SUMMARY OF PRODUCT CHARACTERISTICS

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1 NAME OF THE MEDICINAL PRODUCT

Tivicay 50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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 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)

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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).

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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).

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'.

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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").

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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% Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	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. 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

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		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.

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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% $C\tau$ ↑ 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% $C\tau$ ↓ 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		

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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	Dolutegravir ↓ AUC ↓ 39% C_{max} ↓ 37% C_{24} ↓ 39% (Complex binding to polyvalent ions)	Calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).
Iron supplements	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% C_{24} ↓ 56% (Complex binding to polyvalent ions)	
Multivitamin	Dolutegravir ↓ AUC ↓ 33% C_{max} ↓ 35% C_{24} ↓ 32% (Complex binding to polyvalent ions)	
Corticosteroids		
Prednisone	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 6% C_{τ} ↑ 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	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

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	dolutegravir 50mg twice daily: Metformin AUC ↑ 145 % C_{max} ↑ 111%	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% (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

Women of childbearing potential

Women of childbearing potential (WOCBP) should be counselled about the potential risk of neural tube defects with dolutegravir (see below), including consideration of effective contraceptive measures.

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If a woman plans pregnancy, the benefits and the risks of continuing treatment with dolutegravir should be discussed with the patient.

Pregnancy

Human experience from a birth outcome surveillance study in Botswana shows a small increase of neural tube defects; 7 cases in 3,591 deliveries (0.19%; 95% CI 0.09%, 0.40%) to mothers taking dolutegravir-containing regimens at the time of conception compared to 21 cases in 19,361 deliveries (0.11%: 95% CI 0.07%, 0.17%) to women exposed to non-dolutegravir regimens at the time of conception.

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%). Most neural tube defects occur within the first 4 weeks of embryonic development after conception (approximately 6 weeks after the last menstrual period). If a pregnancy is confirmed in the first trimester while on dolutegravir, the benefits and risks of continuing dolutegravir versus switching to another antiretroviral regimen should be discussed with the patient taking the gestational age and the critical time period of neural tube defect development into account.

Data analysed from the Antiretroviral Pregnancy Registry do not indicate an increased risk of major birth defects in over 600 women exposed to dolutegravir during pregnancy but are currently insufficient to address the risk of neural tube defects.

In animal reproductive toxicity studies, no adverse development outcomes, including neural tube defects, were identified (see section 5.3). Dolutegravir was shown to cross the placenta in animals.

More than 1000 outcomes from exposure during second and third trimester of pregnancy indicate no evidence of increased risk of foeto/neonatal toxicity. Dolutegravir may be used during the second and third trimester of pregnancy when the expected benefit justifies the potential risk to the foetus.

Breast-feeding

Dolutegravir is excreted in human milk in small amounts. 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).

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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).

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Table 4 Adverse Reactions

Immune system disorders	Uncommon	Hypersensitivity (see section 4.4)
	Uncommon	Immune Reconstitution Syndrome (see section 4.4)**
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***
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

**see below under Description of selected adverse reactions.
***in combination with increased transaminases

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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 Yellow Card Scheme Website: http://www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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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.

SUMMARY OF PRODUCT CHARACTERISTICS

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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 - -0.8log_{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.

SUMMARY OF PRODUCT CHARACTERISTICS

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5.2 Pharmacokinetic properties

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.

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).

SUMMARY OF PRODUCT CHARACTERISTICS

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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 50 mg film-coated tablets

5 years

6.4 Special precautions for storage

Tivicay 50 mg film-coated tablets

This medicinal product does not require any special storage conditions.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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.

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

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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 35728/0046

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

01/12/2023