescents (12 to less than 18 years of age), there were no additional types of adverse reactions beyond those observed in the adult population.

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 (*see Warnings and Precautions*).

Post-marketing data

Table 3 Post marketing adverse reactions

Hepatobiliary disorders	Rare	Acute hepatic failure *
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia
	Uncommon	Myalgia
Investigations	Common	Weight increased

* Acute hepatic failure has been reported in a dolutegravir-containing regimen. The contribution of dolutegravir in these cases is unclear.

4.9 Overdose

Symptoms and signs

There is currently limited experience with overdosage in *TIVICAY*.

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

Further 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 dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

ATC code

Pharmacotherapeutic group: Antiviral for systemic use, Other Antivirals.

ATC code: J05AJ03

Mechanism of action

TIVICAY inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV 1 integrase and pre-processed substrate DNA resulted in IC50 values of 2.7 nM and 12.6 nM. In vitro, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex (t ½ 71 hours).

Pharmacodynamic effects

In a randomized, dose-ranging trial, HIV 1–infected subjects treated with *TIVICAY* 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 log10 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.

Antiviral Activity in cell culture

Peripheral blood mononuclear cells (PBMC) infected with HIV-1 strain BaL or HIV-1 strain NL432 gave DTG EC50s of 0.51 nM and 0.53 nM, respectively. MT-4 cells infected with HIV-1 strain IIIB and incubated with dolutegravir for 4 or 5 days resulted in EC50s of 0.71 and 2.1 nM.

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 EC50 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 EC50 was 0.20 nM and EC50 values ranged from 0.02 to 2.14 nM for HIV-1, while the geometric mean EC50 was 0.18 nM and EC50 values ranged from 0.09 to 0.61 nM for HIV-2 isolates.

Antiviral Activity in combination with other antiviral agents

No drugs with inherent anti-HIV activity were antagonistic with dolutegravir (in vitro assessments were conducted in checkerboard format in combination with stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide, maraviroc, adefovir and raltegravir). In addition, antivirals without inherent anti-HIV activity (ribavirin) had no apparent effect on dolutegravir activity.

Effect of Human Serum and Serum Proteins

In vitro studies suggested a 75-fold shift in EC50 of dolutegravir in the presence of 100% human serum (by method of extrapolation), and the protein adjusted EC90 (PA-EC90) in PBMCs was estimated to be 64 ng/mL. Dolutegravir trough concentration for a single 50 mg dose in integrase inhibitor naïve subjects was 1.20 μg/mL and therefore 19 times higher than the estimated PA-EC90.

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 wildtype subtype B, C, and A/G viruses in the presence of DTG 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: 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 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. 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 wildtype, 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 Subjects: 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 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, of note 16 (9%) of the 184 isolates with Q148 +1 INSTI-resistance substitution and 25 (27%) of the 92 clinical isolates with Q148 + ≥2 INSTI-resistance substitutions had greater than 10 fold change.

Resistance in vivo: integrase inhibitor naïve patients

No INI-resistant mutations or treatment emergent resistance to the NRTI backbone therapy were isolated with *TIVICAY* 50 mg once daily in treatment–naive studies (SPRING-1, SPRING-2, SINGLE and FLAMINGO 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 subjects had a unique R263K integrase substitution, with a maximum FC of 1.93, 1 subject 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 (*see Clinical Studies*).

Resistance in vivo: integrase inhibitor resistant patients

The VIKING-3 study examined *TIVICAY* (plus optimized background therapy) in subjects with pre-existing INI resistance. Thirty six subjects (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 subjects with virus exhibiting treatment-emergent mutations harboured Q148 pathway virus present at baseline or historically. Five further subjects 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).

The VIKING-4 study examined *TIVICAY* (plus optimized background therapy) in subjects with

primary genotypic resistance to INIs at Screening in 30 subjects. Treatment-emergent mutations observed were consistent with those observed in the VIKING-3 study.

Effects on Electrocardiogram

In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single dose oral administrations of placebo, DTG 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. Dolutegravir did not prolong the QTc interval for 24 hours post dose. 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).

Effects on Renal Function

The effect of *TIVICAY* 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 *TIVICAY* 50 mg once daily (n=12), 50 mg twice daily (n=13) or placebo once daily (n=12) for 14 days. A modest decrease in CrCl was observed with dolutegravir within the first week of treatment, consistent with that seen in clinical studies. Dolutegravir at both doses had no significant effect on GFR or ERPF. These data support in vitro studies which suggest that the small 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.

5.2 Pharmacokinetic properties

Dolutegravir pharmacokinetics is similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is between low to moderate. In Phase 1 studies in healthy subjects, between-subject CVb% for AUC and Cmax ranged from ~20 to 40% and C_τ from 30 to 65% across studies. The between-subject PK variability of DTG was higher in HIV-infected subjects than healthy subjects. Within-subject variability (CVw%) is lower than between-subject variability.

Absorption

Dolutegravir is rapidly absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for film-coated tablet formulation. The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, in general, *TIVICAY* 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.

TIVICAY 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 $AUC_{(0-\infty)}$ by 33%, 41%, and 66%, increased C_{max} by 46%, 52%, and 67%, prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. 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 DTG 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 12 treatment-naïve subjects receiving a regimen of dolutegravir plus abacavir/lamivudine (3TC) for 16 weeks, dolutegravir concentration in CSF averaged 15.4 ng/mL at Week 2 and 12.6 ng/mL at Week 16, ranging from 3.7 to 23.2 ng/mL (comparable to unbound plasma concentration). CSF:plasma concentration ratio of DTG ranged from 0.11 to 2.04%. Dolutegravir concentrations in CSF exceeded the IC50, supporting the median reduction from baseline in CSF HIV-1 RNA of 2.2 log after 2 weeks of therapy and 3.4 log after 16 weeks (*see Pharmacodynamics*).
Dolutegravir is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue, and vaginal tissue were 6 to 10% of that in corresponding plasma at steady-state. AUC was 7% in semen and 17% in rectal tissue, of those in corresponding plasma at steady-state.

Metabolism

Dolutegravir is primarily metabolized 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 drug is low (< 1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the feces. It is unknown if all or part of this is due to unabsorbed drug 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 DTG (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

Children

In a paediatric study including 23 antiretroviral treatment-experienced HIV-1 infected adolescents aged 12 to 18 years of age, the pharmacokinetics of dolutegravir was evaluated in 10 adolescents and showed that *TIVICAY* 50 mg once daily dosage resulted in dolutegravir exposure in paediatric subjects comparable to that observed in adults who received *TIVICAY* 50 mg once daily (Table 4).

Table 4 Paediatric pharmacokinetic parameters (n=10)

Age/weight	*TIVICAY* Dose	Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (CV%)		
		$AUC_{(0-24)}$ μg.hr/mL	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 drug is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CrCl < 30 mL/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CrCl < 30mL/min) and matching healthy subjects were observed. No dosage adjustment is necessary for patients with renal impairment. There is limited information on dolutegravir in patients on dialysis, though differences in exposure are not expected.

Hepatic impairment

Dolutegravir is primarily metabolized 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 to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in Drug Metabolising Enzymes

There is no evidence that common polymorphisms in drug 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.

Gender

The dolutegravir exposure in healthy subjects appear to be slightly higher (~20%) in women than men based on data obtained in a healthy subject study (males n=17, females n=24). Population PK analyses using pooled pharmacokinetic data from Phase 2b and Phase 3 adult trials revealed no clinically relevant effect of gender on the exposure of dolutegravir.

Race

Population PK analyses using pooled pharmacokinetic data from Phase 2b and Phase 3 adult trials revealed no clinically relevant effect of race on the exposure of dolutegravir. The pharmacokinetics of dolutegravir following single dose oral administration to Japanese subjects appear similar to observed parameters in Western (US) subjects.

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.

5.3 Preclinical safety data

Non-Clinical Information

Carcinogenesis/mutagenesis

Dolutegravir was not mutagenic or clastogenic using in vitro tests in bacteria and cultured mammalian cells, and an in vivo rodent micronucleus assay. Dolutegravir was not carcinogenic in long term studies in the mouse and rat.

Reproductive Toxicology

Fertility

Dolutegravir did not affect male or female fertility in rats at doses up to 1000 mg/kg/day, the highest dose tested (33 times the 50 mg human clinical exposure based on AUC).

Pregnancy

Oral administration of dolutegravir to pregnant rats at doses up to 1000 mg/kg daily from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (37.9 times the 50 mg 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 (0.56 times the 50 mg 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 (0.56 times the 50 mg human clinical exposure based on AUC).

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 32 and 1.2 times the 50 mg 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 30 times the human mg/kg equivalent dose (based on 50 kg human), and 11 times the human mg/m^2 equivalent dose for a total daily clinical dose of 50 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Mannitol
Microcrystalline Cellulose
Povidone K29/32
Sodium Starch Glycolate
Sodium Stearyl Fumarate
Tablet coating:
Polyvinyl alcohol-partially hydrolyzed
Titanium Dioxide
Macrogol/PEG
Talc
Iron oxide yellow

6.2 Incompatibilities

No incompatibilities have been identified.

6.3 Shelf life

The expiry date is indicated on the packaging.

6.4 Special precautions for storage

The storage conditions are detailed on the packaging

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

TIVICAY tablets are supplied in HDPE (high density polyethylene) bottles.

6.6 Special precautions for disposal <and other handling>

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

7. <APPLICANT/MANUFACTURER>

Applicant:

GlaxoSmithKline Pharmaceutical Nigeria Limited

1 Industrial Avenue, Ilupeju

Lagos

Manufacturer:

Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations)

Priory Street

Ware

Hertfordshire SG12 0DJ

UK