TIVICAY

Dolutegravir

QUALITATIVE AND QUANTITATIVE COMPOSITION

White, round, biconvex tablets debossed with ‘SV H7S’ on one side and ‘5’ on the other side.

Each tablet contains 5 mg of dolutegravir (as dolutegravir sodium).

CLINICAL INFORMATION

Indications

Treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults and children aged at least 4 weeks of age or older and weighing at least 3 kg.

Dosage and Administration

Pharmaceutical form:

Dispersible tablets.

Posology

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

TIVICAY is available as dispersible tablets for patients aged at least 4 weeks and weighing at least 3 kg, or for patients in whom film-coated tablets are not appropriate. *TIVICAY* is available as film-coated tablets for patients aged at least 6 years and weighing at least 14 kg. The bioavailability of dispersible tablets and film-coated tablets is not comparable therefore they must not be used as direct replacements (*see Pharmacokinetics*). For example, the recommended adult dose for dispersible tablets is 30 mg versus 50 mg for film-coated tablets. Patients changing between dispersible and film-coated tablets should follow the dosing recommendations that are specific for the formulation.

TIVICAY can be taken with or without food.

The 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 (*see Instructions for Use*). Do not chew, cut or crush the tablets.

Method of Administration

Adults

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

The recommended dose of dolutegravir dispersible tablets is 30 mg once daily.

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

The recommended dose of dolutegravir dispersible tablets is 30 mg twice daily. The decision to use dolutegravir for such patients should be informed by the integrase resistance pattern (*see Clinical studies*).

Adolescents, children and infants aged at least 4 weeks and weighing at least 3 kg

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

The recommended dose of dolutegravir dispersible tablets is determined according to weight and age and is presented in the table below.

Table 1 Dispersible tablet dose recommendations in adolescents, children and infants aged at least 4 weeks and weighing at least 3 kg

Body Weight (kg)	**Dose**
3 to less than 6	5 mg once daily (Taken as one 5 mg dispersible tablet)
6 to less than 10	
< 6 months	10 mg once daily (Taken as two 5 mg dispersible tablets)
≥ 6 months	15 mg once daily (Taken as three 5 mg dispersible tablets)
10 to less than 14	20 mg once daily (Taken as four 5 mg dispersible tablets)
14 to less than 20	25 mg once daily (Taken as five 5 mg dispersible tablets)
20 or greater	30 mg once daily (Taken as six 5 mg dispersible tablets)

If swallowing the dispersible tablets whole with water, do not swallow more than one tablet at a time to reduce the risk of choking. There are insufficient safety and efficacy data available to recommend a dose for dolutegravir dispersible tablets in children below age 4 weeks or weighing less than 3 kg.

Patients infected with HIV-1 with resistance to the integrase class

There are insufficient data to recommend a dose for dolutegravir dispersible tablets in integrase inhibitor resistant adolescents, children and infants.

Missed doses

If the patient misses a dose of *TIVICAY*, the patient should take *TIVICAY* as soon as possible, providing the next dose is not due within 4 hours. If the next dose is due within 4 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

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*).

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).

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

Warnings and Precautions

- **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.

- **Transmission of infection**

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

- **Drug 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).*

Factors that decrease *TIVICAY* exposure should be avoided in the presence of integrase class resistance. This includes co-administration with medicinal products that reduce *TIVICAY* exposure (e.g. magnesium/aluminum-containing antacids, iron and calcium supplements, multivitamins and inducing agents, tipranavir/ritonavir, efavirenz, rifampicin and certain anti-epileptic drugs) (*see Interactions*).

The recommended adult dose of *TIVICAY* should be given twice daily when co-administered with etravirine (without boosted protease inhibitors), efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin, carbamazepine, phenytoin, phenobarbital, and St. John's wort (*see Interactions*). In paediatric patients, the weight-based once daily dose should be administered twice daily.

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*).

- **Dual regimens**

Rilpivirine and dolutegravir

The dual regimen of rilpivirine and dolutegravir is only suitable for the treatment of HIV-1 infection to replace the current antiretroviral regimen in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of virological failure and where there is no known or suspected resistance to either ART component.

Lamivudine and dolutegravir

The dual regimen of lamivudine and dolutegravir is only suitable for the treatment of HIV-1 infection in adults and adolescents above 12 years of age and weighing at least 40 kg, where there is no known or suspected resistance to either ART component.

- **Osteonecrosis**

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

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.

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 2).

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 2).

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 the recommended dose 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 2). 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 2. 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 2 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% Cτ ↓ 88% ETR ↔	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended dose of *TIVICAY* should be given twice daily when co-administered with etravirine without boosted protease inhibitors. *TIVICAY* should not be used with etravirine without co-administration of darunavir/ritonavir or lopinavir/ritonavir in INI-resistant patients.
Protease Inhibitor: Lopinavir/ritonavir + Etravirine	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% Cτ ↑ 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% Cτ ↓ 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% Cτ ↓ 75% EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of *TIVICAY* should be given 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* should be given 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% Cτ ↑ 180% ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV/RTV)	Dolutegravir↑ AUC ↑ 62% C_{max} ↑ 34% 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* should be given 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% 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 ↓ 4% C_{max} ↔ Cτ ↓ 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% Cτ ↓ 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% Cτ ↓ 8% Tenofovir ↔ AUC ↑ 12 % C_{max} ↑ 9% Cτ ↑ 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%	Carbamazepine decreased dolutegravir plasma concentration.

	C_{max} ↓ 33% Cτ ↓ 73%	The recommended dose of *TIVICAY* should be given 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* should be given 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 *TIVICAY* 50 mg film-coated tablets QD: Metformin AUC ↑ 79% C_{max} ↑ 66% When co-administered with *TIVICAY* 50 mg film-coated tablets 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↓ AUC ↓ 54% C_{max} ↓ 43% Cτ ↓ 72%	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of *TIVICAY* should be given 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%	Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir did not change

	C_{max} ↑ 29% Cτ ↑ 45% Daclatasvir ↔	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

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 infants 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). It is recommended that mothers taking *TIVICAY* do not breast feed.

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. However, patients should be informed that dizziness has been reported during treatment with dolutegravir. 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

Adverse Reactions

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 3 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 data from the ongoing P1093 (ING112578) and ODYSSEY (201296) studies in 172 infants, children and adolescents (aged at least 4 weeks to less than 18 years, and weighing at least 3 kg) who received the recommended doses of either film-coated tablets or dispersible tablets once daily, 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 4 Post marketing adverse reactions

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

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

Overdose

Symptoms and signs

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

Limited experience of single higher doses (up to 250 mg film-coated tablets 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

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 IC_{50} 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 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.

Antiviral Activity in cell culture

The EC_{50} for dolutegravir in various labstrains using PBMC was 0.5 nM, and when using MT-4 cells it ranged from 0.7-2 nM. Similar EC_{50}s were seen for clinical isolates without any major difference between subtypes; in a panel of 24 HIV-1 isolates of clades A, B, C, D, E, F and G and group O, the mean EC_{50} value was 0.2 nM (range 0.02-2.14). The mean EC_{50} for 3 HIV-2 isolates was 0.18 nM (range 0.09-0.61).

Antiviral Activity in combination with other antiviral agents

No antagonistic effects *in vitro* were seen with dolutegravir and other antiretrovirals tested agents: stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide, maraviroc and raltegravir. In addition, no antagonistic effects were seen for dolutegravir and adefovir, and ribavirin had no apparent effect on dolutegravir activity.

Effect of Human Serum and Serum Proteins

In 100% human serum, the mean protein fold shift was 75-fold, resulting in protein adjusted EC_{90} of 0.064 µg/mL.

Resistance in vitro

Serial passage is used to study resistance evolution *in vitro*. When using the lab-strain HIVIII during passage over 112 days, mutations selected appeared slowly, with substitutions at positions S153Y and F, resulting in a maximal fold change in susceptibility of 4 (range 2-4). These mutations were not selected in patients treated with dolutegravir in the clinical studies. Using strain NL432, mutations E92Q (FC 3) and G193E (also FC 3) were selected. The E92Q mutation has been selected in patients with pre-existing raltegravir resistance who were then treated with dolutegravir (listed as a secondary mutation for dolutegravir).

In further selection experiments using clinical isolates of subtype B, mutation R263K was seen in all five isolates (after 20 weeks and onwards). In subtype C (n=2) and A/G (n=2) isolates the integrase substitution R263K was selected in one isolate, and G118R in two isolates. R263K was reported from two ART-experienced, INI-naïve individual patients with subtypes B and C in the clinical program, but without effects on dolutegravir susceptibility *in vitro*. G118R lowers the susceptibility to dolutegravir in site directed mutants (FC 10) but was not detected in patients receiving dolutegravir in the Phase III program.

Primary mutations for raltegravir/elvitegravir (Q148H/R/K, N155H, Y143R/H/C, E92Q and T66I) do not affect the *in vitro* susceptibility of dolutegravir as single mutations. When mutations listed as secondary integrase inhibitor associated mutations (for raltegravir/elvitegravir) are added to these primary mutations in experiments with site directed mutants, dolutegravir susceptibility is still unchanged (FC <2 vs wild type virus), except in the case of the Q148-mutation, where a FC of 5-10 or higher is seen with the combination of secondary mutations. The effect by the Q148-mutations (H/R/K) was also verified in passage experiments with site directed mutants. In serial passage with strain NL432, starting with site directed mutants harbouring N155H or E92Q, no further selection of resistance was seen (FC unchanged around 1). In contrast, starting with mutants harbouring mutation Q148H (FC 1), a variety of secondary mutations were seen with a consequent increase of FC to values >10.

A clinically relevant phenotypic cut-off value (FC vs wild type virus) has not been determined; genotypic resistance was a better predictor for outcome.

Seven hundred and five raltegravir resistant isolates from raltegravir-experienced patients were analyzed for susceptibility to dolutegravir. Dolutegravir has a less than or equal to 10 FC against 94% 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

In previously untreated patients receiving dolutegravir + 2 NRTIs in Phase IIb and Phase III, no development of resistance to the integrase class or to the NRTI class was seen (n=1118, follow-up of 48-96 weeks).

In patients with prior failed therapies, but naïve to the integrase class (SAILING study), integrase inhibitor substitutions were observed in 4/354 patients (follow-up 48 weeks) treated with dolutegravir, which was given in combination with an investigator selected background regimen (BR). Of these four, two subjects had a unique R263K integrase substitution, with a maximum FC of 1.93, one subject had a polymorphic V151V/I integrase substitution, with maximum FC of 0.92, and one subject had pre-existing integrase mutations and is assumed to have been integrase experienced or infected with integrase resistant virus by transmission. The R263K mutation was also selected *in vitro* (see above).

In the presence of integrase class-resistance (VIKING-3 study), the following mutations were selected in 32 patients with protocol defined virological failure (PDVF) through Week 24 and with paired genotypes (all treated with dolutegravir 50 mg twice daily + optimized background agents): 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). Treatment-emergent integrase resistance typically appeared in patients with a history of the Q148-mutation (baseline or historic). 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.

Resistance in vivo: virologically supressed subjects

SWORD-1 and SWORD-2 are identical studies that examined stable suppressed subjects receiving 2 NRTIs plus either an INI, an NNRTI, or a PI, that switched to dolutegravir plus rilpivirine (n=513) or remained on their current antiviral regimen (n=511). The number of subjects who met the protocol-defined confirmed virologic withdrawal (CVW) criteria was low across the pooled SWORD-1 and SWORD-2 studies. Two subjects from each treatment arm met CVW criteria at any time through Week 48. NNRTI resistance associated substitution K101K/E mixture with no decreased susceptibility to rilpivirine (FC = 1.2) was observed in one subject with identified adherence issues that received dolutegravir plus rilpivirine. No integrase resistance was observed. This patient's viral load was 1,059,771 copies/mL at the suspected virologic withdrawal visit, and on resumption of dolutegravir plus rilpivirine the viral load decreased to 1,018 copies/mL at the confirmatory visit and was <50 copies/mL at the withdrawal visit. No resistance associated substitutions were observed for the other three subjects meeting CVW criteria.

In the pooled analyses from Week 48 through Week 148, nine additional subjects receiving dolutegravir plus rilpivirine met CVW criteria at any time. Of the eight who had resistance testing results available, six (described below) had postbaseline results or resistance associated substitutions (NNRTI and/or INI).

- Subjects receiving dolutegravir plus rilpivirine from study start who met CVW criteria: At Week 88, one subject had the NNRTI-resistance-associated substitution mixture E138E/A with no decreased susceptibility to rilpivirine (FC = 1.6), and one subject had K103N with

rilpivirine FC = 5.2. Neither subject had INSTI resistance-associated substitutions or decreased susceptibility to dolutegravir. At Week 100, one subject with baseline NNRTI-resistance-associated substitutions K101E, E138A had M230M/L in addition to K101E and E138A with rilpivirine FC = 31. Integrase resistance testing failed at virologic failure. At Week 112, one subject had M230M/L mixture with rilpivirine FC = 2, and INSTI polymorphic substitutions E157Q, G193E, T97T/A at baseline and E157Q, G193E at virologic failure with no decreased susceptibility to dolutegravir (FC = 1.5).

- Subjects receiving dolutegravir plus rilpivirine from Week 52 who met CVW criteria: At Week 64, one subject had integrase substitutions N155H, G163G/R at baseline and only polymorphic integrase V151I/V mixture at virologic failure, and no NNRTI resistance. Integrase phenotype assay failed, and HIV-1 RNA was less than 50 copies per mL at withdrawal visit. At Week 136, one subject had NNRTI-resistance-associated substitutions E138A and L100L/I with rilpivirine FC = 4.1 and integrase resistance testing failed at virologic failure.

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 over 24 hours postdose.

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.

Pharmacokinetics

Dolutegravir pharmacokinetics are 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 C_{max} ranged from ~20 to 40% and $C\tau$ 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.

Film-coated tablets and dispersible tablets do not have the same bioavailability. The relative bioavailability of dispersible tablets is approximately 1.6-fold higher as compared to film-coated tablets Thus, a 30 mg *TIVICAY* dose administered as six 5 mg dispersible tablets will have similar exposure to a 50 mg *TIVICAY* dose administered as film-coated tablet(s). Similarly, a 25 mg *TIVICAY* dose administered as five 5 mg dispersible tablets, will provide comparable exposure to a 40 mg *TIVICAY* dose administered as four 10 mg film-coated tablets.

Absorption

Dolutegravir is rapidly absorbed following oral administration, with median T_{max} at 1 to 3 hours post dose for the dispersible tablet formulation. The linearity of dolutegravir pharmacokinetics is dependent of 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 17 L to 20 L in HIV-infected patients, based on a population pharmacokinetic analysis. Binding of dolutegravir to plasma proteins was independent of dolutegravir 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. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin (<35 g/L) as seen in subjects with moderate hepatic impairment.

Dolutegravir is present in cerebrospinal fluid (CSF). In 12 treatment-naïve subjects on a stable dolutegravir plus abacavir/lamivudine (3TC) regimen, the median dolutegravir concentration in CSF was 18 ng/mL (comparable to unbound plasma concentration, and above the IC_{50}).

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

The pharmacokinetics of *TIVICAY* film-coated and dispersible tablets in HIV-1 infected infants, children and adolescents aged ≥ 4 weeks to < 18 years were evaluated in two on-going studies (P1093/ING112578 and ODYSSEY/201296). Steady state plasma exposure at weight band doses are summarized in Table 5.

Table 5 Summary of *TIVICAY* PK Parameters following Administration of *TIVICAY* at Weight Band Doses in Paediatric HIV-1 Infected Subjects

Weight Band (kg)	TIVICAY Dosage Form[a]	Once Daily Dose (mg)	N	PK Parameter Geometric Mean (%CV)		
				Cmax (μg/mL)	AUC0-24h (μg*h/mL)	C24h (ng/mL)
3 to <6	DT	5	8	3.80 (34)	49.37 (49)	962 (98)
6 to <10[b]	DT	10	4	5.68 (38)	85.49 (32)	1821 (41)
6 to <10[c]	DT	15	17	5.27 (50)	57.17 (76)	706 (177)
10 to <14	DT	20	13	5.99 (33)	68.75 (48)	977 (100)
14 to <20	DT	25	19	5.97 (42)	58.97 (44)	725 (75)
≥20	DT[d]	30	9	7.16 (26)	71.53 (26)	759 (73)
	FCT	50	49	4.92 (40)	54.98 (43)	778 (62)
Target: Geometric Mean (range)					**46 (37-134)**	**995 (697-2260)**

DT=dispersible tablet
FCT=film-coated tablet
a. The bioavailability of *TIVICAY* DT is ~1.6-fold *TIVICAY* FCT.
b. <6 months of age
c. ≥6 months of age
d. ≥ 20 to <25 kg weight band

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 a single 50 mg dose of dolutegravir film-coated tablets 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 film-coated tablets 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).

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 IIb and Phase III 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.

Clinical Studies

Antiretroviral naïve subjects

The efficacy of dolutegravir in HIV-infected, therapy naive subjects is based on data from two randomized, international, double-blind, active-controlled trials, 96 week data from SPRING-2 (ING113086) and SINGLE (ING114467). This is supported by 96 week data from an open-label and active-controlled study FLAMINGO (ING114915) and additional data from the open-label phase of SINGLE to 144 weeks.

In SPRING-2, 822 adults were randomized and received at least one dose of either *TIVICAY* 50 mg film-coated tablets once daily or raltegravir 400 mg twice daily, both administered with fixed-dose dual NRTI therapy (either ABC/3TC or TDF/FTC). At baseline, median patient age was 36 years, 14% were female, 15% non-white, and 12% had hepatitis B and/or C co-infection and 2% were CDC Class C, these characteristics were similar between treatment groups.

In SINGLE, 833 subjects were randomized and received at least one dose of either *TIVICAY* 50 mg film-coated tablets once daily with fixed-dose abacavir-lamivudine (*TIVICAY* + ABC/3TC) or fixed-dose efavirenz-tenofovir-emtricitabine (EFV/TDF/FTC). At baseline, median patient age was 35 years, 16% were female, 32% non-white, 7% had hepatitis C co-infection and 4% were CDC Class C, these characteristics were similar between treatment groups.

The primary endpoint and other week 48 outcomes (including outcomes by key baseline covariates) for SPRING-2 and SINGLE are shown in Table 6.

Table 6 Virologic Outcomes of Randomized Treatment of SPRING-2 and SINGLE at 48 Weeks (Snapshot algorithm)

	SPRING-2		SINGLE	
	TIVICAY 50 mg Once Daily + 2 NRTI N=411	**RAL 400 mg Twice Daily + 2 NRTI N=411**	**TIVICAY 50 mg + ABC/3TC Once Daily N=414**	**EFV/TDF/FTC Once Daily N=419**
HIV-1 RNA < 50 copies/mL*	88%	85%	88%	81%
Treatment Difference*	2.5% (95% CI: -2.2%, 7.1%)		7.4% (95% CI: 2.5%, 12.3%)	
Virologic non response†	5%	8%	5%	6%
No virologic data at Week 48 window	7%	7%	7%	13%
Reasons				
Discontinued study/study drug due to adverse event or death‡	2%	1%	2%	10%
Discontinued study/study drug for other reasons§	5%	6%	5%	3%
Missing data during window but on study	0	0	0	<1%
HIV-1 RNA <50 copies/mL by baseline covariates				
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%)
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%)
NRTI backbone				
ABC/3TC	145 / 169 (86%)	142 / 164 (87%)	N/A	N/A
TDF/FTC	216 / 242 (89%)	209 / 247 (85%)	N/A	N/A
Gender				
Male	308 / 348 (89%)	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%)
African-America/African Heritage/Other	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 subjects who changed BR to new class or changed BR not permitted per protocol or due to lack of efficacy prior to Week 48 (for SPRING-2 only), subjects who discontinued prior to Week 48 for lack or loss of efficacy and subjects who are ≥50 copies in the 48 week window.
‡ Includes subjects who discontinued due to an adverse event or death at any time point from Day 1 through the Week 48 window if this resulted in no virologic data on treatment during the Week 48 window.
§ 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 subjects in each treatment group

In the SPRING-2 study through 96 weeks, virologic suppression (HIV-1 RNA <50 copies/mL) in the dolutegravir group (81%) was non-inferior to the raltegravir group (76%). The median change in CD4+ T cell count from baseline were 230 cells/mm^3 in the group receiving *TIVICAY* and the

raltegravir group at 48 weeks and 276 cells/mm^3 in the group receiving dolutegravir compared to 264 cells/mm^3 the raltegravir group at 96 weeks.

In the SINGLE study at Week 48, virologic suppression (HIV-1 RNA < 50 copies/mL) in the *TIVICAY* + ABC/3TC arm was 88%, which was superior to the EFV/TDF/FTC arm (81%) based on the primary analysis (p=0.003). At 96 weeks virologic suppression was maintained, the *TIVICAY* + ABC/3TC arm (80%) was superior to the EFV/TDF/FTC arm (72%), treatment difference was 8.0 (2.3, 13.8), p=0.006. The adjusted mean change in CD4+ T cell count from baseline were 267 cells/mm^3 in the group receiving *TIVICAY* + ABC/3TC and 208 cells/mm^3 for the EFV/TDF/FTC arm in SINGLE at 48 weeks. The adjusted difference and 95% CI was 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 adjusted for multiplicity. The median time to viral suppression was 28 days in the group receiving *TIVICAY* + ABC/3TC and 84 days in the EFV/TDF/FTC arm in SINGLE at 48 weeks (p<0.0001). This analysis was pre-specified and adjusted for multiplicity. At 144 weeks in the open-label phase, virologic suppression was maintained, the *TIVICAY* + ABC/3TC arm (71%) was superior to the EFV/TDF/FTC arm (63%), treatment difference was 8.3 (2.0, 14.6).

In both SPRING-2 and SINGLE studies virologic suppression (HIV-1 RNA < 50 copies/mL) treatment differences were comparable across baseline characteristics (gender, race and age).

Through 96 weeks in SINGLE and SPRING-2, no INI-resistant mutations or treatment emergent resistance in background therapy were isolated on the dolutegravir-containing arms. In SPRING-2, four subjects on the raltegravir arm failed with major NRTI mutations and one subject developed raltegravir resistance; in SINGLE, six subjects on the EFV/TDF/FTC arm failed with mutations associated with NNRTI resistance and one developed a major NRTI mutation.

In FLAMINGO (ING114915), an open-label and active-controlled study, 484 HIV-1 infected antiretroviral naïve adults were randomized and received one dose of either *TIVICAY* 50 mg film-coated tablets once daily or darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily, both administered with fixed-dose dual NRTI therapy (either ABC/3TC or TDF/FTC). At baseline, median patient age was 34 years, 15% were female, 28% non-white, 10% had hepatitis B and/or C co-infection, and 3% were CDC Class C; these characteristics were similar between treatment groups. Virologic suppression (HIV-1 RNA <50 copies/mL) in the *TIVICAY* group (90%) was superior to the DRV/r group (83%) at 48 weeks. The adjusted difference in proportion and 95% CI were 7.1% (0.9, 13.2), p=0.025. At 96 weeks virologic suppression in the *TIVICAY* group (80%) was superior to the DRV/r group (68%). No treatment-emergent primary INI, PI or NRTI resistance mutations were observed for subjects in the *TIVICAY* or DRV+RTV treatment groups.

Sustained virological response was demonstrated in the SPRING-1 study (ING112276), in which 88% of patients receiving a 50 mg dose of *TIVICAY* film-coated tablets (n=51) once daily had HIV-1 RNA <50 copies/mL, compared to 72% of patients in the efavirenz group (n=50) at 96 weeks. No INI-resistant mutations or treatment emergent resistance in background therapy were isolated with *TIVICAY* through 96 weeks.

Antiretroviral experienced (and integrase inhibitor naïve) subjects

In the international, multicentre, double-blind SAILING study (ING111762), 719 HIV-1 infected, ART-experienced adults were randomized and received either *TIVICAY* 50 mg film-coated tablets once daily or raltegravir 400 mg twice daily with investigator selected background regimen (BR) consisting of up to 2 agents (including at least one fully active agent). At baseline, median patient age was 43 years, 32% were female, 50% non-white, 16% had hepatitis B and/or C co-infection,

and 46% were CDC Class C. All subjects had at least two class ART resistance, and 49% of subjects had at least 3-class ART resistance at baseline.

Week 48 outcomes (including outcomes by key baseline covariates) for SAILING are shown in Table 7.

Table 7 Virologic Outcomes of Randomized Treatment of SAILING at 48 Weeks (Snapshot algorithm)

	TIVICAY 50 mg Once Daily + BR N=354§	RAL 400 mg Twice Daily + BR N=361§
HIV-1 RNA <50 copies/mL	71%	64%
Adjusted Treatment Difference‡	7.4% (95% CI: 0.7%, 14.2%)	
Virologic non response	20%	28%
No virologic data at Week 48	9%	9%
Reasons		
Discontinued study/study drug due to adverse event or death‡	3%	4%
Discontinued study/study drug for other reasons§	5%	4%
Missing data during window but on study	2%	1%
HIV-1 RNA <50 copies/mL by baseline covariates		
Baseline Plasma Viral Load (copies/mL)	n / N (%)	n / N (%)
≤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%)
DRV/r in BR		
No DRV/r use	143/214 (67%)	126/209 (60%)
DRV/r use with Primary PI mutations	58/68 (85%)	50/75 (67%)
DRV/r use without Primary PI mutations	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-America/African Heritage/Other	118 / 175 (67%)	105 / 185 (57%)
Age (years)		
<50	196 / 269 (73%)	172 / 277 (62%)
≥50	55 / 85 (65%)	58 / 84 (69%)
HIV sub type		
Clade B	173 / 241 (72%)	159 / 246 (65%)
Clade C	34 / 55 (62%)	29 / 48 (60%)
Other†	43 / 57 (75%)	42 / 67 (63%)

‡ Adjusted for baseline stratification factors
§ 4 subjects 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 ART with at least one fully active agent, however, n=11 PSS 0, n=2 PSS 3.
†Other clades included: Complex (43), F1 (32), A1 (18), BF (14), all others <10.
Notes: BR = background regimen, RAL = raltegravir; N = Number of subjects in each treatment group

In the SAILING study, virologic suppression (HIV-1 RNA <50 copies/mL) in the *TIVICAY* arm (71%) was statistically superior to the raltegravir arm (64%), at Week 48 (p=0.030). Virologic suppression (HIV-1 RNA <50 copies/mL) treatment differences were comparable across the baseline characteristics of gender, race, and HIV sub type. The mean changes in CD4+ T cell count from baseline were 113 cells/mm^3 at week 24 and 162 cells/mm^3 at week 48 in the group receiving *TIVICAY* and 106 cells/mm^3 at week 24 and 153 cells/mm^3 at week 48 for the raltegravir group.

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

Integrase inhibitor resistant subjects

In the multicentre, open-label, single arm VIKING-3 study (ING112574), HIV-1 infected, ART-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 but with optimised background ART from Day 8. The study enrolled 183 patients, 133 with INI-resistance at Screening and 50 with only historical evidence of resistance (and not at Screening).

Raltegravir/elvitegravir was part of the current failing regimen in 90/183 patients (part of prior failing therapies in the others). At baseline, median patient age was 48 years, 23% were female, 29% non-white, and 20% had hepatitis B and/or C co-infection. Median baseline CD4+ was 140 cells/mm^3, median duration of prior ART was 14 years, and 56% were CDC Class C. Subjects showed multiple class ART resistance at baseline: 79% had ≥2 NRTI, 75% ≥1 NNRTI, and 71% ≥2 PI major mutations; 62% had non-R5 virus.

Mean change from baseline in HIV RNA at day 8 (primary endpoint) was -1.4log$_{10}$ copies/mL (95% CI: -1.3, -1.5log$_{10}$, p<0.001). Response was associated with baseline INI mutation pathway, as shown in Table 8. Patients who stopped dolutegravir therapy for non-efficacy reasons, or who were protocol deviations for incorrect dolutegravir dosing or prohibited medication use are excluded in the analysis of the Virological Outcome (VO) population. The VO population is a subset of the ITT-E population.

Table 8 Virologic response (Day 8) after 7 days of functional monotherapy, in patients with RAL/EVG as part of current failing regimen, VIKING 3

Baseline parameters	**Dolutegravir 50 mg BID N=88**		
	n	Mean (SD) Plasma HIV-1 RNA log$_{10}$ c/mL	Median
Derived IN mutation group at Baseline with ongoing RAL/EVG			
No Q148[a]	48	-1.59 (0.47)	-1.64
Q148+1[b]	26	-1.14 (0.61)	-1.08
Q148+ ≥2[b]	14	-0.75 (0.84)	-0.45
[a] Included primary IN resistance mutations N155H, Y143C/H/R, T66A, E92Q. [b] Secondary mutations from G140A/C/S, E138A/K/T, L74I.			

In patients without a primary mutation detected at baseline (N=60) (i.e. RAL/EVG not part of current failing therapy) there was a 1.63 log$_{10}$ reduction in viral load at Day 8.

After the functional monotherapy phase, subjects had the opportunity to re-optimize their background regimen when possible. Based on 24-week data for all 183 patients, 126 (69%) had <50 copies/mL RNA at Week 24 (ITT-E, Snapshot algorithm). Corresponding response for the VO population was 75% (120/161).

The response was lower when the Q148-mutation was present at baseline, and in particular in the presence of ≥2 secondary mutations, Table 9. The overall susceptibility score (OSS) of the optimised background regimen (OBR) was not associated with Week 24 response.

Table 9 Response by baseline Resistance, VIKING-3 VO Population (HIV-1 RNA <50 c/mL, Snapshot algorithm)

	Week 24 (N=161)					**Week 48 (N=160)**
Derived IN Mutation Group	**OSS=0**	**OSS=1**	**OSS=2**	**OSS>2**	**Total**	**Total**
No primary IN mutation[1]	2/2 (100%)	15/20 (75%)	19/21 (90%)	9/12 (75%)	45/55 (82%)	38/55 (69%)
No Q148H/K/R mutations[2]	2/2 (100%)	20/20 (100%)	21/27 (78%)	8/10 (80%)	51/59 (86%)	50/58 (86%)
Q148 + 1 secondary mutation[3]	2/2 (100%)	8/12 (67%)	10/17 (59%)	-	20/31 (65%)	19/31 (61%)
Q148 + ≥2 secondary mutations[3]	1/2 (50%)	2/11 (18%)	1/3 (33%)	-	4/16 (25%)	4/16 (25%)

[1] Historical or phenotypic evidence of INI resistance only.
[2] N155H, Y143C/H/R, T66A, E92Q.
[3] G140A/C/S, E138A/K/T, L74I.
OSS: combined genotypic and phenotypic resistance (Monogram Biosciences Net Assessment).

The response rate at week 48 was sustained with 116/183 (63%) subjects having HIV-1 RNA <50 copies/mL (ITT-E, Snapshot algorithm). Background overall susceptibility score (OSS) was not associated with Week 48 response.

The median change in CD4+ T cell count from baseline for VIKING-3 based on observed data was 61 cells/mm^3 at Week 24 and 110 cells/mm^3 at Week 48.

In the double blind, placebo controlled VIKING-4 study (ING116529), 30 HIV-1 infected, ART-experienced adults with primary genotypic resistance to INIs at Screening, were randomized to receive either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days followed by an open label phase with all subjects receiving dolutegravir. At baseline, median patient age was 49 years, 20% were female, 58% non-white, and 23% had hepatitis B and/or C co-infection. Median baseline CD4+ was 160 cells/mm^3, median duration of prior ART was 13 years, and 63% were CDC Class C. Subjects showed multiple class ART resistance at baseline: 80% had ≥2 NRTI, 73% ≥1 NNRTI, and 67% ≥2 PI major mutations; 83% had non-R5 virus. Sixteen of 30 subjects (53%) harboured Q148 virus at baseline. The primary endpoint at Day 8 showed that dolutegravir 50 mg twice daily was superior to placebo, with an adjusted mean treatment difference for the change from Baseline in Plasma HIV-1 RNA of -1.2 $\log_{10}$ copies/mL (95% CI: -1.5, -0.8

log_{10} copies/mL, p<0.001). The Day 8 responses in this placebo-controlled study were consistent with those seen in VIKING-3, including by baseline integrase resistance categories. At week 48, 12/30 (40%) subjects had HIV-1 RNA <50 copies/mL (ITT-E, Snapshot algorithm).

In a combined analysis of VIKING-3 and VIKING-4 (n=186, VO population), the proportion of subjects with HIV RNA <50 copies/mL at Week 48 was 123/186 (66%). The proportion of subjects with HIV RNA <50 copies/mL was 96/126 (76%) for No Q148 mutations, 22/41 (54%) for Q148+1 and 5/19 (26%) for Q148+ ≥2 secondary mutations.

Antiretroviral Pregnancy Registry

The APR has received reports of over 600 exposures to *TIVICAY* during pregnancy resulting in live births, as of July 2019. These consist of over 370 exposures during the first trimester, over 230 exposures during the second/third trimester and included 12 and 9 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to dolutegravir in the first trimester was 3.2% (1.7%, 5.5%) and in the second/third trimester, 3.8% (1.7%, 7.0%).

The available data from the APR shows no significant increase in risk of major birth defects for dolutegravir compared to the background rates in the two population based surveillance systems (Metropolitan Atlanta Congenital Defects Program with defects of 2.72 per 100 live births and the Texas Birth Defects Registry with 4.17 per 100 live births).

Children

In an ongoing Phase I/II 48 week multicentre, open-label study (P1093/ING112578), the pharmacokinetic parameters, safety, tolerability and efficacy of *TIVICAY* were evaluated in combination regimens in HIV-1 infected infants, children and adolescents aged ≥ 4 weeks to < 18 years, the majority of whom were treatment-experienced.

The efficacy results (Table 10) include participants who received the recommended doses of either film-coated tablets or dispersible tablets.

Table 10 Antiviral and Immunological Activity Through Week 24 and Week 48 in Paediatric Patients

	Week 24 N=75		**Week 48 N=66**	
	n/N	**% (95% CI)**	**n/N**	**% (95% CI)**
Proportion of participants with HIV RNA <50 c/mL[a, b]	42/75	56 (44.1 – 67.5)	43/66	65.2 (52.4 – 76.5)
Proportion of participants with HIV RNA <400 c/mL[b]	62/75	82.7 (72.2 – 90.4)	53/66	80.3 (68.7 – 89.1)
	Median (n)	**(Q1, Q3)**	**Median (n)**	**(Q1, Q3)**
Change from baseline in CD4+ cell count (cells/mm^3)	145 (72)	(-64, 489)	184 (62)	(-179, 665)
Change from baseline in CD4+ percent	6 (72)	(2.5, 10)	8 (62)	(0.4, 11)

Q1, Q3= First and third quartiles, respectively.

[a] Results of <200 c/mL from HIV-1 RNA testing using an LLOD of 200 c/mL were censored to >50 c/mL in this analysis

[b] Snapshot algorithm was used in the analyses

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 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 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 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 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 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.

PHARMACEUTICAL INFORMATION

List of Excipients

Tablet Core:

Mannitol (E421)
Microcrystalline cellulose
Povidone (K29/32)
Sodium starch glycolate
Silicified microcrystalline cellulose
crospovidone
Sodium stearyl fumarate
Purified water
Calcium sulfate dihydrate
Sucralose

Strawberry cream flavour permaseal PHS-132963

Tablet coating:

Titanium dioxide (E171)
Hypromellose
Polyethylene glycol

Shelf Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging.

Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Do not remove desiccant.

Nature and Contents of Container

TIVICAY dispersible tablets are supplied in HDPE (high density polyethylene) bottles, with polypropylene (PP) child resistant closures. A desiccant is included in the bottle.

A dosing cup and syringe are supplied with the pack.

Incompatibilities

No incompatibilities have been identified.

Use and Handling

See the Instructions for Use section for complete instructions with illustrations.

Product Registrant

GlaxoSmithKline Pte. Ltd.

23 Rochester Park, Singapore 139234

Version number: GDS20/IPI04(SI)

Date of issue: 15 October 2021

[ViiV Healthcare logo]

Step-by-step instructions

Read this Instructions for use before giving a dose of medicine.
Follow the steps, using clean drinking water to prepare and give a dose to an infant or a child who cannot swallow the tablets.

Important information

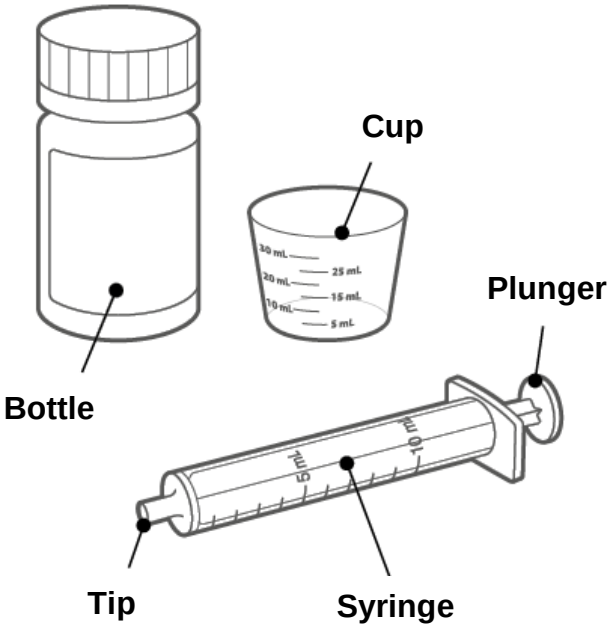
Always give this medicine exactly as your healthcare provider tells you. Talk to your healthcare provider if you are not sure.

Do not chew, cut, or crush the tablets.

If you forget to give a dose of medicine, give 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 give 2 doses at the same time or give more than your healthcare provider has prescribed.

If you give too much medicine, get emergency medical help right away.

If your child is able and prefers to swallow the tablets then you may skip the following steps.



Your pack contains:

- A bottle containing 60 tablets.
- Dosing kit:
    - **Cup:** use this to prepare and give the medicine to **children.**
    - **Syringe**: use this to give the medicine to **infants.**

You will also need:

- Clean drinking water.

Getting ready

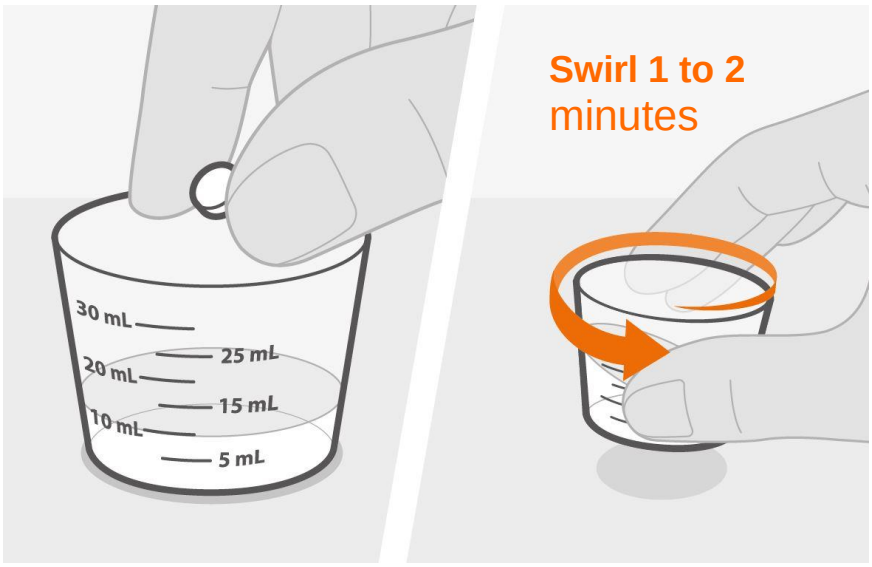
1. Pour water

Water Volume Guide						
Number of tablets	1	2	3	4	5	6
Volume of water	5 mL			10 mL		

- Pour clean drinking water into the cup.
  The Water Volume Guide above shows the amount of water needed for the prescribed dose.

Use drinking water only.
Do not use any other drink or food to prepare the dose.

2. Prepare the medicine



- Add the prescribed number of tablet(s) to the water.
- Swirl the cup gently for 1 to 2 minutes to disperse the tablet(s). The medicine will become cloudy. Take care not to spill any of the medicine.
- Check that the medicine is ready. If there are any lumps of tablet swirl the cup until they are gone.

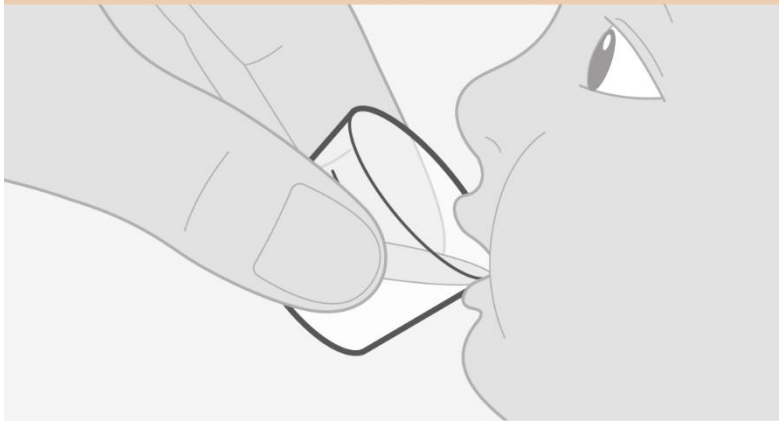
If you spill any medicine, clean up the spill.
Throw away the rest of the prepared medicine and make a new dose.

You must give the dose of medicine within 30 minutes of preparing the dose. If it has been more than 30 minutes wash the dose away and prepare a new dose of medicine.

Giving the medicine

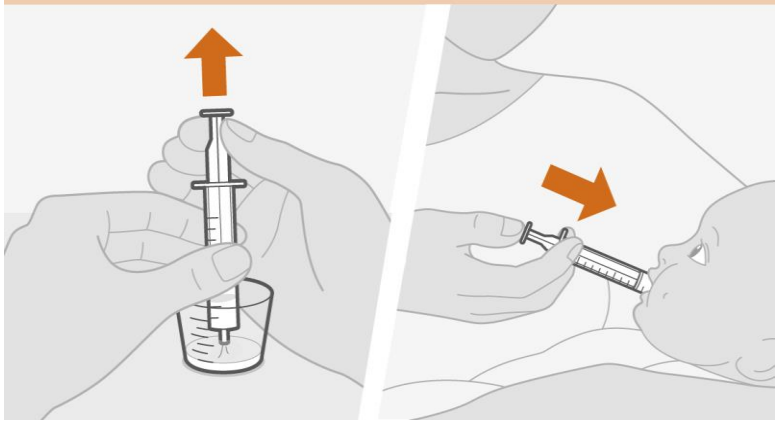
3. Give the medicine

Give the medicine to a Child



- Make sure that the child is upright. Give all the prepared medicine to the child.
- Add another 5 mL of drinking water to the cup, swirl and give it all to the child.
- Repeat if any medicine remains to make sure the child gets the full dose.

Give the medicine to an Infant

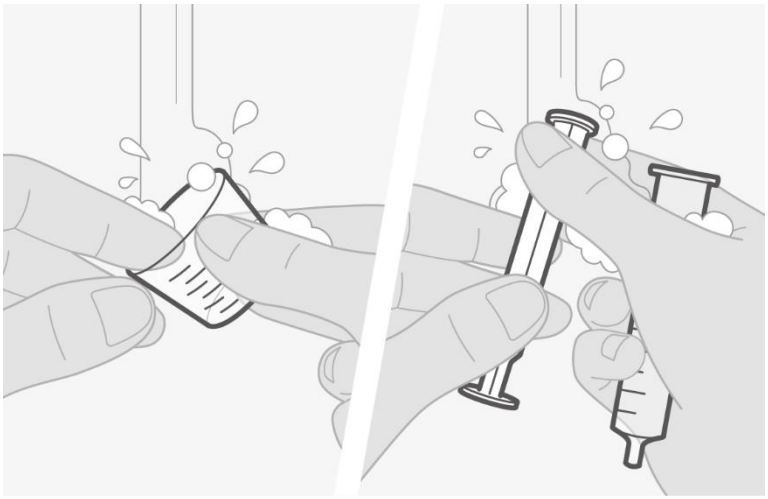


- Place the tip of the syringe into the prepared medicine and draw up all the medicine into the syringe by pulling up on the plunger.
- Place the tip of the syringe against the inside of the infant's cheek. Gently push down the plunger to give the dose slowly.
- Add another 5 mL of drinking water to the cup and swirl. Draw up the remaining medicine into the syringe and give it all to the infant.
- Repeat if any medicine remains to make sure the infant gets the full dose.

Allow time for the medicine to be swallowed.

Cleaning

4. Clean the dosing items



- Wash the cup with water.
- Pull the plunger out of the syringe and wash the syringe parts separately in water. Allow parts to dry completely before reassembling and storing.
- All used parts will need to be clean before preparing the next dose.

Storage information

Keep the tablets in the bottle. Keep the bottle tightly closed.

The bottle contains a desiccant canister which helps to keep the tablets dry. **Do not** eat the desiccant. **Do not** remove the desiccant.

Keep all medicines out of reach of children.

Disposal information

When all the tablets in the bottle have been taken or are no longer needed, throw away the bottle, cup and syringe. Dispose of them using your local household waste guidelines.

You will get a new cup and syringe in your next pack.