▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

TIVICAY (dolutegravir) film-coated tablets and TIVICAY PD (dolutegravir) dispersible tablets

1 NAME OF THE MEDICINE

Dolutegravir

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Dolutegravir sodium is a white to light yellow powder.

Film-coated tablets

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

TIVICAY film-coated tablets each contain 10.5 mg, 26.3 mg or 52.6 mg of dolutegravir sodium, equivalent to 10 mg, 25 mg or 50 mg of dolutegravir free acid.

Dispersible tablets

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

TIVICAY PD dispersible tablets each contain 5.26 mg of dolutegravir sodium, equivalent to 5 mg of dolutegravir free acid.

TIVICAY and TIVICAY PD tablets also contain mannitol.

TIVICAY PD dispersible tablets contain sucralose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Film-coated tablets

10 mg – White, film-coated, round, biconvex tablets debossed with ‘SV 572’ on one side and ‘10’ on the other side.

25 mg – Pale yellow, film-coated, round, biconvex tablets debossed with ‘SV 572’ on one side and ‘25’ on the other side.

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

Dispersible tablets

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TIVICAY and TIVICAY PD are indicated for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults and children of at least 4 weeks in age or older and weighing 3 kg or more (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Dual regimens).

4.2 DOSE AND METHOD OF ADMINISTRATION

Posology

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

Dolutegravir is available as film-coated tablets for patients aged at least 6 years and weighing at least 14 kg. Dolutegravir is also 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. The bioavailability of film-coated tablets and dispersible tablets is not comparable therefore they must not be used as direct replacements (see Section 5.2 Pharmacokinetic Properties). For example, the recommended adult dose for film-coated tablets is 50 mg versus 30 mg for dispersible tablets. Patients changing between film-coated and dispersible tablets should follow the dosing recommendations that are specific for the formulation.

TIVICAY and TIVICAY PD can be taken with or without food.

Dispersible tablets

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. Do not chew, cut or crush the tablets.

Method of administration

Film-coated tablets

Adults

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

The recommended dose of TIVICAY film-coated tablets is 50 mg once daily.

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

The recommended dose of TIVICAY film-coated tablets is 50 mg twice daily. The decision to use dolutegravir for such patients should be informed by the integrase resistance pattern (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

The following should be considered prior to initiating treatment with TIVICAY film-coated tablets 50 mg twice daily:

- Reduced virologic response was observed in subjects treated with TIVICAY 50 mg twice daily with an INI-resistance Q148H/K/R mutation plus 2 or more additional INI-resistance mutations including, but not limited to G140A/C/S, E138A/K/T, or L74I (see Section 5 PHARMACOLOGICAL PROPERTIES).

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 20 kg) the recommended dose of TIVICAY film-coated tablets is 50 mg once daily.

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

Children aged at least 6 years and weighing at least 14 kg

In patients infected with HIV-1 without resistance to the integrase class, the recommended dose of dolutegravir film-coated tablets in children (6 to less than 12 years of age and weighing at least 14 kg) is determined according to the weight of the child. Dose recommendations according to weight are presented in the table below.

Table 1a Film-coated tablet dose recommendations in children aged at least 6 years and weighing at least 14 kg

Body Weight (kg)	Dose
14 to less than 20	40 mg once daily (Taken as four 10 mg film-coated tablets)
20 or greater	50 mg once daily (Taken as one 50 mg film-coated tablet)

To reduce the risk of choking, do not swallow more than one tablet at a time, and where possible, children weighing 14 to less than 20 kg should preferentially take the dispersible tablet formulation.

There are insufficient safety and efficacy data available to recommend a dose for TIVICAY film-coated tablets in children below age 6 or weighing less than 14 kg.

There is insufficient data to recommend a dose for dolutegravir film-coated tablets in integrase inhibitor resistant children.

Dispersible tablets

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 Section 5.1 Pharmacodynamic Properties, Clinical trials).

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 1b 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 TIVICAY PD dispersible tablets in integrase inhibitor resistant adolescents, children and infants.

Populations

Elderly

There are limited data available on the use of TIVICAY and TIVICAY PD in patients aged 65 years and over. However, there is no evidence that elderly patients require a different dose than younger adult patients (see Section 5.2 PHARMACOKINETIC PROPERTIES - 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. No data are available in patients receiving dialysis, although differences in pharmacokinetics are not expected in this population (see Section 5.2 PHARMACOKINETIC PROPERTIES - Special patient populations).

TIVICAY and TIVICAY PD has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when TIVICAY or TIVICAY PD is coadministered with a drug that has dosing adjustment recommendations guided by estimated creatinine clearance.

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 Section 5.2 PHARMACOKINETIC PROPERTIES - Special patient populations).

Women of child bearing potential and pregnancy

A benefit-risk assessment should be considered for pregnant women and women of childbearing potential (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in pregnancy).

4.3 CONTRAINDICATIONS

TIVICAY and TIVICAY PD are contraindicated in combination with dofetilide.

TIVICAY and TIVICAY PD are contraindicated in patients with known hypersensitivity to dolutegravir or to any of the excipients.

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 todofetilide, pilsicainide or fampridine (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions
Hypersensitivity reactions have been reported with integrase inhibitors, including TIVICAY and TIVICAY PD, and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. Discontinue TIVICAY/TIVICAY PD 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/TIVICAY PD 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 dolutegravir 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 coinfected patients (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Opportunistic infections
Patients receiving TIVICAY/TIVICAY PD 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.

Serum lipids and blood glucose
Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Dual regimens
Rilpivirine and dolutegravir:

The dual regimen of rilpivirine and dolutegravir is only suitable for the treatment of HIV-1 infection in those patients who are virologically suppressed (HIV-1 RNA <50 copies/mL) 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 where there is no known or suspected resistance to either ART component.

Use in hepatic impairment
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES - Special patient populations.

Use in renal impairment
See Section 4.2 DOSE AND METHOD AND ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES - Special patient populations.

Use in the elderly
There are limited data available on the use of TIVICAY and TIVICAY PD in patients aged 65 years and over. However, there is no evidence that elderly patients require a different dose than younger adult patients (see Section 5.2 PHARMACOKINETICS PROPERTIES - Special patient populations).

Paediatric use
The safety and efficacy of TIVICAY and TIVICAY PD has not yet been established in children (< 4 weeks or weighing less than 3 kg).

Effects on laboratory tests
See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Table 4.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Caution should be given to co-administering medications (prescription and nonprescription) that may change the exposure of TIVICAY/TIVICAY PD or medications that may have their exposure changed by TIVICAY/TIVICAY PD (see Section 4.3 CONTRAINDICATIONS).

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

TIVICAY and TIVICAY PD should not be co-administered with polyvalent cation-containing antacids. TIVICAY and TIVICAY PD are recommended to be administered two hours before or six hours after these agents.

TIVICAY and TIVICAY PD are recommended to be administered 2 hours before or 6 hours after taking calcium, magnesium or iron supplements, or alternatively, administered with food.

Dolutegravir 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.

Effect of dolutegravir on the pharmacokinetics of other agents

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). *In vivo,* dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2. *In vivo* dolutegravir may increase plasma concentrations of drugs in which excretion is dependent upon OCT2 or MATE1 (for example dofetilide, pilsicainide, fampridine or metformin) (see Table 2). Given dolutegravir's *in vivo* exposure, it has a low potential to affect the transport of MATE2-K substrates *in vivo.*

In vitro, dolutegravir inhibited the basolateral renal transporters: organic anion transporter (OAT) 1 (IC_{50} = 2.12 µM) and OAT3 (IC_{50} = 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.

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC_{50} > 50 µM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MRP2, or MRP4. *In vitro,* dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4. Based on these data, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

In drug interaction studies, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, ritonavir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, boceprevir, daclatasvir and oral contraceptives containing norgestimate and ethinyl estradiol.

Effect of other agents on the pharmacokinetics of dolutegravir

Dolutegravir is metabolised by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp *in vitro.* Drugs that induce those enzymes or transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir. Co-administration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentrations.

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% $C\tau$ ↓ 88% ETR ↔	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended dose of dolutegravir should be given twice daily when co-administered with etravirine without boosted protease inhibitors. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in INI-resistant patients.
Protease Inhibitor: Lopinavir/ritonavir + Etravirine	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% $C\tau$ ↑ 28% LPV ↔ RTV ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir + Etravirine	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% $C\tau$ ↓ 36% DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% $C\tau$ ↓ 75% EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of dolutegravir 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. Alternative combinations that do not include nevirapine should be used where possible in INI-resistant patients.
Protease Inhibitor (PI): Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% $C\tau$ ↑ 180% ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir or Concomitant Drug**	**Clinical Comment**
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 dolutegravir 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. Using cross-study comparisons to historical pharmacokinetic data for each interacting drug, dolutegravir did not appear to affect the pharmacokinetics of lopinavir or ritonavir.
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.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir or Concomitant Drug	Clinical Comment
Other Agents		
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide ↑	Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 or MATE 1 transporters; 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	Fampridine ↑	Co-administration of dolutegravir has the potential to cause seizures due to increased fampridine plasma concentration via inhibition of OCT2 transporter; coadministration has not been studied. Fampridine co-administration with dolutegravir is contraindicated.
Carbamazepine	Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33% $C\tau$ ↓ 73%	Carbamazepine decreased dolutegravir plasma concentration. The recommended dose of dolutegravir 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 dolutegravir 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. Dolutegravir 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%	Dolutegravir is recommended to be administered 2 hours before or 6 hours after taking products containing calcium, or alternatively, administer with food.
Iron supplements	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% C24 ↓ 56%	Dolutegravir is recommended to be administered 2 hours before or 6 hours after taking products containing iron, or alternatively, administer with food.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir or Concomitant Drug	Clinical Comment
Metformin	Metformin ↑ When co-administered with dolutegravir 50 mg film-coated tablets QD: Metformin AUC ↑ 79% C_{max} ↑ 66% When co-administered with dolutegravir 50 mg film-coated tablets BID: Metformin AUC ↑ 145 % C_{max} ↑ 111%	Co-administration of dolutegravir increased metformin plasma concentration via inhibition of OCT2 or MATE 1 transporters; co-administration has not been studied. 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%	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of dolutegravir should be given twice daily when co-administered with rifampicin. Alternatives to rifampicin should be used where possible for INI-resistant patients.
Rifabutin	Dolutegravir ↔ AUC ↓ 5% C_{max} ↑ 16% Cτ ↓ 30%	No dose adjustment is necessary.
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 dolutegravir.
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 dolutegravir.
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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There are no data on the effects of TIVICAY and TIVICAY PD on human male or female fertility. Dolutegravir did not affect male or female mating or fertility in rats at doses up to 1000 mg/kg/day associated with an exposure level 24 times the clinical exposure based on AUC at the maximum recommended dose of 50 mg BID.

Use in pregnancy
(Category B1)

TIVICAY and TIVICAY PD can be used in pregnancy if the expected benefit justifies the potential risk to the fetus.

Summary

Data from two, ongoing birth outcome surveillance studies in Botswana and Eswatini which together include over 14,000 individuals evaluated during pregnancy show similar prevalence of neural tube defects among infants born to individuals taking dolutegravir at the time of conception compared to those born to individuals taking non-dolutegravir-containing regimens at conception or infants born to HIV-negative individuals.

There are insufficient human data on the use of dolutegravir during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. However, available human data from the Antiretroviral Pregnancy Registry (APR) do not indicate an increased risk of birth defects. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

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

The Eswatini birth outcome surveillance study includes 9,743 individuals exposed to dolutegravir at conception, 1,838 individuals exposed to non-dolutegravir-containing regimens, and 32,259 HIV-negative pregnant individuals. The prevalence of neural tube defects in infants delivered to individuals taking dolutegravir at conception was 0.08% (95% CI: 0.04-0.16%). The observed prevalence rate did not differ significantly from that of infants delivered to individuals taking non-dolutegravir-containing regimens (0.22%, 95% CI: 0.06-0.56%) or to HIV-negative individuals (0.08%, 95% CI: 0.06-0.12%). The observed prevalence

of neural tube defects in infants delivered to individuals taking non-dolutegravir-containing regimens had a wide confidence interval due to low sample size.

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

The APR has received prospective reports of over 1,506 exposures to dolutegravir-containing regimens during pregnancy resulting in live births, as of July 2023. These consist of 957 exposures during the first trimester, 549 exposures during the second/third trimester and included 32 and 29 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to dolutegravir-containing regimens in the first trimester was 3.3% (2.3%, 4.7%) and in the second/third trimester, 5.3% (3.6%, 7.5%).

In the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP), the background birth defect rate was 2.7%. The background risk for major birth defects for the treatment-indicated population is unknown.

In animal reproductive toxicity studies, no adverse development outcomes, including neural tube defects, were identified.

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 human clinical exposure based on AUC at the maximum recommended dose of 50 mg BID).

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation was associated with marked maternal toxicity, but did not elicit developmental toxicity or teratogenicity in the offspring (0.4 times the clinical exposure based on AUC).

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

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

Use in lactation

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). Breast feeding is not advised because of the potential for HIV transmission from mother to child, and the potential risk of adverse events due to antiretroviral drug excretion in breast milk.

In settings where formula feeding is unsafe or unavailable, the World Health Organisation has provided Guidelines.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data

Antiretroviral naïve patients

The safety assessment of TIVICAY in HIV-1 infected treatment-naïve patients is based on the analyses of 96-week data from 2, international, multicentre, double-blind trials, SPRING-2 (ING113086) and SINGLE (ING114467) and 48-week data from the international, multicentre, open-label FLAMINGO (ING114915) trial.

In SPRING-2, 822 patients were randomised and received at least 1 dose of either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) treatment (either abacavir sulfate/lamivudine or emtricitabine/tenofovir). Through 96 weeks the rates of discontinuation due to adverse events were 1% in patients receiving TIVICAY 50 mg once daily + either abacavir sulfate/lamivudine (ABC/3TC) or tenofovir/ emtricitabine (TDF/FTC) and 2% in patients receiving raltegravir 400 mg twice daily + either abacavir sulfate/lamivudine or emtricitabine/tenofovir.

In SINGLE, 833 patients were randomised and received at least 1 dose of either TIVICAY 50 mg with fixed-dose abacavir sulfate/lamivudine once daily or fixed-dose efavirenz/ tenofovir/emtricitabine (EFV/TDF/FTC) once daily. Through 96 weeks, the rates of discontinuation due to adverse events were 3% in patients receiving TIVICAY 50 mg once daily + abacavir sulfate/lamivudine and 12% in patients receiving efavirenz/emtricitabine/tenofovir once daily.

Treatment emergent adverse reactions (adverse events assessed as causally related by the investigator) of moderate to severe intensity with a $\geq$ 2% frequency in either treatment arm in SPRING-2 and SINGLE trials are provided in Table 3. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 3 Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4) and ≥ 2% Frequency in Treatment-Naive Patients in SPRING-2 and SINGLE Trials (Week 96 Analysis)

Body System/ Preferred Term	SPRING-2		SINGLE	
	TIVICAY 50 mg Once Daily + 2 NRTIs (N = 411)	Raltegravir 400 mg Twice Daily + 2 NRTIs (N = 411)	TIVICAY 50 mg + KIVEXA (ABC/3TC) Once Daily (N = 414)	EFV/TDF/FTC Once Daily (N = 419)
Psychiatric				
Insomnia	1 (<1%)	1 (<1%)	14 (3%)	10 (2%)
Depression	1 (<1%)	1 (<1%)	5 (1%)	9 (2%)
Abnormal dreams	2 (<1%)	1 (<1%)	3 (<1%)	8 (2%)
Nervous System				
Dizziness	1 (<1%)	1 (<1%)	2 (<1%)	21 (5%)
Headache	3 (<1%)	4 (<1%)	8 (2%)	9 (2%)
Gastrointestinal				
Nausea	6 (1%)	5 (1%)	3 (<1%)	12 (3%)
Diarrhea	3 (<1%)	2 (<1%)	3 (<1%)	7 (2%)
General Disorders				
Fatigue	2 (<1%)	2 (<1%)	7 (2%)	7 (2%)
Skin and Subcutaneous Tissue				
Rash [a]	0	3 (<1%)	2 (<1%)	25 (6%)
Ear and Labyrinth				
Vertigo	0	1 (<1%)	0	7 (2%)

[a] Includes pooled terms: rash, rash generalised, rash macular, rash maculo-papular, rash pruritic, and drug eruption.

Laboratory abnormalities with a worsening grade from baseline in ≥ 2% (for Grades 3 to 4 combined) of patients are presented in Table 4. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 4 Laboratory Abnormalities (≥ 2% for Grades 3 to 4 Combined) in Treatment-Naive Patients in SPRING-2 and SINGLE Trials (Week 96 Analysis)

Laboratory Parameter Preferred Term (Unit)	SPRING-2		SINGLE	
	TIVICAY 50 mg Once Daily + 2 NRTIs (N = 411)	Raltegravir 400 mg Twice Daily + 2 NRTIs (N = 411)	TIVICAY 50 mg + KIVEXA (ABC/3TC) Once Daily (N = 414)	EFV/TDF/FTC Once Daily (N = 419)
ALT (IU/L)				
Grade 3 (5.1-10.0 x ULN)	5 (1%)	6 (1%)	1 (<1%)	1 (<1%)
Grade 4 (>10.0 x ULN)	5 (2%)	2 (<1%)	1 (<1%)	1 (<1%)
AST (IU/L)				
Grade 3 (5.1-10.0 x ULN)	8 (2%)	8 (2%)	1 (<1%)	9 (2%)
Grade 4 (>10.0 x ULN)	6 (1%)	2 (<1%)	0	2 (<1%)
Creatine kinase (IU/L)				
Grade 3 (10.0-19.9 x ULN)	9 (2%)	10 (2%)	11 (3%)	11 (3%)
Grade 4 (≥20.0 x ULN)	18 (4%)	8 (2%)	10 (2%)	17 (4%)
Lipase (U/L)				
Grade 3 (3.1-5.0 x ULN)	6 (1%)	13 (3%)	10 (2%)	11 (3%)
Grade 4 (>5.0 x ULN)	3 (<1%)	6 (1%)	6 (1%)	2 (<1%)
Total neutrophils ($10^3/\mu L$)				
Grade 3 (0.50-0.749 x 10^9)	5 (1%)	3 (<1%)	8 (2%)	7 (2%)
Grade 4 (<0.50 x 10^9)	3 (<1%)	5 (<1%)	2 (<1%)	7 (2%)

ULN = Upper limit of normal.

In a multicentre, open-label trial (FLAMINGO), 243 subjects received TIVICAY 50 mg once daily versus 242 subjects who received darunavir 800 mg/ritonavir 100 mg once daily, both in combination with investigator-selected NRTI background regimen (either ABC/3TC or TDF/FTC). There were 484 subjects included in the efficacy and safety analyses. Through 48 weeks, the rates of adverse events leading to discontinuation were 2% in subjects receiving TIVICAY and 4% in subjects receiving darunavir/ritonavir. The ADRs observed in FLAMINGO were generally consistent with those seen in SPRING-2 and SINGLE.

Laboratory abnormalities observed in the FLAMINGO trial were generally consistent with observations in SPRING-2 and SINGLE.

In identical 148-week, randomised, double-blind, multicentre, non-inferiority studies (GEMINI-1 and GEMINI-2), 1433 subjects where treated with a two-drug regimen of dolutegravir 50 mg

plus lamivudine 300 mg once daily (n=716) verses fixed dose tenofovir/emtricitabine (TDF/FTC) (n=717) (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). Through 48 weeks, the rates of adverse events leading to discontinuation in the pooled analysis were 2% of subjects in both treatment arms. The ADRs observed for the combination of dolutegravir and lamivudine in these studies were generally consistent with the ADR profiles and severities for the individual components when administered with other antiretroviral agents.

Antiretroviral experienced (and integrase inhibitor naïve) patients

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

The only treatment-emergent adverse reaction (adverse event assessed as causally related by the investigators) of moderate to severe intensity with a ≥ 2% frequency in either treatment group was diarrhea, 2% (6/357) in patients receiving TIVICAY 50 mg once daily + background regimen and 1% (5/362) in patients receiving raltegravir 400 mg twice daily + background regimen.

Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naïve (SPRING-2 and SINGLE) trials.

Integrase inhibitor resistant patients

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

Treatment-emergent ADRs in VIKING-3 were generally similar compared with observations with the 50 mg once-daily dose in adult Phase III trials.

The most common treatment-emergent laboratory abnormalities (> 5% for Grades 2 to 4 combined) observed in VIKING-3 at Week 48 were elevated ALT (9%), AST (8%), cholesterol (10%), creatine kinase (6%), hyperglycemia (14%), and lipase (10%). Two percent (4/183) of subjects had a Grade 3 to 4, treatment-emergent hematology laboratory abnormality, with neutropenia (2% [3/183]) being the most frequently reported.

Changes in clinical laboratory values

Increases in serum creatinine occurred within the first week of treatment with dolutegravir 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 (GFR) (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Effects on renal function).

Small increases in total bilirubin (without clinical jaundice) were observed on dolutegravir and raltegravir (but not efavirenz) arms in the clinical trials. These changes are not considered clinically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway, uridine diphosphate glucuronosyltransferase (UGT1A1).

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

Less common adverse reactions observed in treatment naïve and treatment-experienced trials

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

Gastrointestinal disorders: Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting.

General disorders: Fatigue.

Hepatobiliary disorders: Hepatitis.

Psychiatric disorders: Suicidal ideation, attempt, behavior, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness.

Immune system disorders: Hypersensitivity, immune reconstitution syndrome.

Skin and subcutaneous tissue disorders: Pruritus.

Paediatric population

Based on data from the ongoing P1093 (ING112578) and ODYSSEY (201296) studies in 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 patients 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Post marketing data

Blood and lymphatic system disorders

Very rare: Sideroblastic anaemia*

Musculoskeletal and connective tissue disorders

Uncommon: arthralgia, myalgia

Psychiatric disorders

Common: anxiety

Investigations

Common: weight increased

Hepatobiliary disorders

Rare: acute hepatic failure**

*Reversible sideroblastic anaemia has been reported with dolutegravir-containing regimens. The contribution of dolutegravir in these cases is unclear.

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms and signs

There is currently limited experience with overdosage in TIVICAY and TIVICAY PD.

Limited experience of single higher doses (up to 250 mg film-coated tablets in healthy patients) 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/TIVICAY PD. 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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
TIVICAY film-coated tablets and TIVICAY PD dispersible tablets contain dolutegravir (as dolutegravir sodium) which is an integrase inhibitor active against Human Immunodeficiency Virus (HIV).

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. 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 (t½ 71 hours).

Pharmacodynamic effects
In a randomised, dose-ranging trial, HIV-1 infected patients treated with dolutegravir monotherapy (ING111521) demonstrated rapid and dose-dependent antiviral activity, with mean declines from baseline to day 11 in HIV-1 RNA of 1.5, 2.0, and 2.5 log10 for dolutegravir 2 mg, 10 mg, and 50 mg once daily, respectively. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

PK/PD modelling using pooled data from clinical studies in integrase resistant patients suggest that increasing the dose from 50 mg film-coated tablet twice daily to 100 mg film-coated tablet twice daily may increase the effectiveness of dolutegravir in patients with integrase resistance and limited treatment options due to advanced multi class resistance. The proportion of responders (HIV-1 RNA <50 c/mL) at week 24 was predicted to increase around 4-18% in the subjects with Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I. Although these simulated results have not been confirmed in clinical trials, this high dose may be considered in the presence of the Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I in patients with overall limited treatment options due to advanced multi class resistance. There is no clinical data on the safety or efficacy of the 100 mg film-coated tablet twice daily dose. Co-treatment with atazanavir increases the exposure of dolutegravir markedly, and should not be used in combination with this high dose, since safety with the resulting dolutegravir exposure has not been established.

Antiviral activity in cell culture

Dolutegravir exhibited antiviral activity against laboratory strains of wild type HIV-1 in peripheral blood mononuclear cells (PBMC) and MT4 cells with mean EC_{50s} of 0.5 nM to 2.1 nM.

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

Antiviral activity in combination with other antiviral agents

The antiviral activity of dolutegravir *in vitro* was not antagonistic with the integrase inhibitor (INI) raltegravir; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz or nevirapine; the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir or stavudine; the protease inhibitors (PIs) amprenavir or lopinavir; the CCR5 co-receptor antagonist maraviroc; or the fusion inhibitor enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor adefovir, or inhibited by the antiviral ribavirin.

Resistance *in vitro*

Dolutegravir-resistant viruses were selected in studies of potential resistance using different wild type strains and clades of HIV-1. Amino acid substitutions that emerged during passaging included E92Q, G193E, G118R, S153F or Y, and R263K, and were associated with decreased susceptibility to dolutegravir of up to 11-fold.

In resistance development studies starting with the single raltegravir resistance mutants Q148H, Q148K or Q148R, additional mutations detected during passage with dolutegravir included E138K/Q148K, E138K/Q148R, Q140S/Q148R and G140S/Q148R, which all exhibited greater than ten-fold reductions in sensitivity to dolutegravir.

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

Cross resistance: integrase inhibitor-resistant HIV-1 strains: Sixty integrase inhibitor-resistant mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) were produced from wild-type virus NL-432 using site-directed mutagenesis. Dolutegravir showed anti-HIV activity (susceptibility) with FC < 5 against 27 of 28 integrase inhibitor-resistant mutant viruses with single substitutions including T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R, and N155H. A G118R substitution conferred a 10-fold reduction in dolutegravir susceptibility but has not been observed during dolutegravir clinical studies. The single INSTI resistance substitutions T66K, I151L, and S153Y conferred a > 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a > 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference).

Cross resistance: integrase inhibitor resistant HIV-2 strains: Site-directed mutant HIV-2 viruses were constructed based on patients infected with HIV-2 and treated with raltegravir who showed virologic failure. HIV-2 mutants with combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D were associated with four-fold reductions in dolutegravir susceptibility, while susceptibility of viruses with E92Q/N155H and G140S/Q148R substitutions were decreased 8.5 and 17-fold, respectively.

Clinical isolates from raltegravir treatment virologic failure patients: Thirty clinical isolate samples with genotypic and phenotypic resistance to raltegravir (median FC > 81) were examined for susceptibility to dolutegravir (median FC 1.5). The median FC to dolutegravir for

isolates containing changes at G140S + Q148H was 3.75; G140S + Q148R was 13.3; T97A + Y143R was 1.05 and N155H was 1.37.

Seven hundred and five raltegravir resistant isolates from raltegravir experienced patients were analysed for susceptibility to dolutegravir. Dolutegravir has a less than or equal to 10 FC against 93.9% of the 705 clinical isolates. Dolutegravir has a ≤ 10 FC against 67 (73%) of the 92 clinical isolates with Q148 + ≥ 2 INSTI-resistance substitutions and 168 (91%) of the 184 isolates with Q148 + 1 INSTI-resistance substitutions.

Resistance *in vivo*: integrase inhibitor naïve patients

No INI-resistant mutations or treatment emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg film-coated tablets once daily in treatment-naïve studies (SPRING-1, SPRING-2, SINGLE, FLAMINGO and GEMINI studies). In the SAILING study for treatment experienced (and integrase naïve) patients (n = 354 in the dolutegravir arm), treatment-emergent integrase substitutions were observed at week 48 in 4 of 17 patients receiving dolutegravir with virologic failure. Of these four, 2 subjects had a unique R263K integrase substitution, with a maximum FC of 1.93, 1 subject had a polymorphic V151V/I integrase substitution, with maximum FC of 0.92, and 1 subject had pre-existing integrase mutations and is assumed to have been integrase experienced or infected with integrase resistant virus by transmission (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

Resistance *in vivo*: integrase inhibitor resistant patients

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

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 subject'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/R539 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 NNRTIresistance-associated substitutions E138A and L100L/I with rilpivirine FC = 4.1 and integrase resistance testing failed at virologic failure.

Effects on electrocardiogram

In a randomised, placebo-controlled, cross-over trial, 42 healthy patients 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. Dolutegravir did not prolong the QTc interval for 24 hours post dose. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) was 1.99 msec (1-sided 95% upper CI: 4.53 msec).

Effects on renal function

The effect of dolutegravir on serum creatinine clearance (CrCl), glomerular filtration rate (GFR) using iohexol as the probe and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was evaluated in an open-label, randomised, 3 arm, parallel, placebo-controlled study in 37 healthy patients, who were administered dolutegravir film-coated tablets 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.

Clinical trials

Antiretroviral naïve patients

The efficacy of TIVICAY in HIV-infected, therapy naïve patients is based on data from two randomised, 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 randomised 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 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%) based on a margin of -10% [difference (95% CI) 4.5% (-1.1%, 10.0%)]. The median change in CD4+ T cell count from baseline were 230 cells/mm3 in the group receiving TIVICAY and the raltegravir group at 48 weeks and 276 cells/mm3 in the group receiving dolutegravir compared to 264 cells/mm3 the raltegravir group at 96 weeks.

In SINGLE, 833 patients were randomised and received at least one dose of either TIVICAY 50 mg film-coated tablets once daily with fixed-dose abacavir-lamivudine (DTG + 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.

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 week 96, the percentage of participants virologically suppressed (i.e. having < 50 copies/mL using a missing, switch or discontinuation = failure analysis) was 80% for those on the TIVICAY + ABC/3TC regimen vs. 72% for those on EFV/TDF/FTC [difference (95% CI) 8.0% (2.3%, 13.8%)]. The higher responses on DTG + ABC/3TC were driven by withdrawals due to AEs and missing data.

The adjusted mean change in CD4+ T cell count from baseline were 267 cells/mm3 in the group receiving TIVICAY + ABC/3TC and 208 cells/mm3 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 prespecified and adjusted for multiplicity.

At 144 weeks in the open-label phase, virologic suppression in the dolutegravir + ABC/3TC arm was 71% and in the EFV/TDF/FTC arm it was 63%, treatment difference was 8.3% (2.0%, 14.6%).

The primary endpoint and other week 48 outcomes (including outcomes by key baseline covariates) for SPRING-2 and SINGLE are shown in Table 5.

Table 5 Virologic Outcomes of Randomised Treatment of SPRING-2 and SINGLE at 48 Weeks (Snapshot algorithm-missing, switch or discontinuation = failure)

	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%) P=0.003	
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%)
Treatment Difference	0.4% (95% CI: -4.5%, 5.3%)		7.7% (95% CI: 2.1%, 13.3%)	
>100,000	94 / 114 (82%)	87 / 116 (75%)	111 / 134 (83%)	100 / 131 (76%)
Treatment Difference	7.5% (95% CI: -3.1%, 18.0%)		6.5% (95% CI: -3.2%, 16.2%)	
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%)

	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
NRTI backbone				
ABC/3TC	145 / 169 (86%)	142 / 164 (87%)	N/A	N/A
Treatment Difference	-0.8% (95% CI: -8.2%, 6.6%)			
TDF/FTC	216 / 242 (89%)	209 / 247 (85%)	N/A	N/A
Treatment Difference	4.6% (95% CI: -1.3%, 10.6%)			
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 patients who changed background regimen (BR) to new class or changed BR not permitted per protocol or due to lack of efficacy prior to Week 48 (for SPRING-2 only), patients who discontinued prior to Week 48 for lack or loss of efficacy and patients who are ≥50 copies in the 48 week window.
‡ Includes patients who discontinued due to an adverse event or death at any time point from Day 1 through the Week 48 window if this resulted in no virologic data on treatment during the Week 48 window.
§ Includes reasons such as withdrew consent, loss to follow-up, moved, protocol deviation.
¶ For Single, Treatment Differences (95% CIs) for Baseline CD4+ stratification factor: for ≤200 cells/mm^3: 1.5% (-13.3%, 16.4%), for >200: 8.1% (3.0%, 13.3%)
Notes: ABC/3TC = abacavir 600 mg, lamivudine 300 mg in the form of Kivexa fixed dose combination (FDC).
EFV/TDF/FTC = efavirenz 600 mg, tenofovir 300 mg, emtricitabine 200 mg FDC.
N = Number of patients in each treatment group.

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 TIVICAY containing arms. In SPRING-2, four patients on the raltegravir arm failed with major NRTI mutations and one patient developed raltegravir resistance; in SINGLE, six patients 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 randomised and received one dose of either dolutegravir 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, snapshot algorithm - missing, switch or discontinuation = failure) in the dolutegravir 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 Week 96 virologic suppression in the dolutegravir group was 80% and in the DRV/r group it was 68%, treatment difference was 12.4% (4.7%, 20.2%). No treatment emergent primary INI, PI or NRTI resistance mutations were observed for subjects in the dolutegravir or DRV + RTV treatment groups. Treatment failure due to “no virologic data” was 10 (4%) in the dolutegravir group and 24 (10%) in the DRV + RTV group.

Sustained virological response was demonstrated in the SPRING-1 study (ING112276), in which 88% of patients receiving 50 mg dose of dolutegravir 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 dolutegravir through 96 weeks.

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 film-coated tablets plus lamivudine 300 mg once daily or dolutegravir 50 mg film-coated tablets once daily with fixed dose tenofovir/emtricitabine (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, 32% 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) 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%.

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 noninferiority margin of -10%. The mean increase in CD4+ T-cell counts was 269 cells/mm3 in the DTG+3TC arm and 259 cells/mm3 in the DTG+FTC/TDF arm, at week 96.

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/mm3 in the DTG+3TC arm and 300 cells/mm3 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.

For both pooled treatment groups, the overall lipid profiles were generally improved from baseline, and the proportions of subjects showing favourable improvements in total cholesterol/HDL cholesterol ratio were similar between the 2 treatment groups.

Table 6 Mean Change from Baseline in Fasted Lipid Values in GEMINI-1 and GEMINI-2 (Week 48 Pooled Analysis[a])

Laboratory Parameter Preferred Term	Dolutegravir plus lamivudine (n = 716)	Dolutegravir plus TDF*/emtricitabine (n = 717)
Cholesterol (mmol/L)	0.35	-0.18
HDL cholesterol (mmol/L)	0.15	0.02
LDL cholesterol (mmol/L)	0.19	-0.16
Triglycerides (mmol/L)	0.04	-0.08
Total cholesterol/HDL cholesterol ratio	-0.1	-0.3

[a] Subjects on lipid-lowering agents at baseline are excluded (dolutegravir plus lamivudine, n = 29; dolutegravir plus tenofovir/emtricitabine FDC, n = 23). Lipid last observation carried forward data were used such that the last available fasted, on-treatment lipid value prior to the initiation of a lipid-lowering agent is used in place of future observed values. A total of 23 and 13 subjects receiving dolutegravir plus lamivudine and dolutegravir plus tenofovir/emtricitabine FDC, respectively, initiated lipid-lowering agents post-baseline.

* tenofovir disoproxil fumarate

Antiretroviral experienced (and integrase inhibitor naïve) patients

In the international, multicentre, double-blind SAILING study (ING111762), 719 HIV-1 infected, ART-experienced adults were randomised 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 patients had at least two class ART resistance, and 49% of patients had at least 3 class ART resistance at baseline.

In the SAILING study, virologic suppression (HIV-1 RNA < 50 copies/mL) in the dolutegravir 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 subtype. The mean changes in CD4+ T cell count from baseline based on observed data were 113 cells/mm^3 (n = 326) at week 24 and 162 cells/mm^3 (n = 294) at week 48 in the group receiving TIVICAY and 106 cells/mm^3 (n = 326) at week 24 and 153 cells/mm^3 (n = 283) at week 48 for the raltegravir group.

At week 48, 21 (6%) DTG subjects and 45 (12%) RAL subjects experienced PDVF. Statistically fewer patients failed therapy with treatment-emergent resistance in the IN gene on TIVICAY (4/354, 1%) than on raltegravir (17/361, 5%) (p = 0.003).

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

Table 7 Virologic Outcomes of Randomised Treatment of SAILING at 48 Weeks (Snapshot algorithm - missing, switch or discontinuation = failure)

	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%) P=0.003	
Virologic non response	20%	28%
No virologic data at Week 48		
Reasons	9%	9%
Discontinued study/study drug due to adverse event or death‡	3%	4%
Discontinued study/study drug for other reason§	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%)
Treatment difference	3.8% (95% CI: -3.9%, 11.6%)	
>50,000 copies/mL	65 / 105 (62%)	50 / 107 (47%)
Treatment difference	15.2% (95% CI: 1.9%, 28.4%)	

	SAILING	
	TIVICAY 50 mg Once Daily + BR N=354§	**RAL 400 mg Twice Daily + BR N=361§**
Baseline CD4+ (cells/mm³)		
<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 (72%)
Background Regimen		
Phenotypic Susceptibility Score* <2	70 / 104 (67%)	61 / 94 (65%)
Treatment Difference	2.4% (95% CI: -10.8%, 15.6%)	
Phenotypic Susceptibility Score* =2	181 / 250 (72%)	169/ 267 (63%)
Treatment Difference	9.1% (95% CI: 1.1%, 17.1%)	
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	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 patients were excluded from the efficacy analysis due to data integrity at one study site.
*The Phenotypic Susceptibility Score (PSS) and the Genotypic Susceptibility Score (GSS) were defined as the total number of ARTs in BR to which a patient'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.
¶ Treatment Differences (95% CIs) for stratification factor DRV/r use without primary PI mutations: for category "No": 9.3% (1.6%, 17.0%), for category "Yes": -0.7% (-15.4%, 14.1%).
†Other clades included: Complex (n=42), F1 (n=32), A1 (n=18), BF (n=14), all others n <10.
Notes: BR = background regimen, RAL = raltegravir; N = Number of patients in each treatment group.

Integrase inhibitor resistant patients

In the phase IIb, international multicentre, open-label, single-arm, non-comparative sequential cohort VIKING pilot study (ING112961), two sequential cohorts of patients with multiclass resistance including resistance to HIV integrase inhibitors were enrolled to examine the antiviral activity of a 50 mg dose of film-coated tablets once daily (n = 27) vs. a 50 mg dose of dolutegravir film-coated tablets twice daily (n = 24) after 10 days of functional monotherapy. Responses were greater with twice daily (1.8 log10 change from baseline in HIV RNA) than

with once daily dosing (1.5 log10 change from baseline, adjusted difference 0.3 log10, p = 0.017). Higher response rates with twice daily dosing were maintained with continued TIVICAY dosing and optimization of the background regimen through 48 weeks of therapy (33% vs. 71% < 50 copies/mL, intent-to-treat exposed (ITT-E) population TLOVR analysis). A comparable safety profile was observed across doses. Subsequently, VIKING-3 examined the effect of TIVICAY 50 mg film-coated tablets twice daily over 7 days of functional monotherapy, followed by optimised background therapy and continued TIVICAY twice daily treatment.

In the multicentre, open-label, single-arm, non-comparative 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. One hundred and eighty-three patients enrolled, 133 with INI-resistance at screening and 50 with only historical evidence of resistance (and not at screening). 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. Patients 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. The Virological Outcome (VO) population excluded patients who stopped therapy for non-efficacy reasons, and those with major protocol deviations (incorrect dolutegravir dosing, intake of prohibited co-medication). The VO population is a subset of the ITT-E population.

Mean change from baseline in HIV RNA at day 8 (primary endpoint) was -1.4 log10 (95% CI -1.3 to -1.5 log10, p < 0.001). Response was associated with baseline INI mutation pathway, as shown in Table 8.

Table 8 Virologic Response (Plasma HIV-1 RNA) at Day 8 by Derived baseline IN Resistance Mutation Group [Day 8 Virologic Outcome (VO) Population]

Derived IN Mutation Group	Number of patients (VO population)	Mean Change from baseline (SD) at Day 8	% > 1 log10 decline at Day 8*
No Q148H/K/R mutations#	122	-1.60 (0.52)	92%
Q148 + 1 secondary mutation^	35	-1.18 (0.52)	71%
Q148 + ≥ 2 secondary mutations^	20	-0.92 (0.81)	45%
VO Population: The Virological Outcome (VO) population excluded patients who stopped therapy for non-efficacy reasons, and those with major protocol deviations (incorrect dolutegravir dosing, intake of prohibited co-medication). The VO population is a subset of the ITT-E population. # Includes primary INI resistance mutations N155H, Y143C/H/R, T66A, E92Q, or historical evidence of INI-resistance only * Includes patients with HIV RNA <50 copies/mL at Day 8 ^ G140A/C/S, E138A/K/T, L74I			

After the monotherapy phase, patients had the opportunity to re-optimise their background regimen when possible.

Of the 183 patients who completed 24 weeks on study or discontinued before data cut-off, 126 (69% [95% CI: 62%, 76%]) had < 50 copies/mL RNA at week 24 (ITT-E, Snapshot algorithm). Patients harbouring virus with Q148 with additional Q148-associated secondary mutations

had lower response at week 24 (Table 9). Background overall susceptibility score (OSS) was not associated with Week 24 response.

Table 9 Week 24 Virologic Response by Derived baseline IN Resistance mutation Group and OSS of Optimised Background Regimen (OBR) (HIV-1 RNA < 50 c/mL, Snapshot algorithm), Week 24 VO Population

Derived IN Mutation Group	OSS=0	OSS=1	OSS=2	OSS>2	Total
No Q148H/K/R mutations[1]	4/4 (100%)	35/40 (88%)	40/48 (83%)	17/22 (77%)	96/114 (84%)
Q148 + 1 secondary mutation[2]	2/2 (100%)	8/12 (67%)	10/17 (59%)	-	20/31 (65%)
Q148 + ≥ 2 secondary mutations[2]	1/2 (50%)	2/11 (18%)	1/3 (33%)	-	4/16 (25%)

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

The response rate at week 48 was sustained with 116/183 (63% [95% CI: 56%, 70%]) subjects having HIV-1 RNA < 50 copies/mL (ITT-E, snapshot algorithm). Response was also sustained through week 48 in subjects harbouring virus with Q148 with additional Q148-associated secondary mutations. The proportion of subjects with HIV RNA < 50 copies/mL at week 48 was 88/113 (78%) for no Q148 mutations, 19/31 (61%) for Q148 + 1 and 4/16 (25%) for Q148 + ≥ 2 secondary mutations (VO population, snapshot algorithm).

Virologic suppression (HIV-1 RNA < 50 copies/mL) was comparable across baseline characteristics (gender, race and age). 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 (n = 163) and 110 cells/mm^3 at week 48 (n = 145).

In the multicentre, double-blind, placebo-controlled VIKING-4 study (ING116529), 30 HIV-1 infected, ART-experienced adults with current virological failure on an integrase inhibitor containing regimen and primary genotypic resistance to INIs at screening, were randomised to receive either dolutegravir 50 mg film-coated tablets twice daily or placebo with the current failing regimen for 7 days with all subjects receiving open-label dolutegravir plus optimised background regimen from day 8. 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 treatment comparison at Day 8, showed that dolutegravir was superior to placebo, with an adjusted mean treatment difference for the change from baseline in Plasma HIV-1 RNA at Day 8 of -1.2 log10 copies/mL (95% CI -1.5, -0.8 log10 copies/mL, p < 0.001). 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.

Virologically suppressed patients

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 per mm3; 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 10).

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 10.

Table 10 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%)
Non-White	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.

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 11) include participants who received either film-coated tablets or dispersible tablets as per the dosing recommendations (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Table 11 Antiviral and Immunological Activity Through Week 24 and Week 48 in Paediatric Patients

	Week 24 N=58		Week 48 N=24	
	n/N	% (95% CI)	n/N	% (95% CI)
Proportion of participants with HIV RNA <50 c/mL[a, b]	36/58	62.1 (48.4 - 74.5)	16/24	66.7 (44.7 – 84.4)
Proportion of participants with HIV RNA <400 c/mL[b]	50/58	86.2 (74.6 - 93.9)	18/24	75 (53.3 – 90.2)
	Median (n)	(Q1, Q3)	Median (n)	(Q1, Q3)
Change from baseline in CD4+ cell count (cells/mm)	105 (57)	(-93, 338)	149 (23)	(-17, 291)
Change from baseline in CD4+ percent	5.1 (57)	(1, 9.3)	8 (23)	(0, 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

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

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

5.2 PHARMACOKINETIC PROPERTIES

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected patients. The PK variability of dolutegravir is between low to moderate. In Phase I studies in healthy patients, between-patient CVb% for AUC and C_{max} ranged from ~20 to 40% and C_T from 30 to 65% across studies. The between-patient PK variability of DTG was higher in HIV-infected patients than healthy patients and CVb% was estimated to be 30-50% for AUC and C_{max}, and at 55-140% for C_τ. Within-patient variability (CVw%) is lower than between-patient variability.

The relative bioavailability of dispersible tablets is approximately 1.6-fold higher as compared to film-coated tablets. Thus, a 30 mg DTG dose administered as six 5 mg dispersible tablets will have similar exposure to a 50 mg DTG dose administered as film-coated tablet(s). Similarly, a 25 mg DTG dose administered as five 5 mg dispersible tablets, will provide comparable exposure to a 40 mg DTG 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 film-coated tablet or dispersible tablet formulations. The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, in general, dolutegravir exhibited nonlinear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 to 100 mg; however increase in dolutegravir exposure appears dose proportional from 25 mg to 50 mg.

Dolutegravir may be administered with or without food. Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate, and high fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 34%, 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 may be clinically relevant in the presence of certain integrase class resistance. Therefore, TIVICAY is recommended to be taken with food by patients infected with HIV with integrase class resistance (see section 4.2).

No formal food effect studies were conducted for dispersible tablets. However, based on population pharmacokinetic analysis, a higher food effect is not expected for the dispersible tablet compared to the film coated tablet.

The absolute bioavailability of dolutegravir has not been established.

Distribution
Dolutegravir is highly bound (approximately 99.3%) to human plasma proteins based on *in vitro* data. The apparent volume of distribution (following oral administration of suspension formulation, Vd/F) is estimated at 12.5 L. Binding of dolutegravir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components. Free fraction of dolutegravir in plasma is estimated at approximately 0.2 to 1.1% in healthy patients, approximately 0.4 to 0.5% in patients with moderate hepatic impairment, and 0.8 to 1.0% in patients with severe renal impairment and 0.5% in HIV-1 infected patients.

Dolutegravir is present in cerebrospinal fluid (CSF). In 12 treatment naïve subjects receiving a regimen of dolutegravir plus abacavir/lamivudine (3TC) for 16 weeks, dolutegravir concentrations observed in CSF at both Week 2 and Week 16 exceed the *in vitro* IC_{50} against wild-type viruses (0.2 ng/mL) for all participants.

CSF: plasma concentration ratio of DTG ranged from 0.11 to 2.04%. Dolutegravir concentrations in CSF exceeded the IC_{50}, supporting the median reduction from baseline in CSF HIV-1 RNA of 2.2 log after 2 weeks and 3.4 log after 16 weeks of therapy (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

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 metabolised via UGT1A1 with a minor CYP3A component (9.7% of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged drug is low (< 1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed 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).

Excretion
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 dolutegravir 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 12.

Table 12 Summary of DTG PK Parameters following Administration of DTG at Weight Band Doses in Paediatric HIV-1 Infected Subjects

Weight Band (kg)	DTG 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] FCT	30 50	9 49	7.16 (26) 4.92 (40)	71.53 (26) 54.98 (43)	759 (73) 778 (62)
Target: Geometric Mean (range)					46 (37-134)	995 (697-2260)

DT=dispersible tablet

FCT=film-coated tablet

a. The bioavailability of DTG DT is ~1.6-fold DTG 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 patients 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 patients with severe renal impairment (CrCl < 30 mL/min). No clinically important pharmacokinetic differences between patients with severe renal impairment (CrCl < 30 mL/min) and matching healthy patients were observed. No dosage adjustment is necessary for patients with renal impairment. Caution is warranted for INI-experienced patients (with certain INI-associated resistance substitutions or clinically suspected INI-resistance) with severe renal impairment, as the decrease in dolutegravir concentrations may result in loss of therapeutic effect and development of resistance to dolutegravir or other co-administered antiretroviral agents. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Hepatic impairment

Dolutegravir is primarily metabolised and eliminated by the liver. In a study comparing 8 patients with moderate hepatic impairment (Child-Pugh category B) to 8 matched healthy adult

controls, the single 50 mg dose exposure of dolutegravir film-coated tabelts 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 pharmacogenomic samples collected in clinical studies in healthy patients, patients with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with patients with genotypes associated with normal metabolism via UGT1A1 (n = 41). Polymorphisms in CYP3A4, CYP3A5, and NR1I2 were not associated with differences in the pharmacokinetics of dolutegravir.

Gender

The dolutegravir exposure in healthy patients appear to be slightly higher (~20%) in women than men based on data obtained in a healthy patient study (males n = 17, females n = 24). 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 patients appear similar to observed parameters in Western (US) patients.

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 patients with hepatitis B co-infection.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Dolutegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay.

Carcinogenicity
In long-term oral carcinogenicity studies conducted with dolutegravir no drug-related increases in tumour incidence were found in mice at doses up to 500 mg/kg/day (14 times the human systemic exposure based on AUC at the maximum recommended dose of 50 mg BID) or in rats at doses up to 50 mg/kg/day (12 times the human systemic exposure based on AUC at the maximum recommended dose).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

TIVICAY film-coated tablets also contain: mannitol, microcrystalline cellulose, povidone, sodium starch glycolate type A, sodium stearylfumarate, polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, and iron oxide yellow (25 mg and 50 mg tablets only).

TIVICAY PD dispersible tablets also contain: mannitol, microcrystalline cellulose, povidone, sodium starch glycolate type A, silicified microcrystalline cellulose, crospovidone, sodium stearylfumarate, purified water, calcium sulfate dihydrate, sucralose, Strawberry Cream Flavour PHS-132963, titanium dioxide, hypromellose and polyethylene glycol.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

Film-coated tablets

10 mg tablets only – Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Do not remove desiccant.

Dispersible tablets

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

6.5 NATURE AND CONTENTS OF CONTAINER

Film-coated tablets

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

Dispersible tablets

TIVICAY PD dispersible tablets are supplied in HDPE (high density polyethylene) bottles containing 60 tablets. The bottles contain a desiccant.

A dosing cup and syringe are supplied with the pack.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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

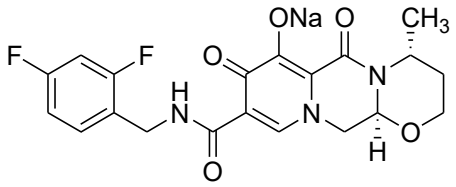
Molecular formula: $C_{20}H_{18}F_2N_3NaO_5$.

Molecular weight of 441.36 g/mol.

The partition coefficient (log P) for dolutegravir sodium is 2.2 and the pKa is 8.2.

Dolutegravir sodium is slightly soluble in water.

Chemical structure



CAS number
1051375-19-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

ViiV Healthcare Pty Ltd

Level 4, 436 Johnston Street,

Abbotsford, Victoria, 3067

9 DATE OF FIRST APPROVAL

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Inclusion of serum lipids and blood glucose level increase

Version 19.0