TIVICAY

Dolutegravir

QUALITATIVE AND QUANTITATIVE COMPOSITION

10 mg - White, round, biconvex tablets debossed with 'SV 572' on one side and '10' on the other side.

25 mg - Pale yellow, round, biconvex tablets debossed with 'SV 572' on one side and '25' on the other side.

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

Each tablet contains 10 mg, 25 mg, or 50 mg of dolutegravir (as dolutegravir sodium).

CLINICAL INFORMATION

Indications

TIVICAY is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and children aged 6 years and older and weighing at least 15 kg (see *Warnings and Precautions – Dual regimens*).

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

- Poor virologic response was observed in subjects treated with *TIVICAY* 50 mg twice daily with an integrase strand transfer inhibitor (INI)-resistance Q148H/K/R substitution plus 2 or more additional INI-resistance substitutions, including, but not limited to L74I, E138A/K/T and G140A/C/S.

Dosage and Administration

Pharmaceutical form:

Film-coated tablets.

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 documented or clinically suspected resistance to the integrase class

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

TIVICAY should be administered twice daily in this population when co-administered with some medicines (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin) (see *Interactions*).

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*).

Co-administration of *TIVICAY* with some medicines should be avoided in this population (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin) (see *Warnings and Precautions* and *Interactions*).

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.

TIVICAY should be administered twice daily in this population when co-administered with some medicines (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin) (see *Interactions*).

There are insufficient data to recommend a dose for *TIVICAY* in integrase inhibitor resistant adolescents under 18 years of age.

Children

In patients infected with HIV-1 who have not previously been treated with an integrase inhibitor, the recommended dose of *TIVICAY* in children (6 to less than 12 years of age) is determined according to the weight of the child. Dose recommendations according to weight are presented in the table below.

The weight-based once daily dose of *TIVICAY* should be administered twice daily in this population when co-administered with some medicines (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin) (see *Interactions*).

Table 1 Paediatric Dose recommendations

Body Weight (kg)	Dose
15 to less than 20	20 mg once daily (Taken as two 10 mg tablets)
20 to less than 30	25 mg once daily
30 to less than 40	35 mg once daily (Taken as one 25 mg and one 10 mg tablet)
40 or greater	50 mg once daily

There are insufficient safety and efficacy data available to recommend a dose for *TIVICAY* in children below age 6 or weighing less than 15 kg.

There are insufficient data to recommend a dose for *TIVICAY* in integrase inhibitor resistant children.

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; see *Interactions*).

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 *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 raised liver enzymes, 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.

TIVICAY should not be used in patients who have experienced a previous hypersensitivity reaction to *TIVICAY*.

• Immune Reconstitution Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jirovecii (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 should be advised that *TIVICAY* or any other antiretroviral therapy does not cure HIV infection and that they 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.

• 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/aluminium-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* 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*). 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 co-administration 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 (IC_{50} >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, MATE2-K, MRP2 or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. *In vivo*, dolutegravir does not seem to have an effect on midazolam, a CYP3A4 probe, however a weak inhibition can presently not be excluded. 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) (IC_{50} = 1.93 μM), multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 μM) and MATE2-K (IC_{50} = 24.8 μM). Based on the *in vitro* data, dolutegravir has a low potential to affect the transport of MATE2-K substrates *in vivo*. *In vivo*, a 10-14% increase of mean serum creatinine (secretory fraction is dependent on OCT2 and MATE-1 transport) was observed in patients but did not progress over time and is not associated with a change in renal glomerular filtration rate. *In vivo*, dolutegravir may increase plasma concentrations of drugs in which excretion is dependent upon OCT2 or MATE-1 (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 (OAT1) (IC_{50} = 2.12 μM) and OAT3 (IC_{50} = 1.97 μM). Based upon the dolutegravir unbound plasma concentration, in silico modelling, and no notable effect on the PK *in vivo* of OAT substrates tenofovir and para-aminohippurate, dolutegravir thus has low propensity to cause drug interactions via inhibition of OAT transporters.

Effect of Other Agents on the Pharmacokinetics of Dolutegravir

All factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance.

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 decrease dolutegravir plasma concentration and reduce the therapeutic effect of *TIVICAY* (see Table 1).

Co-administration of *TIVICAY* and other drugs that inhibit these enzymes 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 transporters are not expected to affect dolutegravir plasma concentration.

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 ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended adult dose of *TIVICAY* is 50 mg twice daily when co-administered with etravirine without boosted protease inhibitors. In paediatric patients, the weight-based once daily dose should be administered twice daily. *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% 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 ↔ (historical	Efavirenz decreased dolutegravir plasma concentrations. The recommended adult dose of *TIVICAY* is 50 mg twice daily when co-administered with efavirenz. In paediatric patients, the weight-based once daily dose should be

	controls) (induction of UGT1A1 and CYP3A enzymes)	administered twice daily. 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 adult dose of *TIVICAY* is 50 mg twice daily when co-administered with nevirapine. In paediatric patients, the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include nevirapine should be used where possible in INI-resistant patients.
Non-nucleoside Reverse Transcriptase Inhibitor: Rilpivirine	Dolutegravir ↔ AUC ↑ 12% C_{max} ↑ 13% Cτ ↑ 22% Rilpivirine ↔	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.
Protease Inhibitor (PI):	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50%	Atazanavir increased dolutegravir plasma concentration. No dose

Atazanavir (ATV)	Cτ ↑ 180% ATV ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV/RTV)	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 34% Cτ ↑ 121% (inhibition of UGT1A1 and CYP3A enzymes)	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% (induction of UGT1A1 and CYP3A enzymes)	Tipranavir/ritonavir decreased dolutegravir concentrations. The recommended adult dose of *TIVICAY* is 50 mg twice daily when co-administered with tipranavir/ritonavir. In paediatric patients, the weight-based once daily dose should be administered twice daily. 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% (induction of UGT1A1 and CYP3A enzymes)	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)	Dolutegravir ↔ AUC ↓ 4% C_{max} ↔ 0%	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

	Cτ ↓ 6% LPV ↔ RTV ↔	
Protease Inhibitor: Darunavir/ritonavir	Dolutegravir ↓ AUC ↓ 22% C_{max} ↓ 11% Cτ ↓ 38% (induction of UGT1A1 and CYP3A enzymes)	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Telaprevir	Dolutegravir ↑ AUC ↑ 25% C_{max} ↑ 19% Cτ ↑ 37% Telaprevir ↔ (historical controls) (inhibition of CYP3A enzyme)	No dose adjustment is necessary.
Protease Inhibitor: Boceprevir	Dolutegravir ↔ AUC ↑ 7% C_{max} ↑ 5% Cτ ↑ 8%	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% Cτ ↓ 73%	Carbamazepine decreased dolutegravir plasma concentration. The recommended adult dose of *TIVICAY* is 50 mg twice daily when co-administered with carbamazepine. In paediatric patients, the weight-based once daily dose should be administered twice daily. Alternatives to carbamazepine should be used where possible for INI-resistant patients.
Oxcarbazepine 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 adult dose of *TIVICAY* is 50 mg twice daily when co-administered with these metabolic inducers. In paediatric patients, the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include these metabolic inducers should be used where possible in INI-resistant patients.
Antacids containing polyvalent cations (e.g. Mg, Al)	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% C_{24} ↓ 74% (Complex binding to polyvalent ions)	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%	*TIVICAY* is recommended to be administered 2 hours before or 6 hours after taking products

	C_{24} ↓ 39%	containing calcium.
Iron supplements	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% C_{24} ↓ 56%	*TIVICAY* is recommended to be administered 2 hours before or 6 hours after taking products containing iron.
Multivitamins	Dolutegravir ↓ AUC ↓ 33% C_{max} ↓ 35% C_{24} ↓ 32% (Complex binding to polyvalent ions)	*TIVICAY* is recommended to be administered 2 hours before or 6 hours after taking products containing multivitamins.
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 co-administration of dolutegravir with metformin, to maintain glycaemic control.
Rifampicin	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 43% Cτ ↓ 72% (induction of UGT1A1 and CYP3A enzymes)	Rifampicin decreased dolutegravir plasma concentration. The recommended adult dose of *TIVICAY* is 50 mg twice daily when co-administered with rifampicin. In paediatric patients, the weight-based once daily dose should be administered twice daily. Alternatives to rifampicin should be used where possible in INI-resistant patients.
Oral contraceptives (Ethinyl estradiol	Effect of dolutegravir: EE ↔ AUC ↑ 3%	Dolutegravir did not change ethinyl estradiol and norelgestromin plasma concentrations to a clinically relevant

(EE) and Norelgestromin (NGMN))	C_{max} ↓ 1% Cτ ↑ 2% Effect of dolutegravir: NGMN ↔ AUC ↓ 2% C_{max} ↓ 11% Cτ ↓ 7%	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; C_{max} = maximum observed concentration; Cτ = concentration at the end of dosing interval

Paediatric population

Interaction studies have only been performed in adults.

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.

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

Summary of the safety profile
The safety profile is based on pooled data from Phase IIb and Phase III clinical studies in 980 previously untreated patients, 357 previously treated patients unexposed to integrase inhibitors and 234 patients with prior treatment failure that included an integrase inhibitor (including integrase class resistance). The most severe adverse reaction, seen in an individual patient, was a hypersensitivity reaction that included rash and severe liver effects (see *Warnings and Precautions*). The most commonly seen treatment-emergent adverse reactions were nausea (15%), diarrhoea (16%) and headache (14%).

The safety profile was similar across the different treatment populations mentioned above.

Tabulated list of adverse reactions
The adverse reactions considered at least possibly related to dolutegravir are listed by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

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
Investigations	Common	Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations
	Common	Creatine phosphokinase (CPK) elevations

** see below under Description of selected adverse reactions.

Description of selected adverse reactions

Changes in laboratory biochemistries
Increases in serum creatinine occurred within the first week of treatment with *TIVICAY* and remained stable through 48 weeks. A mean change from baseline of 9.96 µmol/L was observed after 48 weeks of treatment. Creatinine increases were comparable by various background regimens. 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.

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*).

Immune response syndrome
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see *Warnings and Precautions*).

Paediatric population
Based on limited available data in adolescents (12 to less than 18 years of age and weighing at least 40 kg), there were no additional types of adverse reactions beyond those observed in the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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

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 S153F, 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=0.8) 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 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 C_{max} ranged from ~20 to 40% and $C\tau$ from 30 to 65% across studies. The between-subject PK variability of dolutegravir was higher in HIV-infected subjects than 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 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.

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 through glucuronidation 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 dolutegravir (18.9% of total dose), N-dealkylation metabolite (3.6% of total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose).

Elimination

Dolutegravir has a terminal half-life of ~14 hours. The apparent oral clearance (CL/F) is approximately 1 L/hr in HIV-infected patients based on a population pharmacokinetic analysis.

Special patient populations

Children

The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents 12 to 18 years of age showed that a *TIVICAY* dose of 50 mg once daily resulted in dolutegravir exposure in paediatric subjects comparable to that observed in adults who received *TIVICAY* 50 mg once daily (Table 5).

The pharmacokinetics was evaluated in 11 children 6 to 12 years of age and showed that 25 mg once daily in patients weighing at least 20 kg and 35 mg once daily in patients weighing at least 30 kg resulted in dolutegravir exposure comparable to adults. The recommended dose is 50 mg once daily in patients weighing at least 40 kg (Table 5).

Table 5 Paediatric pharmacokinetic parameters

Age	*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 n=10 [a]	50 mg once daily [a]	46 (43)	3.49 (38)	0.90 (59)
≥6 to <12 years n=11	~1 mg/kg once daily [b]	50 (64)	3.96 (50)	0.93 (89)

[a]One subject weighing 37 kg received 35 mg once daily. [b]Four subjects received 25 mg once daily, 2 subjects received 35 mg once daily, and 5 subjects received 50 mg once daily.

In addition, population PK modelling and simulation analysis showed dosing of *TIVICAY* tablets on a weight-band basis (20 mg, 25 mg, 35 mg, 50 mg) in children of at least 6 years of age weighing at least 15 kg provides comparable exposure to that observed in adults (50 mg), with the lowest weight band of 15 to <20 kg corresponding to 20 mg 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) and matched healthy controls. The exposure to dolutegravir was decreased by approximately 40% in subjects with severe renal impairment. The mechanism for the decrease is unknown. 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).

Gender

Population PK analyses using pooled pharmacokinetic data from Phase IIb and Phase III 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 naïve 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. The efficacy of dolutegravir in combination with lamivudine in adults is supported by 144-week data from two identical 148-week, randomised, multicentre, double-blind, non-inferiority studies GEMINI-1 (204861) and GEMINI-2 (205543).

In SPRING-2, 822 adults were randomized and received at least one dose of either *TIVICAY* 50 mg 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 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/mm³)				
<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-American/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 in 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). 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 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, with a median change in CD4+ count of 325 vs 281 cells/mm^3, respectively. 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 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 *TIVICAY* 50 mg (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. In patients treated with *TIVICAY* 50 mg once daily, *de novo* resistance to the integrase class, or the NRTI background agents were not detected during 96 weeks of follow-up.

In GEMINI-1 (204861) and GEMINI-2 (205543), identical 148-week, randomised, double-blind, multicentre, non-inferiority studies, 1433 adult HIV-1 infected antiretroviral naïve subjects were randomised and received a two-drug regimen dolutegravir 50 mg plus lamivudine 300 mg once daily or dolutegravir 50 mg once daily with fixed dose TDF/FTC. Subjects were enrolled with a screening plasma HIV-1 RNA of 1000 c/mL to ≤500,000 c/mL. At baseline, in the pooled analysis of all patients, median patient age was 33 years, 15% were female, 31% non-white, 6% had hepatitis C co-infection and 9% were CDC Stage 3; these characteristics were similar between treatment groups.

Virologic suppression (HIV-1 RNA <50 copies/mL) in the dolutegravir plus lamivudine group (91% [pooled data]) was non-inferior to the dolutegravir plus TDF/FTC group (93% [pooled data]) at 48 weeks. The adjusted difference in proportion and 95% CI were -1.7% (-4.4, 1.1). The results of the pooled analysis were in line with those of the individual studies, for which the primary endpoint (difference in proportion <50 copies/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm for dolutegravir plus lamivudine versus dolutegravir plus TDF/FTC FDC) was met. The adjusted difference was -2.6% (95% CI: -6.7, 1.5) for GEMINI-1 and -0.7% (95% CI: -4.3, 2.9) for GEMINI-2 with a prespecified non-inferiority margin of 10%.

Table 7 Response (<50 cps/ml, snapshot) in GEMINI-1, GEMINI-2, and pooled data.

	GEMINI-1		GEMINI-2		POOLED	
	DTG + 3TC (N=356) n/N (%)	DTG + TDF/FTC (N=358) n/N (%)	DTG + 3TC (N=360) n/N (%)	DTG + TDF/FTC (N=359) n/N (%)	DTG + 3TC (N=716) n/N (%)	DTG + TDF/FTC (N=717) n/N (%)
All patients	320/356 (90)	332/358 (93)	335/360 (93)	337/359 (94)	655/716 (91)	669/717 (93)
	adjusted diff -2.6 (CI95 -6.7,1.5)[a]		adjusted diff -0.7 (CI95 -4.3, 2.9)[a]		adjusted diff -1.7% (CI95 -4.4,1.1)[a]	
By BL HIV-1 RNA						
≤100,000 cps/mL	255/282 (90)	263/282 (93)	271/294 (92)	268/282 (95)	526/576 (91)	531/564 (94)
>100,000 cps/mL	65/74 (88)	69/76 (91)	64/66 (97)	69/77 (90)	129/140 (92)	138/153 (90)
By CD4+						
≤200 c/mm^3	25/31 (81)	26/29 (90)	25/32 (78)	25/26 (96)	50/63 (79)	51/55 (93)
>200 c/mm^3	295/325 (91)	306/329 (93)	310/328 (95)	312/333 (94)	605/653 (93)	618/662 (93)
Rebound up to week 48 [b]	4 (1)	2 (<1)	2 (<1)	2 (<1)	6 (<1)	4 (<1)

Mean change in CD4+ count from baseline at Week 48, c/mm^3 [c]	222	218	226	217	224	217

[a] Adjusted for BL stratification factors: Plasma HIV-1 RNA (≤100,000 c/mL vs. >100,000 c/mL) and CD4+ cell count (≤200 cells/mm^3 vs. >200 cells/mm^3). The pooled analysis was also stratified by study. [b] Confirmed plasma HIV-1 RNA levels to ≥200 cps/mL after prior confirmed suppression to <200 cps/mL. [c] Adjusted mean is the estimated mean change from baseline at Week 48 in each arm calculated from ANCOVA model (and multiple imputed dataset) adjusting for the following covariates/factors: treatment, baseline plasma HIV-1 RNA (factor) and baseline CD4+ cell count. Pooled analysis also included study as a factor.

At 96 weeks the dolutegravir plus lamivudine group (86% with plasma HIV-1 RNA < 50 copies/mL [pooled data]) remained non-inferior to the dolutegravir plus tenofovir/emtricitabine FDC group (90% with plasma HIV-1 RNA < 50 copies/mL [pooled data]). The adjusted difference in proportions and 95% CI was -3.4% (-6.7, 0.0). The results of the pooled analysis were in line with those of the individual studies, for which the secondary endpoint (difference in proportion <50 copies/mL plasma HIV-1 RNA at Week 96 based on the Snapshot algorithm for dolutegravir plus lamivudine versus dolutegravir plus tenofovir/emtricitabine FDC) was met. The adjusted differences of -4.9 (95% CI: -9.8, 0.0) for GEMINI-1 and -1.8 (95% CI: -6.4, 2.7) for GEMINI-2 were within the prespecified non-inferiority margin of -10%. The mean increase in CD4+ T-cell counts was 269 cells/mm^3 in the DTG+3TC arm and 259 cells/mm^3 in the DTG+FTC/TDF arm, at week 96. Through 96 weeks in the GEMINI-1 and GEMINI-2 studies, no cases of emergent resistance to the integrase- or NRTI-class were seen in either the DTG+3TC or comparator DTG+ TDF/FTC arms.

At 144 weeks in the GEMINI-1 and GEMINI-2 studies, the dolutegravir plus lamivudine group (82% with plasma HIV-1 RNA < 50 copies/mL [pooled data]) remained non-inferior to the dolutegravir plus tenofovir/emtricitabine FDC group (84% with plasma HIV-1 RNA < 50 copies/mL [pooled data]). The results of the pooled analysis were in line with those of the individual studies, for which the secondary endpoint (difference in proportion <50 copies/mL plasma HIV-1 RNA at Week 144 based on the Snapshot algorithm for dolutegravir plus lamivudine versus dolutegravir plus tenofovir/emtricitabine FDC) was met. The adjusted difference in proportions and 95% CI was -1.8% (-5.8, 2.1). The adjusted differences of -3.6 (95% CI: -9.4, 2.1) for GEMINI-1 and 0.0 (95% CI: -5.3, 5.3) for GEMINI-2 were within the prespecified non-inferiority margin of -10%. The mean increase in CD4+ T-cell counts was 302 cells/mm^3 in the DTG+3TC arm and 300 cells/mm^3 in the DTG+FTC/TDF arm, at Week 144. Through 144 weeks in the GEMINI-1 and GEMINI-2 studies, no subjects that met the protocol-defined confirmed virologic withdrawal criteria (CVW) had emergent integrase- or NRTI-class resistance substitutions.

There are no data available on the use of dolutegravir plus lamivudine as a two-drug regimen in paediatric patients.

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 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 8.

Table 8 Virologic Outcomes of Randomized Treatment of SAILING at 48 Weeks (Snapshot algorithm)

	SAILING	
	***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-American/African Heritage/Other	118 / 175 (67%)	105 / 185 (57%)
Age (years)		
<50	196 / 269 (73%)	172 / 277 (62%)
≥50	55 / 85 (65%)	58 / 84 (69%)
HIV sub type		
Clade B	173 / 241 (72%)	159 / 246 (65%)
Clade C	34 / 55 (62%)	29 / 48 (60%)
Other†	43 / 57 (75%)	42 / 67 (63%)

‡ Adjusted for 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. At Week 48, the mean changes in CD4+ T cell count from baseline were 162 cells/mm^3 in the group receiving *TIVICAY* and 153 cells/mm^3 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 9. 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 9 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 10. The overall susceptibility score (OSS) of the optimised background regimen (OBR) was not associated with Week 24 response.

Table 10 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 randomised 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).

Virologically suppressed subjects

The efficacy of dolutegravir plus rilpivirine is supported by data from 2 randomised, open-label, controlled trials (SWORD-1 [201636] and SWORD-2 [201637]) in virologically suppressed patients switching from their current antiretroviral regimen (CAR).

SWORD-1 and SWORD-2 are identical 148-week, Phase III, randomised, multicenter, parallel-group, non-inferiority studies. A total of 1,024 adult HIV-1 infected subjects who were on a stable suppressive antiretroviral regimen (containing 2 NRTIs plus either an INI, an NNRTI, or a PI) received treatment in the studies. Subjects were randomised 1:1 to continue their CAR or be switched to a two-drug regimen dolutegravir plus rilpivirine administered once daily. At Week 52, subjects who were originally assigned to continue their CAR and remained virologically suppressed switched to dolutegravir plus

rilpivirine. The primary efficacy endpoint for the SWORD studies was the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 (Snapshot algorithm for the ITT-E population).

At baseline, in the pooled analysis, the median age of subjects was 43 years, 22% female, 20% non-white, 11% were CDC Class C (AIDS), and 11% had CD4+ cell count less than 350 cells/mm^3; these characteristics were similar between treatment arms. In the pooled analysis, 54%, 26%, and 20% of subjects were receiving an NNRTI, PI, or INI (respectively) as their baseline third treatment agent class prior to randomisation and was similar between treatment arms.

The pooled primary analysis demonstrated that dolutegravir plus rilpivirine is non-inferior to CAR, with 95% of subjects in both arms achieving the primary endpoint of <50 copies/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm (Table 11).

The primary endpoint and other outcomes (including outcomes by key baseline covariates) for the pooled SWORD-1 and SWORD-2 studies are shown in Table 11.

Table 11 Virologic Outcomes of Randomised Treatment for Virologically suppressed subjects at Week 48 (Snapshot algorithm)

	SWORD-1 and SWORD-2 Pooled Data	
	DTG + RPV N=513	**CAR N=511**
HIV-1 RNA <50 copies/mL	95%	95%
Treatment Difference*	-0.2 (-3.0, 2.5)	
Virologic non response†	<1%	1%
Reasons		
Data in window not <50 copies/mL	0	<1%
Discontinued for lack of efficacy	<1%	<1%
Discontinued for other reasons while not <50 copies/mL	<1%	<1%
Change in ART	0	<1%
No virologic data at Week 48 window	5%	4%
Reasons		

Discontinued study/study drug due to adverse event or death	3%	<1%
Discontinued study/study drug for other reasons	1%	3%
Missing data during window but on study	0	<1%
HIV-1 RNA <50 copies/mL by baseline covariates		
	n/N (%)	n/N (%)
Baseline CD4+ (cells/mm^3)		
<350	51 / 58 (88%)	46 / 52 (88%)
≥350	435 / 455 (96%)	439 / 459 (96%)
Baseline Third Treatment Agent Class		
INSTI	99 / 105 (94%)	92 / 97 (95%)
NNRTI	263 / 275 (96%)	265 / 278 (95%)
PI	124 / 133 (93%)	128 / 136 (94%)
Gender		
Male	375 / 393 (95%)	387 / 403 (96%)
Female	111 / 120 (93%)	98 / 108 (91%)
Race		
White	395 / 421 (94%)	380 / 400 (95%)
African-American/African Heritage/Other	91/92 (99%)	105 / 111 (95%)
Age (years)		
<50	350 / 366 (96%)	348 / 369 (94%)
≥50	136 / 147 (93%)	137 / 142 (96%)

* Adjusted for baseline stratification factors and assessed using a non-inferiority margin of -8%.

† Non-inferiority of DTG + RPV to CAR in the proportion of subjects classified as virologic non-responders was demonstrated using a non-inferiority margin of 4%. Adjusted difference (95% CI) -0.6 (-1.7, 0.6).

N = Number of subjects in each treatment group

INSTI = Integrase inhibitor; NNRTI = Non-nucleoside reverse transcriptase inhibitor; PI = Protease Inhibitor

DTG+RPV = dolutegravir plus rilpivirine

CAR = current antiretroviral regimen

At Week 148 in the pooled SWORD-1 and SWORD-2 trials, 84% of subjects who received dolutegravir plus rilpivirine as of study start had plasma HIV-1 RNA < 50 copies/mL based on the Snapshot algorithm. In subjects who initially remained on their CAR and switched to dolutegravir plus rilpivirine at Week 52, 90% had plasma HIV-1 RNA < 50 copies/mL at Week 148 based on the Snapshot algorithm, which was comparable to the response rate (89%) observed at Week 100 (similar exposure duration) in subjects receiving dolutegravir plus rilpivirine as of study start.

There are no clinical study data with dolutegravir plus rilpivirine in the paediatric population.

Children

P1093/ING112578 is a Phase I/II 48 week multicentre, open-label study to evaluate the pharmacokinetic parameters, safety, tolerability and efficacy of *TIVICAY* in combination regimens in HIV-1 infected infants, children and adolescents.

The initial dose-finding stage included intensive pharmacokinetic evaluation in 10 ART treatment-experienced, integrase inhibitor-naïve patients (aged 12 to 18 years with 9 patients weighing ≥40 kg). Dose selection was based upon achieving similar dolutegravir plasma exposure and trough concentration as seen in adults. After dose selection, an additional 13 patients were enrolled for evaluation of long-term safety, tolerability and efficacy.

At 48 weeks, 14 of 23 (61%) adolescents (12 to less than 18 years of age) treated with *TIVICAY* once daily (35 mg n=4, 50 mg n=19) plus OBR achieved viral load less than 50 copies/mL.

At 24 weeks, 14 of 23 (61%) children (6 to less than 12 years of age) treated with *TIVICAY* (70 mg, as 35 mg twice daily, n=1; 50 mg once daily, n=5; 35 mg once daily, n=6; 25 mg once daily, n= 8; and 20 mg once daily, n=3) plus OBR, achieved viral load less than 50 copies/mL.

Table 12 Virologic and Immunologic Activity of Treatment for Subjects 6 Years and Older in P1093

	***TIVICAY* ~1 mg/kg Once Daily**	
	Cohort I (12 to 18 years) Week 48	Cohort IIa (6 to <12 years) Week 24

	(n=23)	(n=23)
HIV-1 RNA <50 copies/mL, n (%)	14 (61%)	14 (61%)
HIV-1 RNA <400 copies/mL, n (%)	17 (74%)	18 (78%)
Virologic non response	6	3
CD4+ Cell Count Median Change from Baseline, cells/mm^3 Median Percent Change from Baseline	 84[a] 5%[a]	 209[b] 8%[b]

[a] 22 subjects contributed Week 48 CD4+ cell count data

[b] 21 subjects contributed Week 24 CD4+ cell count 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 (24 times the 50 mg twice daily human clinical exposure based on AUC).

Pregnancy

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

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity (0.40 times the 50 mg twice daily human clinical exposure based on AUC). In rabbits, maternal toxicity (decreased food consumption, scant/no faeces/urine, suppressed body weight gain) was observed at 1000 mg/kg (0.40 times the 50 mg twice daily 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 21

and 0.82 times the 50 mg twice daily human clinical exposure based on AUC, respectively. Because gastrointestinal (GI) intolerance is considered to be due to local drug administration, mg/kg or mg/m^2 metrics are appropriate determinates of safety cover for this toxicity. GI intolerance in monkeys occurred at 15 times the human mg/kg equivalent dose (based on a 50 kg human), and 5 times the human mg/m^2 equivalent dose for a clinical dose of 50 mg twice daily.

PHARMACEUTICAL INFORMATION

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 (for 25 mg and 50 mg tablets)

Shelf Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging

For 10 mg only - 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 tablets are supplied in HDPE (high density polyethylene) bottles containing 30 film-coated tablets. The 10 mg tablet bottles contain a desiccant.

Incompatibilities

No incompatibilities have been identified.

Use and Handling

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

Not all presentations are available in every country.

Product Registrant

GlaxoSmithKline Pte Ltd

23 Rochester Park, Singapore 139234

Version number: GDS21/IPI20SI

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[ViiV Healthcare Logo]