ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tivicay 10 mg film-coated tablets
Tivicay 25 mg film-coated tablets
Tivicay 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tivicay 10 mg film-coated tablets

Each film-coated tablet contains dolutegravir sodium equivalent to 10 mg dolutegravir.

Tivicay 25 mg film-coated tablets

Each film-coated tablet contains dolutegravir sodium equivalent to 25 mg dolutegravir.

Tivicay 50 mg film-coated tablets

Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Tivicay 10 mg film-coated tablets

White, round, biconvex tablets approximately 6 mm in diameter debossed with ‘SV 572’ on one side and ‘10’ on the other side.

Tivicay 25 mg film-coated tablets

Pale yellow, round, biconvex tablets approximately 7 mm in diameter debossed with ‘SV 572’ on one side and ‘25’ on the other side.

Tivicay 50 mg film-coated tablets

Yellow, round, biconvex tablets approximately 9 mm in diameter debossed with ‘SV 572’ on one side and ‘50’ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children of at least 6 years of age or older and weighing at least 14 kg.

4.2 Posology and method of administration

Tivicay should be prescribed by physicians experienced in the management of HIV infection.

Posology

Adults

Patients infected with HIV-1 without documented or clinically suspected resistance to the integrase class
The recommended dose of dolutegravir is 50 mg orally once daily.

Dolutegravir should be administered twice daily in this population when co-administered with some medicines (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin). Please refer to section 4.5.

Patients infected with HIV-1 with resistance to the integrase class (documented or clinically suspected)
The recommended dose of dolutegravir is 50 mg twice daily.

In the presence of documented resistance that includes Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I, modelling suggests that an increased dose may be considered for patients with limited treatment options (less than 2 active agents) due to advanced multi class resistance (see section 5.2).

The decision to use dolutegravir for such patients should be informed by the integrase resistance pattern (see section 5.1).

Adolescents aged 12 and above, to less than 18 years, and weighing at least 20 kg

In patients infected with HIV-1 without resistance to the integrase class, the recommended dose of dolutegravir is 50 mg once daily. Alternatively, if preferred 25 mg may be taken twice daily (see section 5.2). In the presence of integrase inhibitor resistance, there are insufficient data to recommend a dose for dolutegravir in adolescents.

Children aged 6 and above, to less than 12 years, and weighing at least 14 kg

In patients infected with HIV-1 without resistance to the integrase class, the recommended dose of dolutegravir is determined according to the weight of the child (see Table 1 and section 5.2).

Table 1 Paediatric dose recommendations for film-coated tablets

Body weight (kg)	**Dose**
14 to less than 20	40 mg once daily
20 or greater	50 mg once daily

Alternatively, if preferred the dose may be divided equally into 2 doses, with one dose taken in the morning and one dose taken in the evening (see Table 2 and section 5.2).

Table 2 Alternative paediatric dose recommendations for film-coated tablets

Body weight (kg)	**Dose**
14 to less than 20	20 mg twice daily
20 or greater	25 mg twice daily

In the presence of integrase inhibitor resistance, there are insufficient data to recommend a dose for dolutegravir in children.

Dispersible Tablets
Tivicay is available as film-coated tablets for patients aged 6 years and above and weighing at least 14 kg. Tivicay is also available as dispersible tablets for patients aged 4 weeks and above and weighing at least 3 kg, or for patients in whom film-coated tablets are not appropriate. Patients can change between film-coated tablets and dispersible tablets. However, the bioavailability of film-coated tablets and dispersible tablets is not comparable, therefore they are not interchangeable on a milligram per milligram basis (see section 5.2). 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.

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

Elderly
There are limited data available on the use of dolutegravir in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2).

Renal impairment
No dosage adjustment is required in patients with mild, moderate or severe (CrCl <30 mL/min, not on dialysis) renal impairment. No data are available in subjects receiving dialysis although differences in pharmacokinetics are not expected in this population (see section 5.2).

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); therefore dolutegravir should be used with caution in these patients (see section 5.2).

Paediatric population
Dolutegravir is also available in dispersible tablets for children aged 4 weeks and above and weighing at least 3 kg. However, the safety and efficacy of dolutegravir in children aged less than 4 weeks or weighing less than 3 kg have not yet been established. In the presence of integrase inhibitor resistance, there are insufficient data to recommend a dose for dolutegravir in children and adolescents. Currently available data are described in section 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration

Oral use.
Tivicay can be taken with or without food (see section 5.2). In the presence of integrase class resistance, Tivicay should preferably be taken with food to enhance exposure (particularly in patients with Q148 mutations) (see section 5.2).

To reduce the risk of choking, patients should 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Medicinal products with narrow therapeutic windows that are substrates of organic cation transporter 2 (OCT2), including but not limited to fampridine (also known as dalfampridine; see section 4.5).

4.4 Special warnings and precautions for use

Integrase class resistance of particular concern

The decision to use dolutegravir in the presence of integrase class resistance should take into account that the activity of dolutegravir is considerably compromised for viral strains harbouring Q148+≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I (see section 5.1). To what extent dolutegravir provides added efficacy in the presence of such integrase class resistance is uncertain (see section 5.2).

Hypersensitivity reactions

Hypersensitivity reactions have been reported with dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dolutegravir and other suspect medicinal products should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with dolutegravir or other suspect active substances after the onset of hypersensitivity may result in a life-threatening allergic reaction.

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens 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 CART. Relevant examples are *Cytomegalovirus* retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution, however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Liver biochemistry 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 biochemistries is recommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B co-infected patients (see section 4.8).

Opportunistic infections

Patients should be advised that dolutegravir or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Drug interactions

Factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance. This includes co-administration with medicinal products that reduce dolutegravir exposure (e.g. magnesium/ aluminium-containing antacid, iron and calcium supplements, multivitamins and inducing agents, etravirine (without boosted protease inhibitors), tipranavir/ritonavir, rifampicin, St. John's wort and certain anti-epileptic medicinal products) (see section 4.5).

When taken with food, Tivicay and supplements or multivitamins containing calcium, iron or magnesium can be taken at the same time. If Tivicay is administered under fasting conditions, supplements or

multivitamins containing calcium, iron or magnesium are recommended to be taken 2 hours after or 6 hours before Tivicay (see section 4.5).

Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control (see section 4.5). Metformin is eliminated renally and, therefore, it is of importance to monitor renal function when co-treated with dolutegravir. This combination may increase the risk for lactic acidosis in patients with moderate renal impairment (stage 3a creatinine clearance [CrCl] 45– 59 mL/min) and a cautious approach is recommended. Reduction of the metformin dose should be highly considered.

Osteonecrosis

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

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. For lipids and weight, there is in some cases evidence for a treatment effect. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Lamivudine and dolutegravir

The two-drug regimen of dolutegravir 50 mg once daily and lamivudine 300 mg once daily was explored in two large randomized and blinded studies, GEMINI 1 and GEMINI 2 (see section 5.1). This regimen is only suitable for the treatment of HIV-1 infection where there is no known or suspected resistance to the integrase inhibitor class, or to lamivudine.

Excipients

Tivicay contains less than 1 mmol sodium (23 mg) per tablet, that is to say is essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other agents on the pharmacokinetics of dolutegravir

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

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore, medicinal products that induce those enzymes may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir (see Table 3). Co-administration of dolutegravir and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration (see Table 3).

The absorption of dolutegravir is reduced by certain anti-acid agents (see Table 3).

Effect of dolutegravir on the pharmacokinetics of other agents

In vivo, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on *in vivo* and/or *in vitro* data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of any major enzyme or transporter such as CYP3A4, CYP2C9 and P-gp (for more information see section 5.2).

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE) 1. *In vivo*, a 10-14% decrease of creatinine clearance (secretory fraction is dependent on OCT2 and MATE-1 transport) was observed in patients. *In vivo*, dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OCT2 and/or MATE-1 (e.g. fampridine [also known as dalfampridine], metformin) (see Table 3).

In vitro, dolutegravir inhibited the renal uptake transporters, organic anion transporters (OAT1) and OAT3. Based on the lack of effect on the *in vivo* pharmacokinetics of the OAT substrate tenofovir, *in vivo* inhibition of OAT1 is unlikely. Inhibition of OAT3 has not been studied *in vivo*. Dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OAT3.

Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in Table 3.

Interaction table

Interactions between dolutegravir and co-administered medicinal products are listed in Table 3 (increase is indicated as "↑", decrease as "↓", no change as "↔", area under the concentration versus time curve as "AUC", maximum observed concentration as "Cmax", concentration at end of dosing interval as "Cτ").

Table 3: Drug Interactions

Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors		
Etravirine without boosted protease inhibitors	Dolutegravir ↓ AUC ↓ 71% C_{max} ↓ 52% Cτ ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with etravirine without boosted protease inhibitors. In paediatric patients the weight-based once daily dose should be administered twice daily. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in INI-resistant patients (see further below in table).
Lopinavir/ritonavir + etravirine	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% Cτ ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% Cτ ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary.
Efavirenz	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% Cτ ↓ 75%	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. In paediatric patients the weight-based once daily dose should be administered twice daily.

	Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	In the presence of integrase class resistance alternative combinations that do not include efavirenz should be considered (see section 4.4).
Nevirapine	Dolutegravir ↓ (Not studied, a similar reduction in exposure as observed with efavirenz is expected, due to induction)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance alternative combinations that do not include nevirapine should be considered (see section 4.4).
Rilpivirine	Dolutegravir ↔ AUC ↑ 12% C_{max} ↑ 13% Cτ ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitors		
Tenofovir	Dolutegravir ↔ AUC ↑ 1% C_{max} ↓ 3% Cτ ↓ 8% Tenofovir ↔	No dose adjustment is necessary.
Protease Inhibitors		
Atazanavir	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% Cτ ↑ 180% Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. Tivicay should not be dosed higher than 50 mg twice daily in combination with atazanavir (see section 5.2) due to lack of data.
Atazanavir/ritonavir	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 34% Cτ ↑ 121% Atazanavir ↔ Ritonavir ↔ (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. Tivicay should not be dosed higher than 50 mg twice daily in combination with atazanavir (see section 5.2) due to lack of data.
Tipranavir/ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ 59% C_{max} ↓ 47% Cτ ↓ 76% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir. In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance this combination should be avoided (see section 4.4).
Fosamprenavir/ ritonavir (FPV+RTV)	Dolutegravir ↓ AUC ↓ 35% C_{max} ↓ 24% Cτ ↓ 49% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary in the absence of integrase class resistance. In the presence of integrase class resistance alternative combinations that do not include fosamprenavir/ritonavir should be considered.

Darunavir/ritonavir	Dolutegravir ↓ AUC ↓ 22% C_{max} ↓ 11% C_{24} ↓ 38% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Lopinavir/ritonavir	Dolutegravir ↔ AUC ↓ 4% C_{max} ↔ 0% C_{24} ↓ 6%	No dose adjustment is necessary.
Other Antiviral agents		
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.
Other agents		
Potassium channel blocker		
Fampridine (also known as dalfampridine)	Fampridine ↑	Co-administration of dolutegravir has the potential to cause seizures due to increased fampridine plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Fampridine co-administration with dolutegravir is contraindicated.
Anticonvulsants		
Carbamazepine	Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33% Cτ ↓ 73%	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternatives to carbamazepine should be used where possible for INI resistant patients.
Oxcarbazepine Phenytoin Phenobarbital	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with these metabolic inducers. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include these metabolic inducers should be used where possible in INI-resistant patients.
Azole anti-fungal agents		
Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected.
Herbal products		
St. John's wort	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with St. John's wort. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include St. John's wort should be used where possible in INI-resistant patients.
Antacids and supplements		

Magnesium/ aluminium-containing antacid	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% (Complex binding to polyvalent ions)	Magnesium/ aluminium-containing antacid should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).
Calcium supplements (fasted intake)	Dolutegravir ↓ AUC ↓ 39% C_{max} ↓ 37% C_{24} ↓ 39% (Complex binding to polyvalent ions)	- When taken with food, Tivicay and supplements or multivitamins containing calcium, iron or magnesium can be taken at the same time. - If Tivicay is taken in a fasted state, such supplements should be taken a minimum 2 hours after or 6 hours before the intake of Tivicay. The stated reductions in dolutegravir exposure were observed with the intake of dolutegravir and these supplements during fasted conditions. In fed state, the changes in exposure following intake together with calcium or iron supplements were modified by the food effect, resulting in an exposure similar to that obtained with dolutegravir administered in the fasted state.
Iron supplements (fasted intake)	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% C_{24} ↓ 56% (Complex binding to polyvalent ions)	
Multivitamin (containing calcium, iron and magnesium) (fasted intake)	Dolutegravir ↓ AUC ↓ 33% C_{max} ↓ 35% C_{24} ↓ 32% (Complex binding to polyvalent ions)	
Corticosteroids		
Prednisone	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 6% Cτ ↑ 17%	No dose adjustment is necessary.
Antidiabetics		
Metformin	Metformin ↑ When co-administered with dolutegravir 50mg once daily: Metformin AUC ↑ 79% C_{max} ↑ 66% When co-administered with dolutegravir 50mg twice daily: Metformin AUC ↑ 145 % C_{max} ↑ 111%	A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when coadministered with dolutegravir, because of the increased risk for lactic acidosis in patients with moderate renal impairment due to increased metformin concentration (section 4.4).
Antimycobacterials		
Rifampicin	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 43% Cτ ↓72% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin in the absence of integrase class resistance. In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance this combination should be avoided (see section 4.4).
Rifabutin	Dolutegravir ↔ AUC ↓ 5% C_{max} ↑ 16% Cτ ↓ 30%	No dose adjustment is necessary.

	(induction of UGT1A1 and CYP3A enzymes)	
Oral contraceptives		
Ethinyl estradiol (EE) and Norelgestromin (NGMN)	Dolutegravir ↔ EE ↔ AUC ↑ 3% C_{max} ↓ 1% NGMN ↔ AUC ↓ 2% C_{max} ↓ 11%	Dolutegravir had no pharmacodynamic effect on Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and progesterone. No dose adjustment of oral contraceptives is necessary when co-administered with dolutegravir.
Analgesics		
Methadone	Dolutegravir ↔ Methadone ↔ AUC ↓ 2% C_{max} ↔ 0% Cτ ↓ 1%	No dose adjustment is necessary of either agent.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Tivicay can be used during pregnancy if clinically needed.

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative nor feto/ neonatal toxicity.

Two large birth outcome surveillance studies (more than 14,000 pregnancy outcomes) in Botswana (Tsepamo) and Eswatini, and other sources, do not indicate an increased risk for neural tube defects after dolutegravir exposure.

The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births (0.05-0.1%).

Data from the Tsepamo study show no significant difference in the prevalence of neural tube defects (0.11%) in infants whose mothers were taking dolutegravir at conception (more than 9,400 exposures) compared to those taking non-dolutegravir containing antiretroviral regimens at conception (0.11%), or compared to women without HIV (0.07%).

Data from the Eswatini study show the same prevalence of neural tube defects (0.08%) in infants whose mothers were taking dolutegravir at conception (more than 4,800 exposures), as infants of women without HIV (0.08%).

Data analysed from the Antiretroviral Pregnancy Registry (APR) of more than 1000 pregnancies with first trimester dolutegravir treatment do not indicate an increased risk of major birth defects compared to the background rate or women with HIV.

In animal reproductive toxicity studies, no adverse development outcomes, including neural tube defects, were identified (see section 5.3).

Dolutegravir crosses the placenta in humans. In pregnant women living with HIV, the median foetal umbilical cord concentration of dolutegravir was approximately 1.3-fold greater compared with the maternal peripheral plasma concentration.

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

Breast-feeding

Dolutegravir is excreted in human milk in small amounts (a median dolutegravir breast milk to maternal plasma ratio of 0.033 has been shown). There is insufficient information on the effects of dolutegravir in neonates/infants.

It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility

There are no data on the effects of dolutegravir on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be informed that dizziness has been reported during treatment with dolutegravir. The clinical status of the patient and the adverse reaction profile of dolutegravir should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The most severe adverse reaction, seen in an individual patient, was a hypersensitivity reaction that included rash and severe liver effects (see section 4.4). The most commonly seen treatment emergent adverse reactions were nausea (13%), diarrhoea (18%) and headache (13%).

Tabulated list of adverse reactions

The adverse reactions considered at least possibly related to dolutegravir are listed by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

Table 4 Adverse Reactions

Blood and lymphatic system disorders	Not known	Sideroblastic anaemia[1]
Immune system disorders	Uncommon	Hypersensitivity (see section 4.4)
	Uncommon	Immune Reconstitution Syndrome (see section 4.4)[2]
Psychiatric disorders	Common	Insomnia
	Common	Abnormal dreams
	Common	Depression
	Common	Anxiety
	Uncommon	Panic attack
	Uncommon	Suicidal ideation*, suicide attempt* *particularly in patients with a pre-existing history of depression or psychiatric illness.
	Rare	Completed suicide* *particularly in patients with a pre-existing history of depression or psychiatric illness.
Nervous system disorders	Very common	Headache
	Common	Dizziness
Gastrointestinal disorders	Very common	Nausea
	Very common	Diarrhoea
	Common	Vomiting
	Common	Flatulence
	Common	Upper abdominal pain
	Common	Abdominal pain
	Common	Abdominal discomfort
Hepatobiliary disorders	Common	Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations
	Uncommon	Hepatitis
	Rare	Acute hepatic failure, increased bilirubin[3]
Skin and subcutaneous tissue disorders	Common	Rash
	Common	Pruritus
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia
	Uncommon	Myalgia
General disorders and administration site conditions	Common	Fatigue
Investigations	Common	Creatine phosphokinase (CPK) elevations, weight increased

[1]reversible sideroblastic anaemia has been reported with dolutegravir-containing regimens. The contribution of dolutegravir in these cases is unclear.
[2]see below under Description of selected adverse reactions.
[3]in combination with increased transaminases.

Description of selected adverse reactions

Changes in laboratory biochemistries
Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 48 weeks. A mean change from baseline of 9.96 μmol/L was observed after 48 weeks of treatment. Creatinine increases were comparable by various background regimens. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate.

Co-infection with Hepatitis B or C

In Phase III studies patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn (see section 4.4).

Immune reactivation syndrome
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Paediatric population

Based on available data from the ongoing P1093 (ING112578) and ODYSSEY (201296) studies in 172 infants, children and adolescents (aged 4 weeks and above, to less than 18 years, and weighing at least 3 kg) who received the recommended doses of film-coated tablets or dispersible tablets once daily, there were no additional types of adverse reactions beyond those observed in the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is currently limited experience with overdosage in dolutegravir.

Limited experience of single higher doses (up to 250 mg in healthy subjects) revealed no specific symptoms or signs, apart from those listed as adverse reactions.

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 dolutegravir. If overdose occurs, the patient should be treated supportively with appropriate monitoring, as necessary. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, other antivirals, ATC code: J05AJ03

Mechanism of action

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.

Pharmacodynamic effects

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

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

Effect of human serum
In 100% human serum, the mean protein fold shift was 75 fold, resulting in protein adjusted IC90 of 0.064 µg/mL.

Resistance

Resistance in vitro

Serial passage is used to study resistance evolution *in vitro*. When using the lab-strain HIV-1 IIIB during passage over 112 days, mutations selected appeared slowly, with substitutions at positions S153Y and F, resulting in a maximal fold change in susceptibility of 4 (range 2-4). These mutations were not selected in patients treated with dolutegravir in the clinical studies. Using strain NL432, mutations E92Q (FC 3) and G193E (also FC 3) were selected. The E92Q mutation has been selected in patients with pre-existing raltegravir resistance who were then treated with dolutegravir (listed as a secondary mutation for dolutegravir).

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

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

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

Seven hundred and five raltegravir resistant isolates from raltegravir experienced patients were analyzed for susceptibility to dolutegravir. Dolutegravir has a less than or equal to 10 FC against 94% of the 705 clinical isolates.

Resistance in vivo
In previously untreated patients receiving dolutegravir + 2 NRTIs in Phase IIb and Phase III, no development of resistance to the integrase class, or to the NRTI class was seen (n=1118 follow-up of 48-96 weeks). In previously untreated patients receiving dolutegravir + lamivudine in the GEMINI studies through week 144 (n=716), no development of resistance to the integrase class, or to the NRTI class was seen.

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

In the presence of integrase class-resistance (VIKING-3 study) the following mutations were selected in 32 patients with protocol defined virological failure (PDVF) through Week 24 and with paired genotypes (all treated with dolutegravir 50 mg twice daily + optimized background agents): L74L/M (n=1), E92Q (n=2), T97A (n=9), E138K/A/T (n=8), G140S (n=2), Y143H (n=1), S147G (n=1), Q148H/K/R (n=4), and N155H (n=1) and E157E/Q (n=1). Treatment emergent integrase resistance typically appeared in patients with a history of the Q148-mutation (baseline or historic). Five further subjects experienced PDVF between weeks 24 and 48, and 2 of these 5 had treatment emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were L74I (n=1), N155H (n=2).

The VIKING-4 study examined dolutegravir (plus optimized background therapy) in subjects with primary genotypic resistance to INIs at Screening in 30 subjects. Treatment-emergent mutations observed were consistent with those observed in the VIKING-3 study.

In paediatric patients with prior failed therapies, but naïve to the integrase class, the integrase inhibitor substitution G118R was observed in 5/159 patients treated with dolutegravir, given in combination with an investigator selected background regimen. Of these five, 4 participants had additional integrase associated substitutions as follows: L74M, E138E/K, E92E/Q and T66I. Four of the 5 participants with emergent G118R had phenotypic data available. Dolutegravir FC (fold change as compared to wildtype virus) for these four participants ranged from 6 to 25-fold.

Effects on electrocardiogram

No relevant effects were seen on the QTc interval, with doses exceeding the clinical dose by approximately three fold.

Clinical efficacy and safety

Previously untreated patients
The efficacy of dolutegravir in HIV-infected, therapy naïve subjects is based on the analyses of 96-week data from two randomized, international, double-blind, active-controlled trials, SPRING-2 (ING113086) and SINGLE (ING114467). This is supported by 96 week data from an open-label, randomized and active-controlled study FLAMINGO (ING114915) and additional data from the open-label phase of SINGLE to 144 weeks. The efficacy of dolutegravir in combination with lamivudine in adults is supported by 144-week data from two identical 148-week, randomised, multicentre, double-blind, non-inferiority studies GEMINI-1 (204861) and GEMINI-2 (205543).

In SPRING-2, 822 adults were randomized and received at least one dose of either dolutegravir 50 mg once daily or raltegravir (RAL) 400 mg twice daily, both administered with either ABC/3TC or TDF/FTC. At baseline, median patient age was 36 years, 14% were female, 15% non-white, 11% had hepatitis B and/or C co-infection and 2% were CDC Class C, these characteristics were similar between treatment groups.

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

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

Table 5 Response in SPRING-2 and SINGLE at 48 Weeks (Snapshot algorithm, <50 copies/mL)

	SPRING-2		**SINGLE**	
	Dolutegravir 50 mg Once Daily + 2 NRTI N=411	**RAL 400 mg Twice Daily + 2 NRTI N=411**	**Dolutegravir 50 mg + ABC/3TC Once Daily N=414**	**EFV/TDF/FTC Once Daily N=419**
HIV-1 RNA <50 copies/mL	88%	85%	88%	81%
Treatment Difference*	2.5% (95% CI: -2.2%, 7.1%)		7.4% (95% CI: 2.5%, 12.3%)	
Virologic non-response†	5%	8%	5%	6%
HIV-1 RNA <50 copies/mL by baseline covariates				
Baseline Viral Load (cps/mL)				
≤100,000	267 / 297 (90%)	264 / 295 (89%)	253 / 280 (90%)	238 / 288 (83%)
>100,000	94 / 114 (82%)	87 / 116 (75%)	111 / 134 (83%)	100 / 131 (76%)
Baseline CD4+ (cells/ mm^3)				
<200	43 / 55 (78%)	34 / 50 (68%)	45 / 57 (79%)	48 / 62 (77%)
200 to <350	128 / 144 (89%)	118 / 139 (85%)	143 / 163 (88%)	126 / 159 (79%)
≥350	190 / 212 (90%)	199 / 222 (90%)	176 / 194 (91%)	164 / 198 (83%)
NRTI backbone				
ABC/3TC	145 / 169 (86%)	142 / 164 (87%)	N/A	N/A
TDF/FTC	216 / 242 (89%)	209 / 247 (85%)	N/A	N/A
Gender				
Male	308 / 348 (89%)	305 / 355 (86%)	307 / 347 (88%)	291 / 356 (82%)
Female	53 / 63 (84%)	46 / 56 (82%)	57 / 67 (85%)	47 / 63 (75%)
Race				
White	306 / 346 (88%)	301 / 352 (86%)	255 / 284 (90%)	238 /285 (84%)
African-America/African Heritage/Other	55 / 65 (85%)	50 / 59 (85%)	109 / 130 (84%)	99 / 133 (74%)
Age (years)				
<50	324/370 (88%)	312/365 (85%)	319/361 (88%)	302/375 (81%)
≥50	37/41 (90%)	39/46 (85%)	45/53 (85%)	36/44 (82%)
Median CD4 change from baseline	230	230	246‡	187‡

* Adjusted for baseline stratification factors.
† Includes subjects who changed BR to new class or changed BR not permitted per protocol or due to lack of efficacy prior to Week 48 (for SPRING-2 only), subjects who discontinued prior to Week 48 for lack or loss of efficacy and subjects who are ≥50 copies in the 48 week window.
‡ Adjusted mean treatment difference was statistically significant (p<0.001)

At week 48, dolutegravir was non-inferior to raltegravir in the SPRING-2 study, and in the SINGLE study dolutegravir + ABC/3TC was superior to efavirenz/TDF/FTC (p=0.003), table 5 above. In SINGLE, the median time to viral suppression was shorter in the dolutegravir treated patients (28 vs 84 days, (p<0.0001, analysis pre-specified and adjusted for multiplicity).

At week 96, results were consistent with those seen at week 48. In SPRING-2, dolutegravir was still non-

inferior to raltegravir (viral suppression in 81% vs 76% of patients), and with a median change in CD4 count of 276 vs 264 cells/mm^3, respectively. In SINGLE, dolutegravir + ABC/3TC was still superior to EFV/TDF/FTC (viral suppression in 80% vs 72%, treatment difference 8.0% (2.3, 13.8), p=0.006, and with an adjusted mean change in CD4 count of 325 vs 281 cells/ mm^3, respectively. At 144 weeks in the open-label phase of SINGLE, virologic suppression was maintained, the dolutegravir + ABC/3TC arm (71%) was superior to the EFV/TDF/FTC arm (63%), treatment difference was 8.3% (2.0, 14.6).

In FLAMINGO (ING114915), an open-label, randomised and active-controlled study, 484 HIV-1 infected antiretroviral naïve adults received one dose of either dolutegravir 50 mg once daily (n=242) or darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily (n=242), both administered with either ABC/3TC or TDF/FTC. At baseline, median patient age was 34 years, 15% were female, 28% non-white, 10% had hepatitis B and/or C co-infection, and 3% were CDC Class C; these characteristics were similar between treatment groups. Virologic suppression (HIV-1 RNA <50 copies/mL) in the 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 96 weeks, virologic suppression in the dolutegravir group (80%) was superior to the DRV/r group (68%), (adjusted treatment difference [Dolutegravir-(DRV+RTV)]: 12.4%; 95% CI: [4.7, 20.2].

In GEMINI-1 (204861) and GEMINI-2 (205543), identical 148-week, randomised, double-blind studies, 1433 adult HIV-1 infected antiretroviral naïve subjects were randomised to either a two-drug regimen of dolutegravir 50 mg plus lamivudine 300 mg once daily, or to a three-drug regimen of dolutegravir 50 mg once daily with fixed dose TDF/FTC. Subjects were enrolled with a screening plasma HIV-1 RNA of 1000 c/mL to ≤500,000 c/mL. At baseline, in the pooled analysis, median patient age was 33 years, 15% were female, 31% non-white, 6% had hepatitis C co-infection and 9% were CDC Stage 3. Approximately one third of the patients were infected with an HIV non-B subtype; these characteristics were similar between treatment groups. Virologic suppression (HIV-1 RNA <50 copies/mL) in the dolutegravir plus lamivudine group was non-inferior to the dolutegravir plus TDF/FTC group at 48 weeks, as shown in Table 6. 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) was met. The adjusted difference was -2.6% (95% CI: -6.7; 1.5) for GEMINI-1 and -0.7% (95% CI: -4.3; 2.9) for GEMINI-2 with a prespecified non-inferiority margin of 10%.

Table 6 Response (<50 cps/ml, snapshot) in GEMINI 1 + 2, pooled data at Week 48.

	Dolutegravir + 3TC (N=716) n/N (%)	**Dolutegravir + TDF/FTC (N=717) n/N (%)**
All patients	655/716 (91)	669/717 (93)
	adjusted diff -1.7% (CI95-4.4, 1.1) [a]	
By BL HIV-1 RNA		
≤100,000 cps/mL	526/576 (91)	531/564 (94)
>100,000 cps/mL	129/140 (92)	138/153 (90)
By CD4+		
≤200 c/ mm3	50/63 (79)	51/55 (93)
>200 c/ mm3	605/653 (93)	618/662 (93)
By HIV-1 subtype		
B	424/467 (91)	452/488 (93)
Non-B	231/249 (93)	217/229 (95)
Rebound up to week 48 [b]	6 (<1)	4 (<1)
Mean change in CD4 count from baseline at Week 48, c/ mm3	224	217

[a] adjusted for BL stratification factors: Plasma HIV-1 RNA (≤100,000 cps/mL vs. >100,000 cps/mL) and CD4+ cell count (≤200 cells/mm3 vs. >200 cells/mm3).

[b] Confirmed plasma HIV-1 RNA levels to ≥200 cps/mL after prior confirmed suppression to <200 cps/mL.

At 96 weeks and at 144 weeks in the GEMINI studies, the lower bound of the 95% confidence interval for the adjusted treatment difference of proportion of subjects with HIV-1 RNA <50 copies/mL (snapshot) was greater than the non-inferiority margin of -10%, for the individual studies as well as pooled analysis, see Table 7.

Table 7 Virologic Outcomes (snapshot algorithm) in GEMINI 1 + 2, pooled data at Weeks 96 and 144

	GEMINI-1 and GEMINI-2 Pooled Data*			
	DTG + 3TC N=716	**DTG + TDF/FTC N=717**	**DTG + 3TC N=716**	**DTG + TDF/FTC N=717**
	Week 96		Week 144	
HIV-1 RNA <50 copies/mL	86%	90%	82%	84%
Treatment Difference† (95% confidence intervals)	-3.4% (-6.7, 0.0)		-1.8% (-5.8; 2.1)	
Virologic non response	3%	2%	3%	3%
Reasons				
Data in window, ≥50 cps/mL	<1%	<1%	<1%	<1%
Discontinued, lack of efficacy	1%	<1%	1%	<1%
Discontinued, other reasons, ≥50 cps/mL	<1%	<1%	<1%	2%
Change in ART	<1%	<1%	<1%	<1%
No virologic data at Week 96/Week 144 window	11%	9%	15%	14%
Reasons				
Discontinued study due to AE or death	3%	3%	4%	4%
Discontinued study for other reasons	8%	5%	11%	9%
Loss to follow-up	3%	1%	3%	3%
Withdrew consent	3%	2%	4%	3%
Protocol deviations	1%	1%	2%	1%
Physicians decision	1%	<1%	2%	1%
Missing data in window, on study	0%	<1%	<1%	<1%

DTG=Dolutegravir
* The results of the pooled analysis are in line with those of the individual studies.
† Based on CMH-stratified analysis adjusting for the following baseline stratification factors: Plasma HIV-1 RNA (≤100,000 c/mL vs. >100,000 c/mL) and CD4+ cell count (≤200 cells/mm^3 vs. >200 cells/mm^3). Pooled analysis also stratified by study. Assessed using a non-inferiority margin of 10%.
N = Number of subjects in each treatment group

The mean increase in CD4+ T-cell counts through week 144 was 302 cells/mm^3 in the dolutegravir plus lamivudine arm and 300 cells/mm^3 in the dolutegravir plus tenofovir/emtricitabine arm.

Treatment emergent resistance in previously untreated patients failing therapy
Through 96 weeks in SPRING-2 and FLAMINGO and 144 weeks in SINGLE, no cases of treatment emergent primary resistance to the integrase- or NRTI-class were seen in the dolutegravir-containing arms. For the comparator arms, the same lack of treatment emergent resistance was also the case for patients treated with darunavir/r in FLAMINGO. In SPRING-2, four patients in the RAL-arm failed with major NRTI mutations and one with raltegravir resistance; in SINGLE, six patients in the EFV/TDF/FTC-arm failed with mutations associated with NNRTI resistance, and one developed a major NRTI mutation. Through 144 weeks in the GEMINI-1 and GEMINI-2 studies, no cases of emergent resistance to the integrase- or NRTI-class were seen in either the Dolutegravir+3TC or comparator Dolutegravir+TDF/FTC arms.

Patients with prior treatment failure, but not exposed to the integrase class

In the international multicentre, double-blind SAILING study (ING111762), 719 HIV-1 infected, antiretroviral therapy (ART)-experienced adults were randomized and received either dolutegravir 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 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 subjects had at least 3-class ART resistance at baseline.

Week 48 outcomes (including outcomes by key baseline covariates) for SAILING are shown in Table 8.

Table 8 Response in SAILING at 48 Weeks (Snapshot algorithm, <50 copies/mL)

	Dolutegravir 50 mg Once Daily + BR N=354§	**RAL 400 mg Twice Daily + BR N=361§**
HIV-1 RNA <50 copies/mL	71%	64%
Adjusted treatment difference‡	7.4% (95% CI: 0.7%, 14.2%)	
Virologic non-response	20%	28%
HIV-1 RNA <50 copies/mL by baseline covariates		
Baseline Viral Load (copies/mL)		
≤50,000 copies/mL	186 / 249 (75%)	180 / 254 (71%)
>50,000 copies/mL	65 / 105 (62%)	50 / 107 (47%)
Baseline CD4+ (cells/ mm^3)		
<50	33 / 62 (53%)	30 / 59 (51%)
50 to <200	77 / 111 (69%)	76 / 125 (61%)
200 to <350	64 / 82 (78%)	53 / 79 (67%)
≥350	77 / 99 (78%)	71 / 98 (72%)
Background Regimen		
Genotypic Susceptibility Score* <2	155 / 216 (72%)	129 / 192 (67%)
Genotypic Susceptibility Score* =2	96 / 138 (70%)	101 / 169 (60%)
Use of DRV in background regimen		
No DRV use	143 / 214 (67%)	126 / 209 (60%)
DRV use with primary PI mutations	58 / 68 (85%)	50 / 75 (67%)
DRV use without primary PI mutations	50 / 72 (69%)	54 / 77 (70%)
Gender		
Male	172 / 247 (70%)	156 / 238 (66%)
Female	79 / 107 (74%)	74 / 123 (60%)
Race		
White	133 / 178 (75%)	125 / 175 (71%)
African-America/African Heritage/Other	118 / 175 (67%)	105 / 185 (57%)
Age (years)		
<50	196 / 269 (73%)	172 / 277 (62%)
≥50	55 / 85 (65%)	58 / 84 (69%)
HIV sub type		
Clade B	173 / 241 (72%)	159 / 246 (65%)
Clade C	34 / 55 (62%)	29 / 48 (60%)
Other†	43 / 57 (75%)	42 / 67 (63%)
Mean increase in CD4+ T cell (cells/mm^3)	162	153

‡ Adjusted for baseline stratification factors.

§ 4 subjects were excluded from the efficacy analysis due to data integrity at one study site

*The Genotypic Susceptibility Score (GSS) was defined as the total number of ARTs in BR to which a subject's viral isolate showed susceptibility at baseline based upon genotypic resistance tests.

†Other clades included: Complex (43), F1 (32), A1 (18), BF (14), all others <10.

In the SAILING study, virologic suppression (HIV-1 RNA <50 copies/mL) in the Tivicay arm (71%) was statistically superior to the raltegravir arm (64%), at Week 48 (p=0.03).

Statistically fewer subjects failed therapy with treatment-emergent integrase resistance on Tivicay (4/354, 1%) than on raltegravir (17/361, 5%) (p=0.003) (refer to section 'Resistance in vivo' above for details).

Patients with prior treatment failure that included an integrase inhibitor (and integrase class resistance)
In the multicentre, open-label, single arm VIKING-3 study (ING112574), HIV-1 infected, ART-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received Tivicay 50 mg twice daily with the current failing background regimen for 7 days but with optimised background ART from Day 8. The study enrolled 183 patients, 133 with INI-resistance at Screening and 50 with only historical evidence of resistance (and not at Screening). Raltegravir/elvitegravir was part of the current failing regimen in 98/183 patients (part of prior failing therapies in the others). At baseline, median patient age was 48 years, 23% were female, 29% non-white, and 20% had hepatitis B and/or C co-infection. Median baseline CD4+ was 140 cells/mm^3, median duration of prior ART was 14 years, and 56% were CDC Class C. Subjects showed multiple class ART resistance at baseline: 79% had ≥2 NRTI, 75% ≥1 NNRTI, and 71% ≥2 PI major mutations; 62% had non-R5 virus.

Mean change from baseline in HIV RNA at day 8 (primary endpoint) was -1.4log_{10} copies/mL (95% CI -1.3 – -1.5log_{10}, p<0.001). Response was associated with baseline INI mutation pathway, as shown in Table 9.

Table 9 Virologic response (day 8) after 7 days of functional monotherapy, in patients with RAL/EVG as part of current failing regimen, VIKING 3

Baseline parameters	**Dolutegravir 50 mg BID N=88***		
	n	Mean (SD) Plasma HIV-1 RNA log_{10} c/mL	Median
Derived IN mutation group at Baseline with ongoing RAL/EVG			
Primary mutation other than Q148H/K/R[a]	48	-1.59 (0.47)	-1.64
Q148+1 secondary mutation[b]	26	-1.14 (0.61)	-1.08
Q148+≥2 secondary mutations[b]	14	-0.75 (0.84)	-0.45
*Of 98 on RAL/EVG as part of current failing regimen, 88 had detectable primary INI mutations at Baseline and a Day 8 Plasma HIV-1 RNA outcome for evaluation [a] Included primary IN resistance mutations N155H, Y143C/H/R, T66A, E92Q [b] Secondary mutations from G140A/C/S, E138A/K/T, L74I.			

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

After the functional monotherapy phase, subjects had the opportunity to re-optimize their background regimen when possible. The overall response rate through 24 weeks of therapy, 69% (126/183), was generally sustained through 48 weeks with 116/183 (63%) of patients with HIV-1 RNA <50c/mL (ITT-E, Snapshot algorithm). When excluding patients who stopped therapy for non-efficacy reasons, and those with major protocol deviations (incorrect dolutegravir dosing, intake of prohibited co-medication), namely, "the Virological Outcome (VO)-population)", the corresponding response rates were 75% (120/161, week 24) and 69% (111/160, week 48).

The response was lower when the Q148-mutation was present at baseline, and in particular in the presence of ≥2 secondary mutations, Table 10. The overall susceptibility score (OSS) of the optimised background regimen (OBR) was not associated with Week 24 response, nor with the week 48 response.

Table 10 Response by baseline Resistance, VIKING-3. VO Population (HIV-1 RNA <50 c/mL, Snapshot algorithm)

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

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

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

In the double blind, placebo controlled VIKING-4 study (ING116529), 30 HIV-1 infected, ART-experienced adults with primary genotypic resistance to INIs at Screening, were randomised to receive either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days followed by an open label phase with all subjects receiving dolutegravir. At baseline, median patient age was 49 years, 20% were female, 58% non-white, and 23% had hepatitis B and/or C co-infection. Median baseline CD4+ was 160 cells/mm^3, median duration of prior ART was 13 years, and 63% were CDC Class C. Subjects showed multiple class ART resistance at baseline: 80% had ≥2 NRTI, 73% ≥1 NNRTI, and 67% ≥2 PI major mutations; 83% had non-R5 virus. Sixteen of 30 subjects (53%) harboured Q148 virus at baseline. The primary endpoint at Day 8 showed that dolutegravir 50 mg twice daily was superior to placebo, with an adjusted mean treatment difference for the change from Baseline in Plasma HIV-1 RNA of -1.2 $\log_{10}$ copies/mL (95% CI -1.5 - -0.8$\log_{10}$ copies/mL, p<0.001). The day 8 responses in this placebo controlled study were fully in line with those seen in VIKING-3 (not placebo controlled), including by baseline integrase resistance categories. At week 48, 12/30 (40%) subjects had HIV-1 RNA <50 copies/mL (ITT-E, Snapshot algorithm).

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

Paediatric population

In an ongoing Phase I/II 48 week multicentre, open-label study (P1093/ING112578), the pharmacokinetic parameters, safety, tolerability and efficacy of dolutegravir film-coated tablets and dispersible tablets following once daily dosing 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 the recommended once daily doses of either film-coated tablets or dispersible tablets.

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

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

Q1, Q3= First and third quartiles, respectively.

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

[b] Snapshot algorithm was used in the analyses

In participants experiencing virologic failure, 5/36 acquired integrase inhibitor substitution G118R. Of these five, 4 participants had additional integrase associated substitutions as follows: L74M, E138E/K, E92E/Q and T66I. Four of the 5 participants with emergent G118R had phenotypic data available. Dolutegravir FC (fold change as compared to wildtype virus) for these four participants ranged from 6 to 25-fold.

The European Medicines Agency has deferred the obligation to submit the results of studies with Tivicay in paediatric patients aged 4 weeks to below 6 years with HIV infection (see section 4.2 for information on paediatric use).

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

5.2 Pharmacokinetic properties

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

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

Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate, and high fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 33%, 41%, and 66%, increased C_{max} by 46%, 52%, and 67%, prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively for the film-coated tablet. 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).

The absolute bioavailability of dolutegravir has not been established.

Distribution

Dolutegravir is highly bound (>99%) to human plasma proteins based on *in vitro* data. The apparent volume of distribution is 17 L to 20 L in HIV-infected patients, based on a population pharmacokinetic analysis. Binding of dolutegravir to plasma proteins is independent of dolutegravir concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin (<35 g/L) as seen in subjects with moderate hepatic impairment.

Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve subjects on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/mL (comparable to unbound plasma concentration, and above the IC50).

Dolutegravir is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue and vaginal tissue were 6-10% of those in corresponding plasma at steady state. AUC in semen was 7% and 17% in rectal tissue of those in corresponding plasma at steady state.

Biotransformation

Dolutegravir is primarily metabolized through glucuronidation via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged active substance 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 active substance or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-two 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).

Drug interactions

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC50>50 μM) of the enzymes cytochrome P_{450} (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. Based on this data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of major enzymes or transporters (see section 4.5).

In vitro, dolutegravir was not a substrate of human OATP 1B1, OATP 1B3 or OCT 1.

Elimination

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

Linearity/non-linearity

The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of film-coated 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 for the film-coated tablet

formulation. With 50 mg film-coated tablet twice daily, the exposure over 24 hours was approximately doubled compared to 50 mg film-coated tablet once daily.

Pharmacokinetic/pharmacodynamic relationship(s)

In a randomized, dose-ranging trial, HIV-1–infected subjects treated with dolutegravir monotherapy (ING111521) demonstrated rapid and dose-dependent antiviral activity, with mean decline in HIV-1 RNA of 2.5 $\log_{10}$ at day 11 for 50 mg dose. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg film-coated tablet 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.

Special patient populations

Children
The pharmacokinetics of dolutegravir given once daily as 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 simulated plasma exposure at once daily weight band doses is summarized in Table 12.

Table 12 Summary of Simulated Dolutegravir PK Parameters at Once Daily Doses by Weight Band in Paediatric HIV-1 Infected Subjects

Weight Band (kg)	Dolutegravir Dosage Form[a]	Once Daily Dose (mg)	PK Parameter Geometric Mean (90% CI)		
			Cmax (μg/mL)	AUC0-24h (μg*h/mL)	C24h (ng/mL)
3 to <6	DT	5	4.02 (2.12, 7.96)	49.4 (21.6, 115)	1070 (247, 3830)
6 to <10[b]	DT	10	5.90 (3.23, 10.9)	67.4 (30.4, 151)	1240 (257, 4580)
6 to <10[c]	DT	15	6.67 (3.75, 12.1)	68.4 (30.6, 154)	964 (158, 4150)
10 to <14	DT	20	6.61 (3.80, 11.5)	63.1 (28.9, 136)	719 (102, 3340)
14 to <20	DT	25	7.17 (4.10, 12.6)	69.5 (32.1, 151)	824 (122, 3780)
	FCT	40	6.96 (3.83, 12.5)	72.6 (33.7, 156)	972 (150, 4260)
20 to <25	DT	30	7.37 (4.24, 12.9)	72.0 (33.3, 156)	881 (137, 3960)
	FCT	50	7.43 (4.13, 13.3)	78.6 (36.8, 171)	1080 (178, 4690)
25 to <30	FCT	50	6.74 (3.73, 12.1)	71.4 (33.2, 154)	997 (162, 4250)
30 to <35	FCT	50	6.20 (3.45, 11.1)	66.6 (30.5, 141)	944 (154, 4020)
≥35	FCT	50	4.93 (2.66, 9.08)	54.0 (24.4, 118)	814 (142, 3310)
Target: Geometric Mean				**46 (37-134)**	**995 (697-2260)**

DT=dispersible tablet
FCT=film-coated tablet
a. The bioavailability of dolutegravir DT is ~1.6-fold dolutegravir FCT.
b. <6 months of age
c. ≥6 months of age

Steady state simulated plasma exposure at alternative twice daily weight band doses are summarized in Table 13. In contrast to once daily dosing, simulated data for alternative twice daily dosing have not been confirmed in clinical trials.

Table 13 Summary of Simulated Dolutegravir PK Parameters at Alternative Twice Daily Doses by Weight Band in Paediatric HIV-1 Infected Subjects

Weight Band (kg)	Dolutegravir Dosage Form[a]	Twice Daily Dose (mg)	PK Parameter Geometric Mean (90% CI)		
			Cmax (µg/mL)	AUC0-12h (µg*h/mL)	C12h (ng/mL)
6 to <10[b]	DT	5	4.28 (2.10, 9.01)	31.6 (14.6, 71.4)	1760 (509, 5330)
6 to <10c	DT	10	6.19 (3.15, 12.6)	43.6 (19.4, 96.9)	2190 (565, 6960)
10 to <14	DT	10	4.40 (2.27, 8.68)	30.0 (13.5, 66.0)	1400 (351, 4480)
14 to <20	DT	15	5.78 (2.97, 11.4)	39.6 (17.6, 86.3)	1890 (482, 6070)
	FCT	20	4.98 (2.55, 9.96)	35.9 (16.5, 77.4)	1840 (496, 5650)
20 to <25	DT	15	5.01 (2.61, 9.99)	34.7 (15.8, 76.5)	1690 (455, 5360)
	FCT	25	5.38 (2.73, 10.8)	39.2 (18.1, 85.4)	2040 (567, 6250)
25 to <30	DT	15	4.57 (2.37, 9.05)	32.0 (14.6, 69.1)	1580 (414, 4930)
	FCT	25	4.93 (2.50, 9.85)	35.9 (16.4, 77.4)	1910 (530, 5760)
30 to <35	FCT	25	4.54 (2.31, 9.10)	33.3 (15.3, 72.4)	1770 (494, 5400)
≥35	FCT	25	3.59 (1.76, 7.36)	26.8 (12.1, 58.3)	1470 (425, 4400)

DT=dispersible tablet
FCT=film-coated tablet
a. The bioavailability of dolutegravir DT is ~1.6-fold dolutegravir FCT.
b. <6 months of age
c. ≥6 months of age

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

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

Renal impairment
Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of a single 50 mg dose of dolutegravir film-coated tablets was performed in subjects with severe renal impairment (CLcr <30 mL/min) and matched healthy controls. The exposure to dolutegravir was decreased by approximately 40% in subjects with severe renal impairment. The mechanism for the decrease is unknown. No dosage adjustment is considered necessary for patients with renal impairment. Tivicay has not been studied in patients on dialysis.

Hepatic impairment
Dolutegravir is primarily metabolized and eliminated by the liver. A single 50 mg dose of dolutegravir film-coated tablets was administered to 8 subjects with moderate hepatic impairment (Child-Pugh class B) and to 8 matched healthy adult controls. While the total dolutegravir concentration in plasma was similar, a 1.5- to 2-fold increase in unbound exposure to dolutegravir was observed in subjects with moderate hepatic impairment compared to healthy controls. No dosage adjustment is considered necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of Tivicay has not been studied.

Polymorphisms in drug metabolising enzymes
There is no evidence that common polymorphisms in drug metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n=7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n=41).

Gender
Population PK analyses using pooled pharmacokinetic data from Phase IIb and Phase III adult trials revealed no clinically relevant effect of gender on the exposure of dolutegravir.

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

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

5.3 Preclinical safety data

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

Dolutegravir did not affect male or female fertility in rats at doses up to 1000 mg/kg/day, the highest dose tested (24 times the 50 mg twice daily human clinical exposure based on AUC).

In reproductive toxicity studies in animals, dolutegravir was shown to cross the placenta.

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

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

In a juvenile toxicity study in rats, dolutegravir administration resulted in two preweanling deaths at 75 mg/kg/day. Over the preweaning treatment period, mean body weight gain was decreased in this group and the decrease persisted throughout the entire study for females during the postweaning period. The systemic exposure at this dose (based on AUC) to dolutegravir was ~17-20-fold higher than humans at the recommended pediatric exposure. There were no new target organs identified in juveniles compared to adults. In the rat pre/post-natal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 27 times human exposure at the maximum recommended human dose).

The effect of prolonged daily treatment with high doses of dolutegravir has been evaluated in repeat oral dose toxicity studies in rats (up to 26 weeks) and in monkeys (up to 38 weeks). The primary effect of dolutegravir was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures approximately 21 and 0.82 times the 50 mg twice daily human clinical exposure based on AUC, respectively. Because gastrointestinal (GI) intolerance is considered to be due to local active substance administration, mg/kg or mg/m^2 metrics are appropriate determinates of safety cover for this toxicity. GI intolerance in monkeys occurred at 15 times the human mg/kg equivalent dose (based on a 50 kg human), and 5 times the human mg/m^2 equivalent dose for a clinical dose of 50 mg twice daily.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol (E421)
Microcrystalline cellulose
Povidone
Sodium starch glycolate
Sodium stearyl fumarate

Tablet coating

Poly(vinyl alcohol) partially hydrolyzed
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide yellow (E172) (*for 25 mg and 50 mg tablets*)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Tivicay 10 mg film-coated tablets

5 years

Tivicay 25 mg film-coated tablets

4 years

Tivicay 50 mg film-coated tablets

5 years

6.4 Special precautions for storage

Tivicay 10 mg film-coated tablets

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

Tivicay 25 mg and 50 mg film-coated tablets

This medicinal product does not require any special storage conditions.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

HDPE (high density polyethylene) bottles closed with child resistant polypropylene screw closures, with a polyethylene faced induction heat seal liner. The bottles contain 30 or 90 film-coated tablets.

Tivicay 10 mg film-coated tablets
Each bottle contains a desiccant.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/892/001
EU/1/13/892/002
EU/1/13/892/003

EU/1/13/892/004
EU/1/13/892/005
EU/1/13/892/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 January 2014
Date of latest renewal: 21 September 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Tivicay 5 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains dolutegravir sodium equivalent to 5 mg dolutegravir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet.
White, round, biconvex tablets approximately 6 mm in diameter debossed with 'SV H7S' on one side and '5' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children of at least 4 weeks of age or older and weighing at least 3 kg.

4.2 Posology and method of administration

Tivicay should be prescribed by physicians experienced in the management of HIV infection.

Posology

Adults

Patients infected with HIV-1 without documented or clinically suspected resistance to the integrase class
The recommended dose of dolutegravir is 30 mg (six 5 mg dispersible tablets) orally once daily.

Dolutegravir should be administered twice daily in this population when co-administered with some medicines (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin). Please refer to section 4.5.

Patients infected with HIV-1 with resistance to the integrase class (documented or clinically suspected)
The recommended dose of dolutegravir is 30 mg (six 5 mg dispersible tablets) twice daily.

In the presence of documented resistance that includes Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I, modelling suggests that an increased dose may be considered for patients with limited treatment options (less than 2 active agents) due to advanced multi class resistance (see section 5.2).

The decision to use dolutegravir for such patients should be informed by the integrase resistance pattern (see section 5.1).

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

Patients infected with HIV-1 without resistance to the integrase class
The recommended dose of dolutegravir is determined according to weight and age (see Table 1 and section 5.2).

Table 1 Paediatric dose recommendations for dispersible tablets

Body weight (kg)	**Dose**
3 to less than 6	5 mg once daily
6 to less than 10 < 6 months ≥ 6 months	 10 mg once daily 15 mg once daily
10 to less than 14	20 mg once daily
14 to less than 20	25 mg once daily
20 or greater	30 mg once daily

Alternatively, if preferred the dose may be divided equally into 2 doses, with one dose taken in the morning and one dose taken in the evening (see Table 2 and section 5.2).

Table 2 Alternative paediatric dose recommendations for dispersible tablets

Body weight (kg)	**Dose**
3 to less than 6	---
6 to less than 10 < 6 months ≥ 6 months	 5 mg twice daily 10 mg twice daily
10 to less than 14	10 mg twice daily
14 to less than 20	15 mg twice daily
20 or greater	15 mg twice daily

Patients infected with HIV-1 with resistance to the integrase class
There are insufficient data to recommend a dose for dolutegravir in integrase inhibitor resistant adolescents, children and infants.

Film-coated tablets
Tivicay is available as dispersible tablets for patients aged 4 weeks and above and weighing at least 3 kg, or for patients in whom film-coated tablets are not appropriate. Tivicay is available as film-coated tablets for patients aged 6 years and above and weighing at least 14 kg. Patients can change between dispersible tablets and film-coated tablets. However, the bioavailability of dispersible tablets and film-coated tablets is not comparable, therefore they are not interchangeable on a milligram per milligram basis (see section 5.2). For example, the recommended adult dose for dispersible tablets is 30 mg versus 50 mg for film-coated tablets. Patients changing between dispersible and film-coated tablets should follow the dosing recommendations that are specific for the formulation.

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

Elderly
There are limited data available on the use of dolutegravir in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2).

Renal impairment
No dosage adjustment is required in patients with mild, moderate or severe (CrCl <30 mL/min, not on dialysis) renal impairment. No data are available in subjects receiving dialysis although differences in pharmacokinetics are not expected in this population (see section 5.2).

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); therefore dolutegravir should be used with caution in these patients (see section 5.2).

Paediatric population
The safety and efficacy of dolutegravir in children aged less than 4 weeks or weighing less than 3 kg have not yet been established. There are insufficient data to recommend a dose for dolutegravir in integrase inhibitor resistant adolescents, children and infants. Currently available data are described in section 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration

Oral use.
Tivicay can be taken with or without food (see section 5.2). In the presence of integrase class resistance, Tivicay should preferably be taken with food to enhance exposure (particularly in patients with Q148 mutations) (see section 5.2). The dispersible tablets may be dispersed in drinking water, or swallowed whole with 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. However, tablets should not be chewed, cut or crushed. The dose of medicine must be given within 30 minutes of preparation. If it has been more than 30 minutes the dose should be washed away and a new dose should be prepared. Comprehensive instructions for dispersing the tablet are provided in the package leaflet (see Step-by-step instructions for use).

If swallowing tablets whole, patients should not swallow more than one tablet at a time, to reduce the risk of choking.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Medicinal products with narrow therapeutic windows that are substrates of organic cation transporter 2 (OCT2), including but not limited to fampridine (also known as dalfampridine; see section 4.5).

4.4 Special warnings and precautions for use

Integrase class resistance of particular concern

The decision to use dolutegravir in the presence of integrase class resistance should take into account that the activity of dolutegravir is considerably compromised for viral strains harbouring Q148+≥2 secondary

mutations from G140A/C/S, E138A/K/T, L74I (see section 5.1). To what extent dolutegravir provides added efficacy in the presence of such integrase class resistance is uncertain (see section 5.2).

Hypersensitivity reactions

Hypersensitivity reactions have been reported with dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dolutegravir and other suspect medicinal products should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with dolutegravir or other suspect active substances after the onset of hypersensitivity may result in a life-threatening allergic reaction.

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens 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 CART. Relevant examples are *Cytomegalovirus* retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution, however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Liver biochemistry 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 biochemistries is recommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B co-infected patients (see section 4.8).

Opportunistic infections

Patients should be advised that dolutegravir or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Drug interactions

Factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance. This includes co-administration with medicinal products that reduce dolutegravir exposure (e.g. magnesium/ aluminium-containing antacid, iron and calcium supplements, multivitamins and inducing agents, etravirine (without boosted protease inhibitors), tipranavir/ritonavir, rifampicin, St. John's wort and certain anti-epileptic medicinal products) (see section 4.5).

When taken with food, Tivicay and supplements or multivitamins containing calcium, iron or magnesium can be taken at the same time. If Tivicay is administered under fasting conditions, supplements or multivitamins containing calcium, iron or magnesium are recommended to be taken 2 hours after or 6 hours before Tivicay (see section 4.5).

Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control (see section 4.5). Metformin is eliminated renally and, therefore, it is of importance to monitor renal function when co-treated with dolutegravir. This combination may increase the risk for lactic acidosis in patients with

moderate renal impairment (stage 3a creatinine clearance [CrCl] 45– 59 mL/min) and a cautious approach is recommended. Reduction of the metformin dose should be highly considered.

Osteonecrosis

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

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. For lipids and weight, there is in some cases evidence for a treatment effect. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Lamivudine and dolutegravir

The two-drug regimen of dolutegravir 50 mg film-coated tablets once daily and lamivudine 300 mg once daily was explored in two large randomized and blinded studies, GEMINI 1 and GEMINI 2 (see section 5.1). This regimen is only suitable for the treatment of HIV-1 infection where there is no known or suspected resistance to the integrase inhibitor class, or to lamivudine.

Excipients

Tivicay contains less than 1 mmol sodium (23 mg) per tablet, that is to say is essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other agents on the pharmacokinetics of dolutegravir

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

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore, medicinal products that induce those enzymes may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir (see Table 3). Co-administration of dolutegravir and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration (see Table 3).

The absorption of dolutegravir is reduced by certain anti-acid agents (see Table 3).

Effect of dolutegravir on the pharmacokinetics of other agents

In vivo, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on *in vivo* and/or *in vitro* data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of any major enzyme or transporter such as CYP3A4, CYP2C9 and P-gp (for more information see section 5.2).

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE) 1. *In vivo*, a 10-14% decrease of creatinine clearance (secretory fraction is dependent on OCT2 and MATE-1 transport) was observed in patients. *In vivo*, dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OCT2 and/or MATE-1 (e.g. fampridine [also known as dalfampridine], metformin) (see Table 3).

In vitro, dolutegravir inhibited the renal uptake transporters, organic anion transporters (OAT1) and OAT3. Based on the lack of effect on the *in vivo* pharmacokinetics of the OAT substrate tenofovir, *in vivo* inhibition of OAT1 is unlikely. Inhibition of OAT3 has not been studied *in vivo*. Dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OAT3.

Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in Table 3.

Interaction table
Interactions between dolutegravir and co-administered medicinal products are listed in Table 3 (increase is indicated as "↑", decrease as "↓", no change as "↔", area under the concentration versus time curve as "AUC", maximum observed concentration as "Cmax", concentration at end of dosing interval as "Cτ").

Table 3: Drug Interactions

Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors		
Etravirine without boosted protease inhibitors	Dolutegravir ↓ AUC ↓ 71% C_{max} ↓ 52% Cτ ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended adult dose of dolutegravir should be given twice daily when co-administered with etravirine without boosted protease inhibitors. In paediatric patients the weight-based once daily dose should be administered twice daily. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in INI-resistant patients (see further below in table).
Lopinavir/ritonavir + etravirine	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% Cτ ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% Cτ ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary.
Efavirenz	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% Cτ ↓ 75% Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir should be given twice daily when co-administered with efavirenz. In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance alternative combinations that do not include efavirenz should be considered (see section 4.4).
Nevirapine	Dolutegravir ↓ (Not studied, a similar reduction in exposure as	The recommended adult dose of dolutegravir should be given twice daily when co-administered with nevirapine. In paediatric patients the weight-

	observed with efavirenz is expected, due to induction)	based once daily dose should be administered twice daily. In the presence of integrase class resistance alternative combinations that do not include nevirapine should be considered (see section 4.4).
Rilpivirine	Dolutegravir ↔ AUC ↑ 12% C_{max} ↑ 13% Cτ ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitors		
Tenofovir	Dolutegravir ↔ AUC ↑ 1% C_{max} ↓ 3% Cτ ↓ 8% Tenofovir ↔	No dose adjustment is necessary.
Protease Inhibitors		
Atazanavir	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% Cτ ↑ 180% Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. Tivicay should not be dosed higher than 30 mg twice daily in combination with atazanavir (see section 5.2) due to lack of data.
Atazanavir/ritonavir	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 34% Cτ ↑ 121% Atazanavir ↔ Ritonavir ↔ (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. Tivicay should not be dosed higher than 30 mg twice daily in combination with atazanavir (see section 5.2) due to lack of data.
Tipranavir/ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ 59% C_{max} ↓ 47% Cτ ↓ 76% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir should be given twice daily when co-administered with tipranavir/ritonavir. In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance this combination should be avoided (see section 4.4).
Fosamprenavir/ ritonavir (FPV+RTV)	Dolutegravir ↓ AUC ↓ 35% C_{max} ↓ 24% Cτ ↓ 49% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary in the absence of integrase class resistance. In the presence of integrase class resistance alternative combinations that do not include fosamprenavir/ritonavir should be considered.
Darunavir/ritonavir	Dolutegravir ↓ AUC ↓ 22% C_{max} ↓ 11% C_{24} ↓ 38% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.

Lopinavir/ritonavir	Dolutegravir ↔ AUC ↓ 4% C_{max} ↔ 0% C_{24} ↓ 6%	No dose adjustment is necessary.
Other Antiviral agents		
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.
Other agents		
Potassium channel blocker		
Fampridine (also known as dalfampridine)	Fampridine ↑	Co-administration of dolutegravir has the potential to cause seizures due to increased fampridine plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Fampridine co-administration with dolutegravir is contraindicated.
Anticonvulsants		
Carbamazepine	Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33% Cτ ↓ 73%	The recommended adult dose of dolutegravir should be given twice daily when co-administered with carbamazepine. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternatives to carbamazepine should be used where possible for INI resistant patients.
Oxcarbazepine Phenytoin Phenobarbital	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	The recommended adult dose of dolutegravir should be given twice daily when co-administered with these metabolic inducers. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include these metabolic inducers should be used where possible in INI-resistant patients.
Azole anti-fungal agents		
Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected.
Herbal products		
St. John's wort	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	The recommended adult dose of dolutegravir should be given twice daily when co-administered with St. John's wort. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include St. John's wort should be used where possible in INI-resistant patients.
Antacids and supplements		
Magnesium/ aluminium-containing antacid	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% (Complex binding to polyvalent ions)	Magnesium/ aluminium-containing antacid should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).

Calcium supplements (fasted intake)	Dolutegravir ↓ AUC ↓ 39% C_{max} ↓ 37% C_{24} ↓ 39% (Complex binding to polyvalent ions)	- When taken with food, Tivicay and supplements or multivitamins containing calcium, iron or magnesium can be taken at the same time. - If Tivicay is taken in a fasted state, such supplements should be taken a minimum 2 hours after or 6 hours before the intake of Tivicay. The stated reductions in dolutegravir exposure were observed with the intake of dolutegravir and these supplements during fasted conditions. In fed state, the changes in exposure following intake together with calcium or iron supplements were modified by the food effect, resulting in an exposure similar to that obtained with dolutegravir administered in the fasted state.
Iron supplements (fasted intake)	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% C_{24} ↓ 56% (Complex binding to polyvalent ions)	
Multivitamin (containing calcium, iron and magnesium) (fasted intake)	Dolutegravir ↓ AUC ↓ 33% C_{max} ↓ 35% C_{24} ↓ 32% (Complex binding to polyvalent ions)	
Corticosteroids		
Prednisone	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 6% Cτ ↑ 17%	No dose adjustment is necessary.
Antidiabetics		
Metformin	Metformin ↑ When co-administered with dolutegravir 50mg film-coated tablets once daily: Metformin AUC ↑ 79% C_{max} ↑ 66% When co-administered with dolutegravir 50mg film-coated tablets twice daily: Metformin AUC ↑ 145 % C_{max} ↑ 111%	A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when coadministered with dolutegravir, because of the increased risk for lactic acidosis in patients with moderate renal impairment due to increased metformin concentration (section 4.4).
Antimycobacterials		
Rifampicin	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 43% Cτ ↓72% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir should be given twice daily when co-administered with rifampicin in the absence of integrase class resistance. In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance this combination should be avoided (see section 4.4).
Rifabutin	Dolutegravir ↔ AUC ↓ 5% C_{max} ↑ 16% Cτ ↓ 30% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Oral contraceptives		

Ethinyl estradiol (EE) and Norelgestromin (NGMN)	Dolutegravir ↔ EE ↔ AUC ↑ 3% C_{max} ↓ 1% NGMN ↔ AUC ↓ 2% C_{max} ↓ 11%	Dolutegravir had no pharmacodynamic effect on Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and progesterone. No dose adjustment of oral contraceptives is necessary when co-administered with dolutegravir.
Analgesics		
Methadone	Dolutegravir ↔ Methadone ↔ AUC ↓ 2% C_{max} ↔ 0% Cτ ↓ 1%	No dose adjustment is necessary of either agent.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Tivicay can be used during pregnancy if clinically needed.

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative nor feto/ neonatal toxicity.

Two large birth outcome surveillance studies (more than 14,000 pregnancy outcomes) in Botswana (Tsepamo) and Eswatini, and other sources, do not indicate an increased risk for neural tube defects after dolutegravir exposure.

The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births (0.05-0.1%).

Data from the Tsepamo study show no significant difference in the prevalence of neural tube defects (0.11%) in infants whose mothers were taking dolutegravir at conception (more than 9,400 exposures) compared to those taking non-dolutegravir containing antiretroviral regimens at conception (0.11%), or compared to women without HIV (0.07%).

Data from the Eswatini study show the same prevalence of neural tube defects (0.08%) in infants whose mothers were taking dolutegravir at conception (more than 4,800 exposures), as infants of women without HIV (0.08%).

Data analysed from the Antiretroviral Pregnancy Registry (APR) of more than 1000 pregnancies with first trimester dolutegravir treatment do not indicate an increased risk of major birth defects compared to the background rate or women with HIV.

In animal reproductive toxicity studies, no adverse development outcomes, including neural tube defects, were identified (see section 5.3).

Dolutegravir crosses the placenta in humans. In pregnant women living with HIV, the median foetal umbilical cord concentration of dolutegravir was approximately 1.3-fold greater compared with the maternal peripheral plasma concentration.

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

Breast-feeding

Dolutegravir is excreted in human milk in small amounts (a median dolutegravir breast milk to maternal plasma ratio of 0.033 has been shown). There is insufficient information on the effects of dolutegravir in neonates/infants.

It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility

There are no data on the effects of dolutegravir on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be informed that dizziness has been reported during treatment with dolutegravir. The clinical status of the patient and the adverse reaction profile of dolutegravir should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The most severe adverse reaction, seen in an individual patient, was a hypersensitivity reaction that included rash and severe liver effects (see section 4.4). The most commonly seen treatment emergent adverse reactions were nausea (13%), diarrhoea (18%) and headache (13%).

Tabulated list of adverse reactions

The adverse reactions considered at least possibly related to dolutegravir are listed by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

Table 4 Adverse Reactions

Blood and lymphatic system disorders	Not known	Sideroblastic anaemia[1]
Immune system disorders	Uncommon	Hypersensitivity (see section 4.4)
	Uncommon	Immune Reconstitution Syndrome (see section 4.4)[2]
Psychiatric disorders	Common	Insomnia
	Common	Abnormal dreams
	Common	Depression
	Common	Anxiety
	Uncommon	Panic attack
	Uncommon	Suicidal ideation*, suicide attempt* *particularly in patients with a pre-existing history of depression or psychiatric illness.
	Rare	Completed suicide* *particularly in patients with a pre-existing history of depression or psychiatric illness.
Nervous system disorders	Very common	Headache
	Common	Dizziness
Gastrointestinal disorders	Very common	Nausea
	Very common	Diarrhoea
	Common	Vomiting
	Common	Flatulence
	Common	Upper abdominal pain
	Common	Abdominal pain
	Common	Abdominal discomfort
Hepatobiliary disorders	Common	Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations
	Uncommon	Hepatitis
	Rare	Acute hepatic failure, increased bilirubin[3]
Skin and subcutaneous tissue disorders	Common	Rash
	Common	Pruritus
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia
	Uncommon	Myalgia
General disorders and administration site conditions	Common	Fatigue
Investigations	Common	Creatine phosphokinase (CPK) elevations, weight increased

[1]reversible sideroblastic anaemia has been reported with dolutegravir-containing regimens. The contribution of dolutegravir in these cases is unclear.
[2]see below under Description of selected adverse reactions.
[3]in combination with increased transaminases.

Description of selected adverse reactions

Changes in laboratory biochemistries
Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 48 weeks. A mean change from baseline of 9.96 μmol/L was observed after 48 weeks of treatment. Creatinine increases were comparable by various background regimens. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate.

Co-infection with Hepatitis B or C

In Phase III studies patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn (see section 4.4).

Immune reactivation syndrome
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Paediatric population

Based on available data from the ongoing P1093 (ING112578) and ODYSSEY (201296) studies in 172 infants, children and adolescents (aged 4 weeks and above, to less than 18 years, and weighing at least 3 kg), who received the recommended doses of dispersible tablets or film-coated tablets once daily, there were no additional types of adverse reactions beyond those observed in the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is currently limited experience with overdosage in dolutegravir.

Limited experience of single higher doses (up to 250 mg film-coated tablets in healthy subjects) revealed no specific symptoms or signs, apart from those listed as adverse reactions.

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 dolutegravir. If overdose occurs, the patient should be treated supportively with appropriate monitoring, as necessary. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, other antivirals, ATC code: J05AJ03

Mechanism of action

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.

Pharmacodynamic effects

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

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

Effect of human serum
In 100% human serum, the mean protein fold shift was 75 fold, resulting in protein adjusted IC90 of 0.064 µg/mL.

Resistance

Resistance in vitro

Serial passage is used to study resistance evolution *in vitro*. When using the lab-strain HIV-1 IIIB during passage over 112 days, mutations selected appeared slowly, with substitutions at positions S153Y and F, resulting in a maximal fold change in susceptibility of 4 (range 2-4). These mutations were not selected in patients treated with dolutegravir in the clinical studies. Using strain NL432, mutations E92Q (FC 3) and G193E (also FC 3) were selected. The E92Q mutation has been selected in patients with pre-existing raltegravir resistance who were then treated with dolutegravir (listed as a secondary mutation for dolutegravir).

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

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

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

Seven hundred and five raltegravir resistant isolates from raltegravir experienced patients were analyzed for susceptibility to dolutegravir. Dolutegravir has a less than or equal to 10 FC against 94% of the 705 clinical isolates.

Resistance in vivo
In previously untreated patients receiving dolutegravir + 2 NRTIs in Phase IIb and Phase III, no development of resistance to the integrase class, or to the NRTI class was seen (n=1118 follow-up of 48-96 weeks). In previously untreated patients receiving dolutegravir + lamivudine in the GEMINI studies through week 144 (n=716), no development of resistance to the integrase class, or to the NRTI class was seen.

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

In the presence of integrase class-resistance (VIKING-3 study) the following mutations were selected in 32 patients with protocol defined virological failure (PDVF) through Week 24 and with paired genotypes (all treated with a 50 mg dose of dolutegravir film-coated tablets twice daily + optimized background agents): L74L/M (n=1), E92Q (n=2), T97A (n=9), E138K/A/T (n=8), G140S (n=2), Y143H (n=1), S147G (n=1), Q148H/K/R (n=4), and N155H (n=1) and E157E/Q (n=1). Treatment emergent integrase resistance typically appeared in patients with a history of the Q148-mutation (baseline or historic). Five further subjects experienced PDVF between weeks 24 and 48, and 2 of these 5 had treatment emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were L74I (n=1), N155H (n=2).

The VIKING-4 study examined dolutegravir (plus optimized background therapy) in subjects with primary genotypic resistance to INIs at Screening in 30 subjects. Treatment-emergent mutations observed were consistent with those observed in the VIKING-3 study.

In paediatric patients with prior failed therapies, but naïve to the integrase class, the integrase inhibitor substitution G118R was observed in 5/159 patients treated with dolutegravir, given in combination with an investigator selected background regimen. Of these five, 4 participants had additional integrase associated substitutions as follows: L74M, E138E/K, E92E/Q and T66I. Four of the 5 participants with emergent G118R had phenotypic data available. Dolutegravir FC (fold change as compared to wildtype virus) for these four participants ranged from 6 to 25-fold.

Effects on electrocardiogram

No relevant effects were seen on the QTc interval with doses exceeding the clinical dose by approximately three fold.

Clinical efficacy and safety

Previously untreated patients
The efficacy of dolutegravir in HIV-infected, therapy naïve subjects is based on the analyses of 96-week data from two randomized, international, double-blind, active-controlled trials, SPRING-2 (ING113086) and SINGLE (ING114467). This is supported by 96 week data from an open-label, randomized and active-controlled study FLAMINGO (ING114915) and additional data from the open-label phase of SINGLE to 144 weeks. The efficacy of dolutegravir in combination with lamivudine in adults is supported by 144-week data from two identical 148-week, randomised, multicentre, double-blind, non-inferiority studies GEMINI-1 (204861) and GEMINI-2 (205543).

In SPRING-2, 822 adults were randomized and received at least one dose of either dolutegravir 50 mg film-coated tablets once daily or raltegravir (RAL) 400 mg twice daily, both administered with either ABC/3TC or TDF/FTC. At baseline, median patient age was 36 years, 14% were female, 15% non-white, 11% had hepatitis B and/or C co-infection and 2% were CDC Class C, these characteristics were similar between treatment groups.

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

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

Table 5 Response in SPRING-2 and SINGLE at 48 Weeks (Snapshot algorithm, <50 copies/mL)

	SPRING-2		**SINGLE**	
	Dolutegravir 50 mg Once Daily + 2 NRTI N=411	**RAL 400 mg Twice Daily + 2 NRTI N=411**	**Dolutegravir 50 mg + ABC/3TC Once Daily N=414**	**EFV/TDF/FTC Once Daily N=419**
HIV-1 RNA <50 copies/mL	88%	85%	88%	81%
Treatment Difference*	2.5% (95% CI: -2.2%, 7.1%)		7.4% (95% CI: 2.5%, 12.3%)	
Virologic non-response†	5%	8%	5%	6%
HIV-1 RNA <50 copies/mL by baseline covariates				
Baseline Viral Load (cps/mL)				
≤100,000	267 / 297 (90%)	264 / 295 (89%)	253 / 280 (90%)	238 / 288 (83%)
>100,000	94 / 114 (82%)	87 / 116 (75%)	111 / 134 (83%)	100 / 131 (76%)
Baseline CD4+ (cells/ mm^3)				
<200	43 / 55 (78%)	34 / 50 (68%)	45 / 57 (79%)	48 / 62 (77%)
200 to <350	128 / 144 (89%)	118 / 139 (85%)	143 / 163 (88%)	126 / 159 (79%)
≥350	190 / 212 (90%)	199 / 222 (90%)	176 / 194 (91%)	164 / 198 (83%)
NRTI backbone				
ABC/3TC	145 / 169 (86%)	142 / 164 (87%)	N/A	N/A
TDF/FTC	216 / 242 (89%)	209 / 247 (85%)	N/A	N/A
Gender				
Male	308 / 348 (89%)	305 / 355 (86%)	307 / 347 (88%)	291 / 356 (82%)
Female	53 / 63 (84%)	46 / 56 (82%)	57 / 67 (85%)	47 / 63 (75%)
Race				
White	306 / 346 (88%)	301 / 352 (86%)	255 / 284 (90%)	238 /285 (84%)
African-America/African Heritage/Other	55 / 65 (85%)	50 / 59 (85%)	109 / 130 (84%)	99 / 133 (74%)
Age (years)				
<50	324/370 (88%)	312/365 (85%)	319/361 (88%)	302/375 (81%)
≥50	37/41 (90%)	39/46 (85%)	45/53 (85%)	36/44 (82%)
Median CD4 change from baseline	230	230	246‡	187‡

* Adjusted for baseline stratification factors.
† Includes subjects who changed BR to new class or changed BR not permitted per protocol or due to lack of efficacy prior to Week 48 (for SPRING-2 only), subjects who discontinued prior to Week 48 for lack or loss of efficacy and subjects who are ≥50 copies in the 48 week window.
‡ Adjusted mean treatment difference was statistically significant (p<0.001)

At week 48, dolutegravir was non-inferior to raltegravir in the SPRING-2 study, and in the SINGLE study dolutegravir + ABC/3TC was superior to efavirenz/TDF/FTC (p=0.003), table 5 above. In SINGLE, the median time to viral suppression was shorter in the dolutegravir treated patients (28 vs 84 days, (p<0.0001, analysis pre-specified and adjusted for multiplicity).

At week 96, results were consistent with those seen at week 48. In SPRING-2, dolutegravir was still non-

inferior to raltegravir (viral suppression in 81% vs 76% of patients), and with a median change in CD4 count of 276 vs 264 cells/mm^3, respectively. In SINGLE, dolutegravir + ABC/3TC was still superior to EFV/TDF/FTC (viral suppression in 80% vs 72%, treatment difference 8.0% (2.3, 13.8), p=0.006, and with an adjusted mean change in CD4 count of 325 vs 281 cells/ mm^3, respectively. At 144 weeks in the open-label phase of SINGLE, virologic suppression was maintained, the dolutegravir + ABC/3TC arm (71%) was superior to the EFV/TDF/FTC arm (63%), treatment difference was 8.3% (2.0, 14.6).

In FLAMINGO (ING114915), an open-label, randomised and active-controlled study, 484 HIV-1 infected antiretroviral naïve adults received one dose of either dolutegravir 50 mg film-coated tablets once daily (n=242) or darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily (n=242), both administered with either ABC/3TC or TDF/FTC. At baseline, median patient age was 34 years, 15% were female, 28% non-white, 10% had hepatitis B and/or C co-infection, and 3% were CDC Class C; these characteristics were similar between treatment groups. Virologic suppression (HIV-1 RNA <50 copies/mL) in the 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 96 weeks, virologic suppression in the dolutegravir group (80%) was superior to the DRV/r group (68%), (adjusted treatment difference [Dolutegravir-(DRV+RTV)]: 12.4%; 95% CI: [4.7, 20.2].

In GEMINI-1 (204861) and GEMINI-2 (205543), identical 148-week, randomised, double-blind studies, 1433 adult HIV-1 infected antiretroviral naïve subjects were randomised to either a two-drug regimen of dolutegravir 50 mg film-coated tablets plus lamivudine 300 mg once daily, or to a three-drug regimen of dolutegravir 50 mg film-coated tablets once daily with fixed dose TDF/FTC. Subjects were enrolled with a screening plasma HIV-1 RNA of 1000 c/mL to ≤500,000 c/mL. At baseline, in the pooled analysis, median patient age was 33 years, 15% were female, 31% non-white, 6% had hepatitis C co-infection and 9% were CDC Stage 3. Approximately one third of the patients were infected with an HIV non-B subtype; these characteristics were similar between treatment groups. Virologic suppression (HIV-1 RNA <50 copies/mL) in the dolutegravir plus lamivudine group was non-inferior to the dolutegravir plus TDF/FTC group at 48 weeks, as shown in Table 6. 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) was met. The adjusted difference was -2.6% (95% CI: -6.7; 1.5) for GEMINI-1 and -0.7% (95% CI: -4.3; 2.9) for GEMINI-2 with a prespecified non-inferiority margin of 10%.

Table 6 Response (<50 cps/ml, snapshot) in GEMINI 1 + 2, pooled data at Week 48.

	Dolutegravir + 3TC (N=716) n/N (%)	**Dolutegravir + TDF/FTC (N=717) n/N (%)**
All patients	655/716 (91)	669/717 (93)
	adjusted diff -1.7% (CI95-4.4, 1.1) [a]	
By BL HIV-1 RNA		
≤100,000 cps/mL	526/576 (91)	531/564 (94)
>100,000 cps/mL	129/140 (92)	138/153 (90)
By CD4+		
≤200 c/ mm3	50/63 (79)	51/55 (93)
>200 c/ mm3	605/653 (93)	618/662 (93)
By HIV-1 subtype		
B	424/467 (91)	452/488 (93)
Non-B	231/249 (93)	217/229 (95)
Rebound up to week 48 [b]	6 (<1)	4 (<1)
Mean change in CD4 count from baseline at Week 48, c/ mm3	224	217

[a] adjusted for BL stratification factors: Plasma HIV-1 RNA (≤100,000 cps/mL vs. >100,000 cps/mL) and CD4+ cell count (≤200 cells/mm3 vs. >200 cells/mm3).

[b] Confirmed plasma HIV-1 RNA levels to ≥200 cps/mL after prior confirmed suppression to <200 cps/mL.

At 96 weeks and at 144 weeks in the GEMINI studies, the lower bound of the 95% confidence interval for the adjusted treatment difference of proportion of subjects with HIV-1 RNA <50 copies/mL (snapshot) was greater than the non-inferiority margin of -10%, for the individual studies as well as pooled analysis, see Table 7.

Table 7 Virologic Outcomes (snapshot algorithm) in GEMINI 1 + 2, pooled data at Weeks 96 and 144

	GEMINI-1 and GEMINI-2 Pooled Data*			
	DTG + 3TC N=716	**DTG + TDF/FTC N=717**	**DTG + 3TC N=716**	**DTG + TDF/FTC N=717**
	Week 96		Week 144	
HIV-1 RNA <50 copies/mL	86%	90%	82%	84%
Treatment Difference† (95% confidence intervals)	-3.4% (-6.7, 0.0)		-1.8% (-5.8; 2.1)	
Virologic non response	3%	2%	3%	3%
Reasons				
Data in window, ≥50 cps/mL	<1%	<1%	<1%	<1%
Discontinued, lack of efficacy	1%	<1%	1%	<1%
Discontinued, other reasons, ≥50 cps/mL	<1%	<1%	<1%	2%
Change in ART	<1%	<1%	<1%	<1%
No virologic data at Week 96/Week 144 window	11%	9%	15%	14%
Reasons				
Discontinued study due to AE or death	3%	3%	4%	4%
Discontinued study for other reasons	8%	5%	11%	9%
Loss to follow-up	3%	1%	3%	3%
Withdrew consent	3%	2%	4%	3%
Protocol deviations	1%	1%	2%	1%
Physicians decision	1%	<1%	2%	1%
Missing data in window, on study	0%	<1%	<1%	<1%

DTG=Dolutegravir

* The results of the pooled analysis are in line with those of the individual studies.

† Based on CMH-stratified analysis adjusting for the following baseline stratification factors: Plasma HIV-1 RNA (≤100,000 c/mL vs. >100,000 c/mL) and CD4+ cell count (≤200 cells/mm^3 vs. >200 cells/mm^3). Pooled analysis also stratified by study. Assessed using a non-inferiority margin of 10%.

N = Number of subjects in each treatment group

The mean increase in CD4+ T-cell counts through week 144 was 302 cells/mm^3 in the dolutegravir plus lamivudine arm and 300 cells/mm^3 in the dolutegravir plus tenofovir/emtricitabine arm.

Treatment emergent resistance in previously untreated patients failing therapy

Through 96 weeks in SPRING-2 and FLAMINGO and 144 weeks in SINGLE, no cases of treatment emergent primary resistance to the integrase- or NRTI-class were seen in the dolutegravir-containing arms. For the comparator arms, the same lack of treatment emergent resistance was also the case for patients treated with darunavir/r in FLAMINGO. In SPRING-2, four patients in the RAL-arm failed with major NRTI mutations and one with raltegravir resistance; in SINGLE, six patients in the EFV/TDF/FTC-arm failed with mutations associated with NNRTI resistance, and one developed a major NRTI mutation. Through 144 weeks in the GEMINI-1 and GEMINI-2 studies, no cases of emergent resistance to the integrase- or NRTI-class were seen in either the Dolutegravir+3TC or comparator Dolutegravir+TDF/FTC arms.

Patients with prior treatment failure, but not exposed to the integrase class

In the international multicentre, double-blind SAILING study (ING111762), 719 HIV-1 infected, antiretroviral therapy (ART)-experienced adults were randomized and received either dolutegravir 50 mg film-coated tablets 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 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 subjects had at least 3-class ART resistance at baseline.

Week 48 outcomes (including outcomes by key baseline covariates) for SAILING are shown in Table 8.

Table 8 Response in SAILING at 48 Weeks (Snapshot algorithm, <50 copies/mL)

	Dolutegravir 50 mg Once Daily + BR N=354§	**RAL 400 mg Twice Daily + BR N=361§**
HIV-1 RNA <50 copies/mL	71%	64%
Adjusted treatment difference‡	7.4% (95% CI: 0.7%, 14.2%)	
Virologic non-response	20%	28%
HIV-1 RNA <50 copies/mL by baseline covariates		
Baseline Viral Load (copies/mL)		
≤50,000 copies/mL	186 / 249 (75%)	180 / 254 (71%)
>50,000 copies/mL	65 / 105 (62%)	50 / 107 (47%)
Baseline CD4+ (cells/ mm^3)		
<50	33 / 62 (53%)	30 / 59 (51%)
50 to <200	77 / 111 (69%)	76 / 125 (61%)
200 to <350	64 / 82 (78%)	53 / 79 (67%)
≥350	77 / 99 (78%)	71 / 98 (72%)
Background Regimen		
Genotypic Susceptibility Score* <2	155 / 216 (72%)	129 / 192 (67%)
Genotypic Susceptibility Score* =2	96 / 138 (70%)	101 / 169 (60%)
Use of DRV in background regimen		
No DRV use	143 / 214 (67%)	126 / 209 (60%)
DRV use with primary PI mutations	58 / 68 (85%)	50 / 75 (67%)
DRV use without primary PI mutations	50 / 72 (69%)	54 / 77 (70%)
Gender		
Male	172 / 247 (70%)	156 / 238 (66%)
Female	79 / 107 (74%)	74 / 123 (60%)
Race		
White	133 / 178 (75%)	125 / 175 (71%)
African-America/African Heritage/Other	118 / 175 (67%)	105 / 185 (57%)
Age (years)		
<50	196 / 269 (73%)	172 / 277 (62%)
≥50	55 / 85 (65%)	58 / 84 (69%)
HIV sub type		
Clade B	173 / 241 (72%)	159 / 246 (65%)
Clade C	34 / 55 (62%)	29 / 48 (60%)
Other†	43 / 57 (75%)	42 / 67 (63%)
Mean increase in CD4+ T cell (cells/mm^3)	162	153

‡ Adjusted for baseline stratification factors.

§ 4 subjects were excluded from the efficacy analysis due to data integrity at one study site

*The Genotypic Susceptibility Score (GSS) was defined as the total number of ARTs in BR to which a subject's viral isolate showed susceptibility at baseline based upon genotypic resistance tests.

†Other clades included: Complex (43), F1 (32), A1 (18), BF (14), all others <10.

In the SAILING study, virologic suppression (HIV-1 RNA <50 copies/mL) in the Tivicay arm (71%) was statistically superior to the raltegravir arm (64%), at Week 48 (p=0.03).

Statistically fewer subjects failed therapy with treatment-emergent integrase resistance on Tivicay (4/354, 1%) than on raltegravir (17/361, 5%) (p=0.003) (refer to section 'Resistance in vivo' above for details).

Patients with prior treatment failure that included an integrase inhibitor (and integrase class resistance)
In the multicentre, open-label, single arm VIKING-3 study (ING112574), HIV-1 infected, ART-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received a 50 mg dose of Tivicay film-coated tablets twice daily with the current failing background regimen for 7 days but with optimised background ART from Day 8. The study enrolled 183 patients, 133 with INI-resistance at Screening and 50 with only historical evidence of resistance (and not at Screening). Raltegravir/elvitegravir was part of the current failing regimen in 98/183 patients (part of prior failing therapies in the others). At baseline, median patient age was 48 years, 23% were female, 29% non-white, and 20% had hepatitis B and/or C co-infection. Median baseline CD4+ was 140 cells/mm^3, median duration of prior ART was 14 years, and 56% were CDC Class C. Subjects showed multiple class ART resistance at baseline: 79% had ≥2 NRTI, 75% ≥1 NNRTI, and 71% ≥2 PI major mutations; 62% had non-R5 virus.

Mean change from baseline in HIV RNA at day 8 (primary endpoint) was -1.4log_{10} copies/mL (95% CI -1.3 – -1.5log_{10}, p<0.001). Response was associated with baseline INI mutation pathway, as shown in Table 9.

Table 9 Virologic response (day 8) after 7 days of functional monotherapy, in patients with RAL/EVG as part of current failing regimen, VIKING 3

Baseline parameters	**Dolutegravir 50 mg BID N=88***		
	n	Mean (SD) Plasma HIV-1 RNA log_{10} c/mL	Median
Derived IN mutation group at Baseline with ongoing RAL/EVG			
Primary mutation other than Q148H/K/R[a]	48	-1.59 (0.47)	-1.64
Q148+1 secondary mutation[b]	26	-1.14 (0.61)	-1.08
Q148+≥2 secondary mutations[b]	14	-0.75 (0.84)	-0.45
*Of 98 on RAL/EVG as part of current failing regimen, 88 had detectable primary INI mutations at Baseline and a Day 8 Plasma HIV-1 RNA outcome for evaluation [a] Included primary IN resistance mutations N155H, Y143C/H/R, T66A, E92Q [b] Secondary mutations from G140A/C/S, E138A/K/T, L74I.			

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

After the functional monotherapy phase, subjects had the opportunity to re-optimize their background regimen when possible. The overall response rate through 24 weeks of therapy, 69% (126/183), was generally sustained through 48 weeks with 116/183 (63%) of patients with HIV-1 RNA <50c/mL (ITT-E, Snapshot algorithm). When excluding patients who stopped therapy for non-efficacy reasons, and those with major protocol deviations (incorrect dolutegravir dosing, intake of prohibited co-medication), namely, "the Virological Outcome (VO)-population)", the corresponding response rates were 75% (120/161, week 24) and 69% (111/160, week 48).

The response was lower when the Q148-mutation was present at baseline, and in particular in the presence of ≥2 secondary mutations, Table 10. The overall susceptibility score (OSS) of the optimised background regimen (OBR) was not associated with Week 24 response, nor with the week 48 response.

Table 10 Response by baseline Resistance, VIKING-3. VO Population (HIV-1 RNA <50 c/mL, Snapshot algorithm)

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

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

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

In the double blind, placebo controlled VIKING-4 study (ING116529), 30 HIV-1 infected, ART-experienced adults with primary genotypic resistance to INIs at Screening, were randomised to receive either dolutegravir 50 mg film-coated twice daily or placebo with the current failing regimen for 7 days followed by an open label phase with all subjects receiving dolutegravir. At baseline, median patient age was 49 years, 20% were female, 58% non-white, and 23% had hepatitis B and/or C co-infection. Median baseline CD4+ was 160 cells/mm^3, median duration of prior ART was 13 years, and 63% were CDC Class C. Subjects showed multiple class ART resistance at baseline: 80% had ≥2 NRTI, 73% ≥1 NNRTI, and 67% ≥2 PI major mutations; 83% had non-R5 virus. Sixteen of 30 subjects (53%) harboured Q148 virus at baseline. The primary endpoint at Day 8 showed that dolutegravir 50 mg film-coated tablets twice daily was superior to placebo, with an adjusted mean treatment difference for the change from Baseline in Plasma HIV-1 RNA of -1.2 $\log_{10}$ copies/mL (95% CI -1.5 - -0.8$\log_{10}$ copies/mL, p<0.001). The day 8 responses in this placebo controlled study were fully in line with those seen in VIKING-3 (not placebo controlled), including by baseline integrase resistance categories. At week 48, 12/30 (40%) subjects had HIV-1 RNA <50 copies/mL (ITT-E, Snapshot algorithm).

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

Paediatric population

In an ongoing Phase I/II 48 week multicentre, open-label study (P1093/ING112578), the pharmacokinetic parameters, safety, tolerability and efficacy of dolutegravir following once daily dosing 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 the recommended once daily doses of either dispersible tablets or film-coated tablets.

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

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

Q1, Q3= First and third quartiles, respectively.

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

[b] Snapshot algorithm was used in the analyses

In participants experiencing virologic failure, 5/36 acquired integrase inhibitor substitution G118R. Of these five, 4 participants had additional integrase associated substitutions as follows: L74M, E138E/K, E92E/Q and T66I. Four of the 5 participants with emergent G118R had phenotypic data available. Dolutegravir FC (fold change as compared to wildtype virus) for these four participants ranged from 6 to 25-fold.

The European Medicines Agency has deferred the obligation to submit the results of studies with Tivicay in paediatric patients aged 4 weeks to below 6 years with HIV infection (see section 4.2 for information on paediatric use).

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

5.2 Pharmacokinetic properties

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

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

Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate, and high fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 33%, 41%, and 66%, increased C_{max} by 46%, 52%, and 67%, prolonged T_{max} to 3, 4, and 5 hours from 2 hours under

fasted conditions, respectively for the film-coated tablet. 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 the available data, 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 (>99%) to human plasma proteins based on *in vitro* data. The apparent volume of distribution is 17 L to 20 L in HIV-infected patients, based on a population pharmacokinetic analysis. Binding of dolutegravir to plasma proteins is independent of dolutegravir concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin (<35 g/L) as seen in subjects with moderate hepatic impairment.

Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve subjects on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/mL (comparable to unbound plasma concentration, and above the IC50).

Dolutegravir is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue and vaginal tissue were 6-10% of those in corresponding plasma at steady state. AUC in semen was 7% and 17% in rectal tissue of those in corresponding plasma at steady state.

Biotransformation

Dolutegravir is primarily metabolized through glucuronidation via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged active substance 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 active substance or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-two 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).

Drug interactions

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC50>50 μM) of the enzymes cytochrome P_{450} (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. Based on this data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of major enzymes or transporters (see section 4.5).

In vitro, dolutegravir was not a substrate of human OATP 1B1, OATP 1B3 or OCT 1.

Elimination

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

Linearity/non-linearity

The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of film-coated 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 for the film-coated tablet formulation. With 50 mg film-coated tablet twice daily, the exposure over 24 hours was approximately doubled compared to 50 mg film-coated tablet once daily.

Pharmacokinetic/pharmacodynamic relationship(s)

In a randomized, dose-ranging trial, HIV-1–infected subjects treated with dolutegravir monotherapy (ING111521) demonstrated rapid and dose-dependent antiviral activity, with mean decline in HIV-1 RNA of 2.5 $\log_{10}$ at day 11 for 50 mg film-coated tablet dose. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg film-coated tablet 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.

Special patient populations

Children
The pharmacokinetics of dolutegravir given once daily as dispersible and film-coated 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 simulated plasma exposure at once daily weight band doses is summarized in Table 12.

Table 12 Summary of Simulated Dolutegravir PK Parameters at Once Daily Doses by Weight Band in Paediatric HIV-1 Infected Subjects

Weight Band (kg)	Dolutegravir Dosage Form[a]	Once Daily Dose (mg)	PK Parameter Geometric Mean (90% CI)		
			Cmax (μg/mL)	AUC0-24h (μg*h/mL)	C24h (ng/mL)
3 to <6	DT	5	4.02 (2.12, 7.96)	49.4 (21.6, 115)	1070 (247, 3830)
6 to <10[b]	DT	10	5.90 (3.23, 10.9)	67.4 (30.4, 151)	1240 (257, 4580)
6 to <10[c]	DT	15	6.67 (3.75, 12.1)	68.4 (30.6, 154)	964 (158, 4150)
10 to <14	DT	20	6.61 (3.80, 11.5)	63.1 (28.9, 136)	719 (102, 3340)
14 to <20	DT	25	7.17 (4.10, 12.6)	69.5 (32.1, 151)	824 (122, 3780)
	FCT	40	6.96 (3.83, 12.5)	72.6 (33.7, 156)	972 (150, 4260)
20 to <25	DT	30	7.37 (4.24, 12.9)	72.0 (33.3, 156)	881 (137, 3960)
	FCT	50	7.43 (4.13, 13.3)	78.6 (36.8, 171)	1080 (178, 4690)
25 to <30	FCT	50	6.74 (3.73, 12.1)	71.4 (33.2, 154)	997 (162, 4250)
30 to <35	FCT	50	6.20 (3.45, 11.1)	66.6 (30.5, 141)	944 (154, 4020)
≥35	FCT	50	4.93 (2.66, 9.08)	54.0 (24.4, 118)	814 (142, 3310)
Target: Geometric Mean				**46 (37-134)**	**995 (697-2260)**

DT=dispersible tablet
FCT=film-coated tablet
a. The bioavailability of dolutegravir DT is ~1.6-fold dolutegravir FCT.
b. <6 months of age
c. ≥6 months of age

Steady state simulated plasma exposure at alternative twice daily weight band doses is summarized in Table 13. In contrast to once daily dosing, simulated data for alternative twice daily dosing have not been confirmed in clinical trials.

Table 13 Summary of Simulated Dolutegravir PK Parameters at Alternative Twice Daily Doses by Weight Band in Paediatric HIV-1 Infected Subjects

Weight Band (kg)	Dolutegravir Dosage Form[a]	Twice Daily Dose (mg)	PK Parameter Geometric Mean (90% CI)		
			Cmax (µg/mL)	AUC0-12h (µg*h/mL)	C12h (ng/mL)
6 to <10[b]	DT	5	4.28 (2.10, 9.01)	31.6 (14.6, 71.4)	1760 (509, 5330)
6 to <10c	DT	10	6.19 (3.15, 12.6)	43.6 (19.4, 96.9)	2190 (565, 6960)
10 to <14	DT	10	4.40 (2.27, 8.68)	30.0 (13.5, 66.0)	1400 (351, 4480)
14 to <20	DT	15	5.78 (2.97, 11.4)	39.6 (17.6, 86.3)	1890 (482, 6070)
	FCT	20	4.98 (2.55, 9.96)	35.9 (16.5, 77.4)	1840 (496, 5650)
20 to <25	DT	15	5.01 (2.61, 9.99)	34.7 (15.8, 76.5)	1690 (455, 5360)
	FCT	25	5.38 (2.73, 10.8)	39.2 (18.1, 85.4)	2040 (567, 6250)
25 to <30	DT	15	4.57 (2.37, 9.05)	32.0 (14.6, 69.1)	1580 (414, 4930)
	FCT	25	4.93 (2.50, 9.85)	35.9 (16.4, 77.4)	1910 (530, 5760)
30 to <35	FCT	25	4.54 (2.31, 9.10)	33.3 (15.3, 72.4)	1770 (494, 5400)
≥35	FCT	25	3.59 (1.76, 7.36)	26.8 (12.1, 58.3)	1470 (425, 4400)

DT=dispersible tablet
FCT=film-coated tablet
a. The bioavailability of dolutegravir DT is ~1.6-fold dolutegravir FCT.
b. <6 months of age
c. ≥6 months of age

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

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

Renal impairment
Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of a single 50 mg dose of dolutegravir film-coated tablets was performed in subjects with severe renal impairment (CLcr <30 mL/min) and matched healthy controls. The exposure to dolutegravir was decreased by approximately 40% in subjects with severe renal impairment. The mechanism for the decrease is unknown. No dosage adjustment is considered necessary for patients with renal impairment. Tivicay has not been studied in patients on dialysis.

Hepatic impairment
Dolutegravir is primarily metabolized and eliminated by the liver. A single 50 mg dose of dolutegravir film-coated tablets was administered to 8 subjects with moderate hepatic impairment (Child-Pugh class B) and to 8 matched healthy adult controls. While the total dolutegravir concentration in plasma was similar, a 1.5- to 2-fold increase in unbound exposure to dolutegravir was observed in subjects with moderate hepatic impairment compared to healthy controls. No dosage adjustment is considered necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of Tivicay has not been studied.

Polymorphisms in drug metabolising enzymes
There is no evidence that common polymorphisms in drug metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n=7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n=41).

Gender
Population PK analyses using pooled pharmacokinetic data from Phase IIb and Phase III adult trials revealed no clinically relevant effect of gender on the exposure of dolutegravir.

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

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

5.3 Preclinical safety data

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

Dolutegravir did not affect male or female fertility in rats at doses up to 1000 mg/kg/day, the highest dose tested (24 times the twice daily human clinical exposure based on AUC).

In reproductive toxicity studies in animals, dolutegravir was shown to cross the placenta.

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 twice daily human clinical exposure based on AUC). In the rat pre/post-natal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 27 times human exposure at the maximum recommended human dose).

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

In a juvenile toxicity study in rats, dolutegravir administration resulted in two preweanling deaths at 75 mg/kg/day. Over the preweaning treatment period, mean body weight gain was decreased in this group and the decrease persisted throughout the entire study for females during the postweaning period. The systemic exposure at this dose (based on AUC) to dolutegravir was ~17 to 20-fold higher than humans at the recommended pediatric exposure. There were no new target organs identified in juveniles compared to adults. At the NOAEL dose of 2 mg/kg/day, the AUC values in juvenile rats on Day 13 post-partum was ~3 to 6-fold higher than paediatric patients weighing 3 to <10 kg (ages 4 weeks to >6 months).

The effect of prolonged daily treatment with high doses of dolutegravir has been evaluated in repeat oral dose toxicity studies in rats (up to 26 weeks) and in monkeys (up to 38 weeks). The primary effect of dolutegravir was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures approximately 21 and 0.82 times the twice daily human clinical exposure based on AUC, respectively. Because gastrointestinal (GI) intolerance is considered to be due to local active substance administration, mg/kg or mg/m^2 metrics are appropriate determinates of safety cover for this toxicity. GI intolerance in monkeys occurred at 15 times the human mg/kg equivalent dose (based on a 50 kg human), and 5 times the human mg/m^2 equivalent twice daily dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol (E421)
Microcrystalline cellulose
Povidone
Sodium starch glycolate
Colloidal silicon dioxide and microcrystalline cellulose
Crospovidone
Sodium stearyl fumarate
Calcium sulfate dihydrate
Sucralose
Strawberry cream flavour

Tablet coating

Titanium dioxide (E171)
Hypromellose
Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Do not remove the desiccant. Do not swallow the desiccant. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

HDPE (high density polyethylene) bottles closed with child resistant polypropylene screw closures, with a polyethylene faced induction heat seal liner. The bottles contain 60 dispersible tablets and a desiccant.

A dosing cup and oral syringe, both made from polypropylene with graduation marks, are supplied with the pack. The syringe's plunger is made from HDPE.

6.6 Special precautions for disposal and other handling

Comprehensive instructions for dispersing the tablet are provided in the package leaflet (see Step-by-step instructions for use).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/892/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 January 2014
Date of latest renewal: 21 September 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency . https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Film-coated Tablets:
GLAXO WELLCOME, S.A., Avda. Extremadura 3, 09400 Aranda de Duero, Burgos, Spain
OR
Delpharm Poznań Spółka Akcyjna, ul., Grunwaldzka 189, 60-322 Poznan, Poland.

5 mg Dispersible Tablets:
GLAXO WELLCOME, S.A., Avda. Extremadura 3, 09400 Aranda de Duero, Burgos, Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 10mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Tivicay 10 mg film-coated tablets
dolutegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains dolutegravir sodium equivalent to 10 mg dolutegravir

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/892/003
EU/1/13/892/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tivicay 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL 10 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Tivicay 10 mg tablets
dolutegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains dolutegravir sodium equivalent to 10 mg dolutegravir

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/892/003
EU/1/13/892/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 25mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Tivicay 25 mg film-coated tablets
dolutegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains dolutegravir sodium equivalent to 25 mg dolutegravir

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV

Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/892/005
EU/1/13/892/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tivicay 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL 25 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Tivicay 25 mg tablets
dolutegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains dolutegravir sodium equivalent to 25 mg dolutegravir

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/892/005
EU/1/13/892/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 50mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Tivicay 50 mg film-coated tablets
dolutegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV

Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/892/001
EU/1/13/892/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tivicay 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL 50 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Tivicay 50 mg tablets
dolutegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/892/001
EU/1/13/892/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 5 mg dispersible tablets

1. NAME OF THE MEDICINAL PRODUCT

Tivicay 5 mg dispersible tablets
dolutegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dispersible tablet contains dolutegravir sodium equivalent to 5 mg dolutegravir

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 dispersible tablets

This pack contains a dosing cup and oral syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/892/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tivicay 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL 5 mg dispersible tablets

1. NAME OF THE MEDICINAL PRODUCT

Tivicay 5 mg dispersible tablets
dolutegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dispersible tablet contains dolutegravir sodium equivalent to 5 mg dolutegravir

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 dispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/892/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tivicay 10 mg film-coated tablets
Tivicay 25 mg film-coated tablets
Tivicay 50 mg film-coated tablets
dolutegravir

Read all of this leaflet carefully before you (or your child, if they are the patient) start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you (or your child, if they are the patient) only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tivicay is and what it is used for

Tivicay contains the active ingredient dolutegravir. Dolutegravir belongs to a group of anti-retroviral medicines called *integrase inhibitors (INIs)*.

Tivicay is used to treat **HIV (human immunodeficiency virus) infection** in adults, adolescents and children of at least 6 years of age or older, and who weigh at least 14 kg.

Tivicay does not cure HIV infection; it reduces the amount of virus in your body, and keeps it at a low level. As a result of that, it also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cells that are important in helping your body to fight infection.

Not everyone responds to treatment with Tivicay in the same way. Your doctor will monitor the effectiveness of your treatment.

Tivicay is always used in combination with other anti-retroviral medicines (*combination therapy*).
To control your HIV infection, and to stop your illness from getting worse, you must keep taking all your medicines, unless your doctor tells you to stop taking any.

2. What you need to know before you take Tivicay

Don’t take Tivicay:
- if you (or your child, if they are the patient) are allergic to dolutegravir or any of the other ingredients of this medicine (listed in section 6).
- if you (or your child) are taking another medicine called fampridine (also known as dalfampridine; used in multiple sclerosis).

→ If you think any of these apply to you (or your child), tell your doctor.

Warnings and precautions
Look out for important symptoms
Some people taking medicines for HIV infection develop other conditions, which can be serious. These include:

- symptoms of infections and inflammation
- joint pain, stiffness and bone problems

You need to know about important signs and symptoms to look out for while you (or your child, if they are the patient) are taking Tivicay.

→ **Read the information in Section 4 of this leaflet.**

Children
Do not give this medicine to children under 6 years of age, weighing less than 14 kg or with HIV infection that is resistant to other medicines similar to Tivicay. The use of Tivicay film-coated tablets in children under 6 or weighing less than 14 kg has not yet been studied.

Children must **keep planned doctor's appointments** (*see 'Use in children and adolescents' in Section 3 for more information*).

Other medicines and Tivicay
Tell your doctor if you (or your child) are taking, have recently taken or are planning to take any other medicines.

Don't take Tivicay with the following medicine:

- fampridine (also known as dalfampridine), used in **multiple sclerosis.**

Some medicines can affect how Tivicay works, or make it more likely that you will have side effects. Tivicay can also affect how some other medicines work.
Tell your doctor if you (or your child) are taking any of the medicines in the following list:

- metformin, to treat **diabetes**
- medicines called **antacids**, to treat **indigestion** and **heartburn. Do not take an antacid** during the 6 hours before you take Tivicay, or for at least 2 hours after you take it. (*See also Section 3).*
- supplements or multivitamins containing calcium, iron or magnesium. **If you take Tivicay with food,** you can take supplements or multivitamins containing calcium, iron or magnesium at the same time as Tivicay. **If you do not take Tivicay with food, do not take a supplement or multivitamin containing calcium, iron or magnesium** during the 6 hours before you take Tivicay, or for at least 2 hours after you take it (*see also Section 3*).
- etravirine, efavirenz, fosamprenavir/ritonavir, nevirapine or tipranavir/ritonavir, to treat **HIV infection**
- rifampicin, to treat tuberculosis (TB) and other **bacterial infections**
- phenytoin and phenobarbital, to treat **epilepsy**
- oxcarbazepine and carbamazepine, to treat **epilepsy** or **bipolar disorder**
- **St. John's wort** (*Hypericum perforatum*), a herbal remedy to treat **depression**

→ **Tell your doctor or pharmacist** if you (or your child) are taking any of these. Your doctor may decide to adjust your dose or that you need extra check ups.

Pregnancy
If you are pregnant, think you may be pregnant, or if you are planning to have a baby:

→ **Talk to your doctor** about the risks and benefits of taking Tivicay.

Tell your doctor immediately if you become pregnant or are planning to become pregnant. Your doctor will review your treatment. Do not stop taking Tivicay without consulting your doctor, as this may harm you and your unborn child.

Breast-feeding
Breast-feeding is **not recommended** in women living with HIV because HIV infection can be passed on to the baby in breast milk.

A small amount of the ingredient in Tivicay can pass into your breast milk.

If you are breast-feeding, or thinking about breast-feeding, you should **discuss it with your doctor as soon as possible**.

Driving and using machines
Tivicay can make you dizzy and have other side effects that make you less alert.
→ **Don't drive or operate machinery** unless you are sure you're not affected.

Tivicay contains less than 1 mmol sodium (23 mg) per tablet, that is to say is essentially 'sodium-free.'

3. How to take Tivicay

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- **The usual dose** is 50 mg **once a day.**
- If you are taking **certain other medicines**, the dose is 50 mg **twice a day**.
- **For HIV that is resistant** to other medicines similar to Tivicay, the usual dose is 50 mg, **twice a day**.

Your doctor will decide on the correct dose of Tivicay for you.

Swallow the tablet(s) with some liquid.

Tivicay can be taken **with or without food**. When Tivicay is taken twice a day, your doctor may advise you to take with food.

Tivicay is also available as **dispersible tablets**. Film-coated tablets and dispersible tablets are not the same, therefore **do not switch** between film-coated tablets and dispersible tablets without first talking to your doctor.

Use in children and adolescents
- **Children's dose** of Tivicay needs to be adjusted as they get older or gain weight.
  → It is important therefore that children **keep planned doctor's appointments.**
- Children and adolescents weighing at least 20 kg can take the adult dose of 50 mg, once a day or 25 mg twice daily. Your doctor will decide how Tivicay should be given.
- For children aged between 6 and 12 years your doctor will decide on the correct dose of Tivicay, depending on the weight of your child.
- To reduce the risk of choking, children **must not swallow more than one tablet at a time**.
- Tivicay should **not** be used in children and adolescents with **HIV infection that is resistant** to other medicines similar to Tivicay.

Antacid medicines
Antacids, to treat **indigestion** and **heartburn**, can stop Tivicay being absorbed into your body and make it less effective.
Do not take an antacid during the 6 hours before you take Tivicay, or for at least 2 hours after you take it.
Other acid-lowering medicines like ranitidine and omeprazole can be taken at the same time as Tivicay.
→ Talk to your doctor for further advice on taking acid-lowering medicines with Tivicay.

Supplements or multivitamins containing calcium, iron or magnesium
Supplements or multivitamins containing calcium, iron or magnesium can stop Tivicay being absorbed into your body and make it less effective.
If you take Tivicay with food, you can take supplements or multivitamins containing calcium, iron or magnesium at the same time as Tivicay. **If you do not take Tivicay with food, do not take a supplement or multivitamin containing calcium, iron or magnesium** during the 6 hours before you take Tivicay, or for at least 2 hours after you take it.

→ Talk to your doctor for further advice on taking supplements or multivitamins containing calcium, iron or magnesium with Tivicay.

If you take more Tivicay than you should
If you (or your child) take too many tablets of Tivicay, **contact your doctor or pharmacist for advice**. If possible, show them the Tivicay pack.

If you forget to take Tivicay
If you (or your child) miss a dose, take it as soon as you remember. But if your next dose is due within 4 hours, skip the dose you missed and take the next one at the usual time. Then continue your treatment as before.

Don't take a double dose to make up for a missed dose.

Don’t stop taking Tivicay without advice from your doctor
Take Tivicay for as long as your doctor recommends. Don’t stop unless your doctor advises you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, but not everybody gets them.

Allergic reactions
These are uncommon in people taking Tivicay. Signs include:
- skin rash
- a high temperature (*fever*)
- lack of energy (*fatigue*)
- swelling, sometimes of the face or mouth (*angioedema*), causing difficulty in breathing
- muscle or joint aches.

→ See a doctor straight away. Your doctor may decide to carry out tests on your liver, kidneys or blood, and may tell you to stop taking Tivicay.

Very common side effects
These may affect **more than 1 in 10 people**:
- headache
- diarrhoea
- feeling sick (*nausea*).

Common side effects
These may affect **up to 1 in 10 people**:
- rash
- itching (*pruritus*)
- being sick (*vomiting*)
- stomach pain (*abdominal pain*)
- stomach (*abdominal*) discomfort
- weight gain
- insomnia
- dizziness

- abnormal dreams
- depression (feelings of deep sadness and unworthiness)
- anxiety
- lack of energy (*fatigue*)
- wind (*flatulence*)
- increase in the level of liver enzymes
- increase in the level of enzymes produced in the muscles (*creatine phosphokinase*).

Uncommon side effects
These may affect **up to 1 in 100 people**:
- inflammation of the liver (*hepatitis*)
- suicide attempt*
- suicidal thoughts*
- panic attack
- joint pain
- muscle pain

* *particularly in patients who have had depression or mental health problems before.*

Rare side effects
These may affect **up to 1 in 1000 people**:
- liver failure (signs may include yellowing of the skin and the whites of the eyes or unusually dark urine)
- increase in bilirubin (a test of liver function) in your blood.
- suicide (particularly in patients who have had depression or mental health problems before)

→ **Tell your doctor immediately** if you experience any mental health problems (see also other mental health problems above).

Frequency not known
Cannot be estimated from the available data:
- a condition where red blood cells do not form properly (*sideroblastic anaemia*).

Symptoms of infection and inflammation

People with advanced HIV infection (AIDS) have weak immune systems, and are more likely to develop serious infections (*opportunistic infections*). Such infections may have been "silent" and not detected by the weak immune system before treatment was started. After starting treatment, the immune system becomes stronger, and may attack the infections, which can cause symptoms of infection or inflammation. Symptoms usually include **fever**, plus some of the following:
- headache
- stomach ache
- difficulty breathing

In rare cases, as the immune system becomes stronger, it can also attack healthy body tissue (*autoimmune disorders*). The symptoms of autoimmune disorders may develop many months after you start taking medicine to treat your HIV infection. Symptoms may include:
- palpitations (rapid or irregular heartbeat) or tremor
- hyperactivity (excessive restlessness and movement)
- weakness beginning in the hands and feet and moving up towards the trunk of the body.

If you (or your child) get any symptoms of infection and inflammation or if you notice any of the symptoms above:
→ **Tell your doctor immediately**. Don't take other medicines for the infection without your doctor's advice.

Joint pain, stiffness and bone problems

Some people taking combination therapy for HIV develop a condition called *osteonecrosis*. With this condition, parts of the bone tissue die because of reduced blood supply to the bone. People may be more likely to get this condition:

- if they have been taking combination therapy for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids
- if they drink alcohol
- if their immune systems are very weak
- if they are overweight.

Signs of osteonecrosis include:

- stiffness in the joints
- aches and pains in the joints (especially in the hip, knee or shoulder)
- difficulty moving.

If you notice any of these symptoms:

→ **Tell your doctor**.

Weight, blood lipid and blood glucose effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and lifestyle, and sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tivicay

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated after EXP on the carton and bottle.

Tivicay 10 mg film-coated tablets

Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Do not remove the desiccant. Do not swallow the desiccant. This medicine does not require any special temperature storage conditions.

Tivicay 25 mg and 50 mg film-coated tablets

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tivicay contains

- The active substance is dolutegravir. Each tablet contains dolutegravir sodium equivalent to 10 mg, 25 mg or 50 mg dolutegravir.
- The other ingredients are mannitol (E421), microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, poly(vinyl alcohol) partially hydrolyzed, titanium dioxide (E171), macrogol, talc and for 25 mg and 50 mg tablets, iron oxide yellow (E172).

What Tivicay looks like and contents of the pack
Tivicay 10 mg film-coated tablets are white, round, biconvex tablets marked with the code 'SV 572' on one side and '10' on the other side. The bottle contains a desiccant to reduce moisture. Once the bottle has been opened keep the desiccant in the bottle, do not remove it.

Tivicay 25 mg film-coated tablets are pale yellow, round, biconvex tablets marked with the code 'SV 572' on one side and '25' on the other side.

Tivicay 50 mg film-coated tablets are yellow, round, biconvex tablets marked with the code 'SV 572' on one side and '50' on the other side.

The film-coated tablets are provided in bottles containing 30 or 90 tablets. Not all pack sizes may be available in your country.

Marketing Authorisation Holder
ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands.

Manufacturer
Glaxo Wellcome, S.A., Avda. Extremadura 3, 09400 Aranda De Duero, Burgos, Spain
OR
Delpharm Poznań Spółka Akcyjna, ul., Grunwaldzka 189, 60-322 Poznan, Poland.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
ViiV Healthcare srl/bv
Tél/Tel: + 32 (0) 10 85 65 00

Lietuva
ViiV Healthcare BV
Tel: + 370 80000334

България
ViiV Healthcare BV
Тел.: + 359 80018205

Luxembourg/Luxemburg
ViiV Healthcare srl/bv
Belgique/Belgien
Tél/Tel: + 32 (0) 10 85 65 00

Česká republika
GlaxoSmithKline, s.r.o.
Tel: + 420 222 001 111
cz.info@gsk.com

Magyarország
ViiV Healthcare BV
Tel: + 36 80088309

Danmark
GlaxoSmithKline Pharma A/S
Tlf.: + 45 36 35 91 00
dk-info@gsk.com

Malta
ViiV Healthcare BV
Tel: + 356 80065004

Deutschland
ViiV Healthcare GmbH
Tel.: + 49 (0)89 203 0038-10
viiv.med.info@viivhealthcare.com

Nederland
ViiV Healthcare BV
Tel: + 31 (0)33 2081199

Eesti
ViiV Healthcare BV
Tel: + 372 8002640

Norge
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00

Ελλάδα
GlaxoSmithKline Μονοπρόσωπη A.E.B.E.
Τηλ: + 30 210 68 82 100

España
Laboratorios ViiV Healthcare, S.L.
Tel: + 34 900 923 501
es-ci@viivhealthcare.com

France
ViiV Healthcare SAS
Tél.: + 33 (0)1 39 17 69 69
Infomed@viivhealthcare.com

Hrvatska
ViiV Healthcare BV
Tel: + 385 800787089

Ireland
GlaxoSmithKline (Ireland) Limited
Tel: + 353 (0)1 4955000

Ísland
Vistor ehf.
Sími: + 354 535 7000

Italia
ViiV Healthcare S.r.l
Tel: + 39 (0)45 7741600

Κύπρος
ViiV Healthcare BV
Τηλ: + 357 80070017

Latvija
ViiV Healthcare BV
Tel: + 371 80205045

Österreich
GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

Polska
GSK Services Sp. z o.o.
Tel.: + 48 (0)22 576 9000

Portugal
VIIVHIV HEALTHCARE, UNIPESSOAL, LDA
Tel: + 351 21 094 08 01
viiv.fi.pt@viivhealthcare.com

România
ViiV Healthcare BV
Tel: + 40800672524

Slovenija
ViiV Healthcare BV
Tel: + 386 80688869

Slovenská republika
ViiV Healthcare BV
Tel: + 421 800500589

Suomi/Finland
GlaxoSmithKline Oy
Puh/Tel: + 358 (0)10 30 30 30

Sverige
GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

This leaflet was last revised in {month YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Package leaflet: Information for the patient

Tivicay 5 mg dispersible tablets
dolutegravir

Read all of this leaflet carefully before you (or your child, if they are the patient) start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you (or your child, if they are the patient) only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tivicay is and what it is used for

Tivicay contains the active ingredient dolutegravir. Dolutegravir belongs to a group of anti-retroviral medicines called *integrase inhibitors (INIs)*.

Tivicay is used to treat **HIV (human immunodeficiency virus) infection** in adults, adolescents and children of at least 4 weeks of age or older, and who weigh at least 3 kg.

Tivicay does not cure HIV infection; it reduces the amount of virus in your body, and keeps it at a low level. As a result of that, it also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cells that are important in helping your body to fight infection.

Not everyone responds to treatment with Tivicay in the same way. Your doctor will monitor the effectiveness of your treatment.

Tivicay is always used in combination with other anti-retroviral medicines (*combination therapy*). To control your HIV infection, and to stop your illness from getting worse, you must keep taking all your medicines, unless your doctor tells you to stop taking any.

2. What you need to know before you take Tivicay

Don't take Tivicay:
- if you (or your child, if they are the patient) are allergic to dolutegravir or any of the other ingredients of this medicine (listed in section 6).
- if you (or your child) are taking another medicine called fampridine (also known as dalfampridine; used in multiple sclerosis).

→ If you think any of these apply to you (or your child), tell your doctor.

Warnings and precautions
Look out for important symptoms
Some people taking medicines for HIV infection develop other conditions, which can be serious. These include:

- symptoms of infections and inflammation
- joint pain, stiffness and bone problems

You need to know about important signs and symptoms to look out for while you (or your child, if they are the patient) are taking Tivicay.

→ **Read the information in Section 4 of this leaflet.**

Children
Do not give this medicine to children under 4 weeks of age, weighing less than 3 kg or with HIV infection that is resistant to other medicines similar to Tivicay. The use of Tivicay dispersible tablets in children under 4 weeks or weighing less than 3 kg has not yet been studied.

Children must **keep planned doctor's appointments** (*see 'Children and adolescents' in Section 3 for more information*).

Other medicines and Tivicay
Tell your doctor if you (or your child) are taking, have recently taken or are planning to take any other medicines.

Don't take Tivicay with the following medicine:

- fampridine (also known as dalfampridine), used in **multiple sclerosis.**

Some medicines can affect how Tivicay works, or make it more likely that you will have side effects. Tivicay can also affect how some other medicines work.
Tell your doctor if you (or your child) are taking any of the medicines in the following list:

- metformin, to treat **diabetes**
- medicines called **antacids**, to treat **indigestion** and **heartburn. Do not take an antacid** during the 6 hours before you take Tivicay, or for at least 2 hours after you take it. (*See also Section 3).*
- supplements or multivitamins containing calcium, iron or magnesium. **If you take Tivicay with food,** you can take supplements or multivitamins containing calcium, iron or magnesium at the same time as Tivicay. **If you do not take Tivicay with food, do not take a supplement or multivitamin containing calcium, iron or magnesium** during the 6 hours before you take Tivicay, or for at least 2 hours after you take it (*see also Section 3*).
- etravirine, efavirenz, fosamprenavir/ritonavir, nevirapine or tipranavir/ritonavir, to treat **HIV infection**
- rifampicin, to treat tuberculosis (TB) and other **bacterial infections**
- phenytoin and phenobarbital, to treat **epilepsy**
- oxcarbazepine and carbamazepine, to treat **epilepsy** or **bipolar disorder**
- **St. John's wort** (*Hypericum perforatum*), a herbal remedy to treat **depression**

→ **Tell your doctor or pharmacist** if you (or your child) are taking any of these. Your doctor may decide to adjust your dose or that you need extra check ups.

Pregnancy
If you are pregnant, think you may be pregnant, or if you are planning to have a baby:

→ **Talk to your doctor** about the risks and benefits of taking Tivicay.

Tell your doctor immediately if you become pregnant or are planning to become pregnant. Your doctor will review your treatment. Do not stop taking Tivicay without consulting your doctor, as this may harm you and your unborn child.

Breast-feeding
Breast-feeding is **not recommended** in women living with HIV because HIV infection can be passed on to the baby in breast milk.

A small amount of the ingredient in Tivicay can pass into your breast milk.

If you are breast-feeding, or thinking about breast-feeding, you should **discuss it with your doctor as soon as possible**.

Driving and using machines
Tivicay can make you dizzy and have other side effects that make you less alert.
→ **Don't drive or operate machinery** unless you are sure you're not affected.

Tivicay contains less than 1 mmol sodium (23 mg) per tablet, that is to say is essentially 'sodium-free.'

3. How to take Tivicay

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Adults
- **The usual adult dose** is 30 mg (taken as six 5 mg dispersible tablets) **once a day.**
- If you are taking **certain other medicines**, the dose is 30 mg (taken as six 5 mg dispersible tablets) **twice a day**.
- **For HIV that is resistant** to other medicines similar to Tivicay, the usual dose is 30 mg (taken as six 5 mg dispersible tablets), **twice a day**.

Your doctor will decide on the correct dose of Tivicay for you.

Children and adolescents
- **Children's dose** of Tivicay needs to be adjusted as they get older or gain weight.
  → It is important therefore that children **keep planned doctor's appointments.**
- Children and adolescents weighing at least 20 kg can take the adult dose of 30 mg, once a day or 15 mg twice a day. Your doctor will decide how Tivicay should be given.
- For children aged at least 4 weeks and weighing between 3 and 20 kg, your doctor will decide on the correct dose of Tivicay, depending on the weight and age of your child.
- If swallowing tablets whole with water, children **must not swallow more than one tablet at a time** to reduce the risk of choking.
- Tivicay should **not** be used in children and adolescents with **HIV infection that is resistant** to other medicines similar to Tivicay.

How to take the dispersible tablets
- The dispersible tablets may be dispersed in drinking water or swallowed whole with drinking water. When dispersed, the amount of water will depend on the number of tablets prescribed. The tablet(s) should be fully dispersed before swallowing.
  See the separate instructions for use regarding how to disperse and administer the tablets using the dosing cup and oral syringe provided in this pack.
- **Do not** chew, cut or crush the tablets.
- Tivicay can be taken **with or without food**. When Tivicay is taken twice a day, your doctor may advise you to take with food.

Tivicay is also available as **film-coated tablets.** Film-coated tablets and dispersible tablets are not the same, therefore **do not switch** between film-coated tablets and dispersible tablets without first talking to your doctor.

Antacid medicines
Antacids, to treat **indigestion** and **heartburn**, can stop Tivicay being absorbed into your body and make it less effective.
Do not take an antacid during the 6 hours before you take Tivicay, or for at least 2 hours after you take it. Other acid-lowering medicines like ranitidine and omeprazole can be taken at the same time as Tivicay.
→ Talk to your doctor for further advice on taking acid-lowering medicines with Tivicay.

Supplements or multivitamins containing calcium, iron or magnesium
Supplements or multivitamins containing calcium, iron or magnesium can stop Tivicay being absorbed into your body and make it less effective.
If you take Tivicay with food, you can take supplements or multivitamins containing calcium, iron or magnesium at the same time as Tivicay. **If you do not take Tivicay with food, do not take a supplement or multivitamin containing calcium, iron or magnesium** during the 6 hours before you take Tivicay, or for at least 2 hours after you take it.
→ Talk to your doctor for further advice on taking supplements or multivitamins containing calcium, iron or magnesium with Tivicay.

If you take more Tivicay than you should
If you (or your child) take too many tablets of Tivicay, **contact your doctor or pharmacist for advice**. If possible, show them the Tivicay pack.

If you forget to take Tivicay
If you (or your child) miss a dose, take it as soon as you remember. But if your next dose is due within 4 hours, skip the dose you missed and take the next one at the usual time. Then continue your treatment as before.
Don't take a double dose to make up for a missed dose.

Don’t stop taking Tivicay without advice from your doctor
Take Tivicay for as long as your doctor recommends. Don’t stop unless your doctor advises you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, but not everybody gets them.

Allergic reactions
These are uncommon in people taking Tivicay. Signs include:
- skin rash
- a high temperature (*fever*)
- lack of energy (*fatigue*)
- swelling, sometimes of the face or mouth (*angioedema*), causing difficulty in breathing
- muscle or joint aches.

→ See a doctor straight away. Your doctor may decide to carry out tests on your liver, kidneys or blood, and may tell you to stop taking Tivicay.

Very common side effects
These may affect **more than 1 in 10 people**:
- headache
- diarrhoea
- feeling sick (*nausea*).

Common side effects
These may affect **up to 1 in 10 people**:
- rash
- itching (*pruritus*)
- being sick (*vomiting*)
- stomach pain (*abdominal pain*)
- stomach (*abdominal*) discomfort
- weight gain
- insomnia
- dizziness
- abnormal dreams
- depression (feelings of deep sadness and unworthiness)
- anxiety
- lack of energy (*fatigue*)
- wind (*flatulence*)
- increase in the level of liver enzymes
- increase in the level of enzymes produced in the muscles (*creatine phosphokinase*).

Uncommon side effects
These may affect **up to 1 in 100 people**:
- inflammation of the liver (*hepatitis*)
- suicide attempt*
- suicidal thoughts*
- panic attack
- joint pain
- muscle pain

* *particularly in patients who have had depression or mental health problems before*

Rare side effects
These may affect **up to 1 in 1000 people**:
- liver failure (signs may include yellowing of the skin and the whites of the eyes or unusually dark urine)
- increase in bilirubin (a test of liver function) in your blood.
- suicide (particularly in patients who have had depression or mental health problems before)

→ **Tell your doctor immediately** if you experience any mental health problems (see also other mental health problems above).

Frequency not known
Cannot be estimated from the available data:
- a condition where red blood cells do not form properly (*sideroblastic anaemia*).

Symptoms of infection and inflammation

People with advanced HIV infection (AIDS) have weak immune systems, and are more likely to develop serious infections (*opportunistic infections*). Such infections may have been "silent" and not detected by the weak immune system before treatment was started. After starting treatment, the immune system becomes

stronger, and may attack the infections, which can cause symptoms of infection or inflammation. Symptoms usually include **fever**, plus some of the following:

- headache
- stomach ache
- difficulty breathing

In rare cases, as the immune system becomes stronger, it can also attack healthy body tissue (*autoimmune disorders*). The symptoms of autoimmune disorders may develop many months after you start taking medicine to treat your HIV infection. Symptoms may include:

- palpitations (rapid or irregular heartbeat) or tremor
- hyperactivity (excessive restlessness and movement)
- weakness beginning in the hands and feet and moving up towards the trunk of the body.

If you (or your child) get any symptoms of infection and inflammation or if you notice any of the symptoms above:

→ **Tell your doctor immediately**. Don't take other medicines for the infection without your doctor's advice.

Joint pain, stiffness and bone problems

Some people taking combination therapy for HIV develop a condition called *osteonecrosis*. With this condition, parts of the bone tissue die because of reduced blood supply to the bone. People may be more likely to get this condition:

- if they have been taking combination therapy for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids
- if they drink alcohol
- if their immune systems are very weak
- if they are overweight.

Signs of osteonecrosis include:

- stiffness in the joints
- aches and pains in the joints (especially in the hip, knee or shoulder)
- difficulty moving.

If you notice any of these symptoms:

→ **Tell your doctor**.

Weight, blood lipid and blood glucose effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and lifestyle, and sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tivicay

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated after EXP on the carton and bottle.

Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Do not remove the desiccant. Do not swallow the desiccant. This medicine does not require any special temperature storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tivicay contains

The active substance is dolutegravir. Each tablet contains dolutegravir sodium equivalent to 5 mg dolutegravir.

The other ingredients are mannitol (E421), microcrystalline cellulose, povidone, sodium starch glycolate, colloidal silicon dioxide and microcrystalline cellulose, crospovidone, sodium stearyl fumarate, calcium sulfate dihydrate, sucralose, strawberry cream flavour, titanium dioxide (E171), hypromellose and macrogol.

What Tivicay looks like and contents of the pack

Tivicay 5 mg dispersible tablets are white, round, biconvex tablets marked with the code 'SV H7S' on one side and '5' on the other side. The bottle contains a desiccant to reduce moisture. Once the bottle has been opened keep the desiccant in the bottle, do not remove it.

The dispersible tablets are provided in bottles containing 60 tablets.

A dosing cup and oral syringe are supplied with the pack.

Marketing Authorisation Holder

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands.

Manufacturer

Glaxo Wellcome, S.A., Avda. Extremadura 3, 09400 Aranda De Duero, Burgos, Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
ViiV Healthcare srl/bv
Tél/Tel: + 32 (0) 10 85 65 00

Lietuva
ViiV Healthcare BV
Tel: + 370 80000334

България
ViiV Healthcare BV
Тел.: + 359 80018205

Luxembourg/Luxemburg
ViiV Healthcare srl/bv
Belgique/Belgien
Tél/Tel: + 32 (0) 10 85 65 00

Česká republika
GlaxoSmithKline, s.r.o.
Tel: + 420 222 001 111
cz.info@gsk.com

Magyarország
ViiV Healthcare BV
Tel.: + 36 80088309

Danmark
GlaxoSmithKline Pharma A/S
Tlf.: + 45 36 35 91 00
dk-info@gsk.com

Malta
ViiV Healthcare BV
Tel: + 356 80065004

Deutschland
ViiV Healthcare GmbH
Tel.: + 49 (0)89 203 0038-10
viiv.med.info@viivhealthcare.com

Eesti
ViiV Healthcare BV
Tel: + 372 8002640

Ελλάδα
GlaxoSmithKline Μονοπρόσωπη A.E.B.E.
Τηλ: + 30 210 68 82 100

España
Laboratorios ViiV Healthcare, S.L.
Tel: + 34 900 923 501
es-ci@viivhealthcare.com

France
ViiV Healthcare SAS
Tél.: + 33 (0)1 39 17 69 69
Infomed@viivhealthcare.com

Hrvatska
ViiV Healthcare BV
Tel: + 385 1 800787089

Ireland
GlaxoSmithKline (Ireland) Limited
Tel: + 353 (0)1 4955000

Ísland
Vistor ehf.
Sími: + 354 535 7000

Italia
ViiV Healthcare S.r.l
Tel: + 39 (0)45 7741600

Κύπρος
ViiV Healthcare BV
Τηλ: + 357 80070017

Latvija
ViiV Healthcare BV
Tel: + 371 80205045

Nederland
ViiV Healthcare BV
Tel: + 31 (0)33 2081199

Norge
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00

Österreich
GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

Polska
GSK Services Sp. z o.o.
Tel.: + 48 (0)22 576 9000

Portugal
VIIVHIV HEALTHCARE, UNIPESSOAL, LDA
Tel: + 351 21 094 08 01
viiv.fi.pt@viivhealthcare.com

România
ViiV Healthcare BV
Tel: + 40800672524

Slovenija
ViiV Healthcare BV
Tel: + 386 80688869

Slovenská republika
ViiV Healthcare BV
Tel: + 421 800500589

Suomi/Finland
GlaxoSmithKline Oy
Puh/Tel: + 358 (0)10 30 30 30

Sverige
GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: .
https://www.ema.europa.eu.

Step-by-step instructions for use

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

Important information

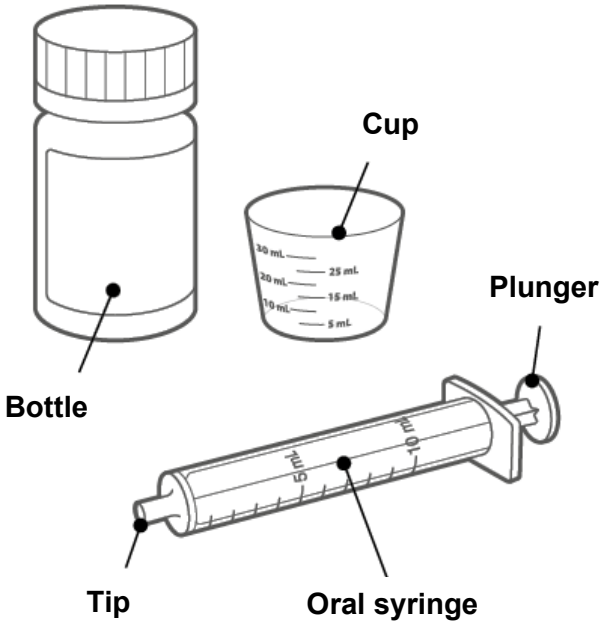
Always give this medicine exactly as your healthcare provider tells you. Talk to your healthcare provider if you are not sure.

Do not chew, cut, or crush the tablets.

If you forget to give a dose of medicine, give it as soon as you remember. But if your next dose is due within 4 hours, skip the dose you missed and take the next one at the usual time. Then continue your treatment as before. Do not give 2 doses at the same time or give more than your healthcare provider has prescribed.

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

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



Your pack contains:

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

You will also need:

- Clean drinking water.

Getting ready

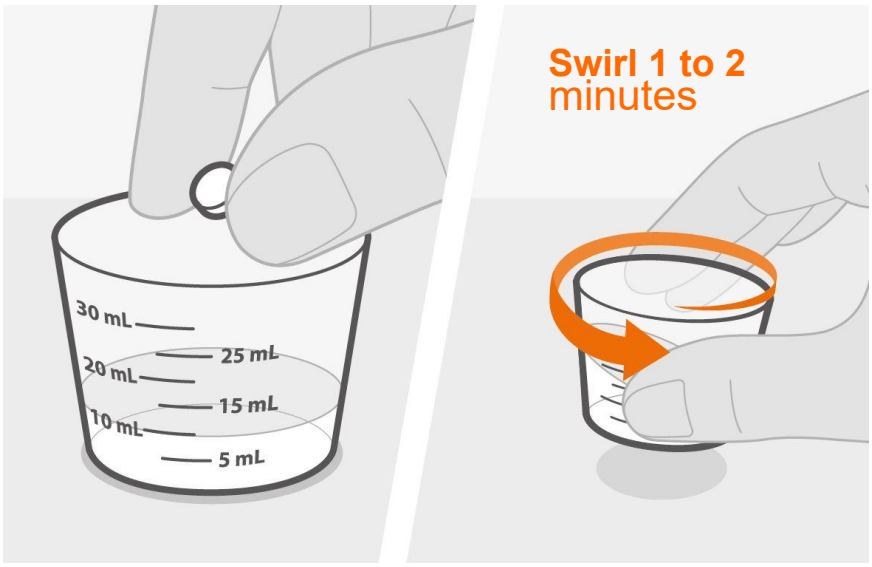
1. Pour water

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

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

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

2. Prepare the medicine



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

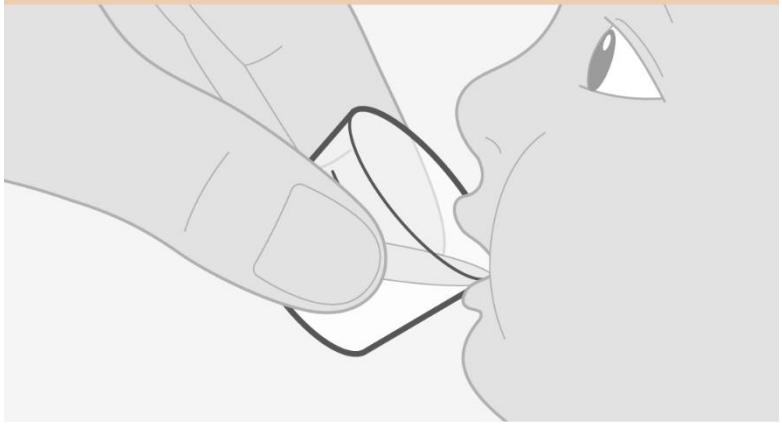
If you spill any medicine, clean up the spill.
Throw away the rest of the prepared medicine and make a new dose.

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

Giving the medicine

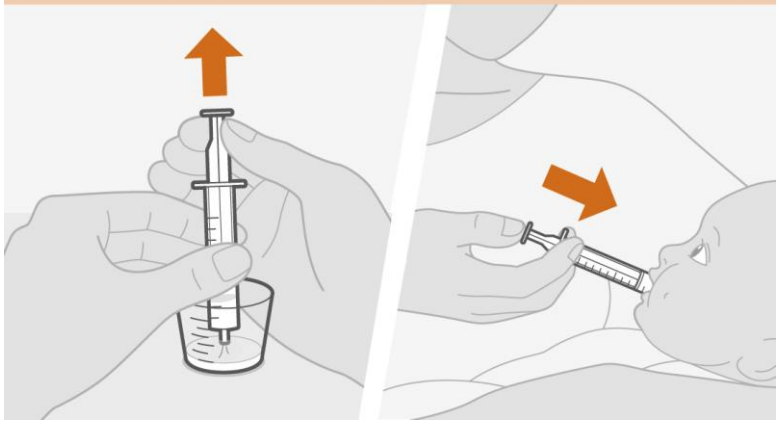
3. Give the medicine

Give the medicine to a Child



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

Give the medicine to an Infant

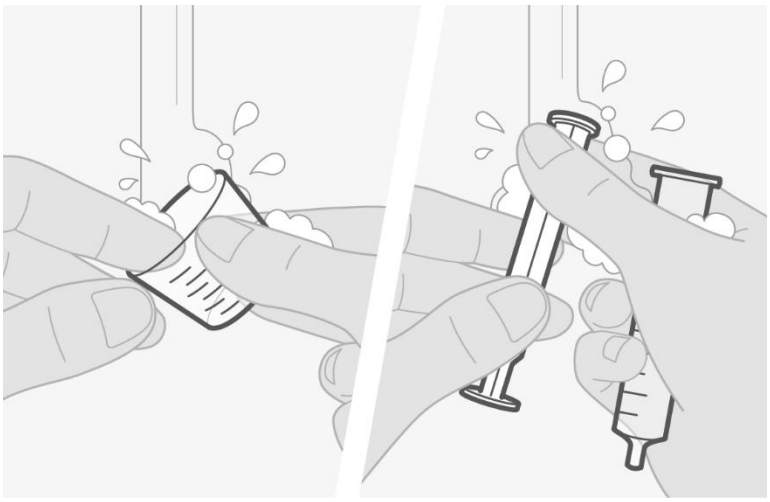


- Place the tip of the oral syringe into the prepared medicine and draw up all the medicine into the oral syringe by pulling up on the plunger.
- Place the tip of the oral syringe against the inside of the infant's cheek. Gently push down the plunger to give the dose slowly.
- Add another 5 mL of drinking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

Allow time for the medicine to be swallowed.

Cleaning

4. Clean the dosing items



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

Storage information

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

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

Keep all medicines out of reach of children.

Disposal information

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

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