DOLUTEGRAVIR

50 mg Film-Coated Tablet
Integrase Strand Transfer Inhibitor

1. Name of the Finished Pharmaceutical Product
Dolutegravir Tablets 50 mg

2. Qualitative and Quantitative Composition
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
Dolutegravir tablets are reddish brown colored, round, biconvex, film coated tablets debossed with 'T over 50' on one side and plain on the other side.

4. Clinical Particulars
4.1 Therapeutic indications
Dolutegravir tablets is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age.

4.2 Posology and Method of Administration
Dolutegravir tablets 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 (one tablet) orally once daily.

Dolutegravir tablets 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 (one tablet) twice daily. The decision to use dolutegravir for such patients should be informed by the integrase resistance pattern (see section 5.1).

Co-administration of dolutegravir tablets with some medicines should be avoided in this population (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin). Please refer to section 4.4 and 4.5.

Missed doses
If the patient misses a dose of dolutegravir tablets, the patient should take dolutegravir tablets 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.

Adolescents aged 12 and above
In adolescents (aged from 12 to 17 years and weighing at least 40 kg) infected with HIV-1 without resistance to the integrase class, the recommended dose of dolutegravir is 50 mg once daily.

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 tablets in children aged less than 12 years or weighing less than 40 kg has not yet been established. In the presence of integrase inhibitor resistance, there are insufficient data to recommend a dose for dolutegravir tablets 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.

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

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Co-administration with dofetilide (see section 4.5).

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

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 harboring 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.

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 agents 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) 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, tipranavir/ritonavir, rifampicin and certain anti-epileptic drugs) (see section 4.5).

Metformin concentrations may be increased by dolutegravir. Patients should be monitored during therapy and a dose adjustment of metformin may be required (see section 4.5).

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.

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, P-gp. and BCRP; therefore, medicinal products that induce those enzymes may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir (see Table 1). Co-administration of dolutegravir and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration (see Table 1).

The absorption of dolutegravir is reduced by certain anti-acid agents (see Table 1).

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 or MATE-1 (e.g. dofetilide, metformin) (see Table 1 and section 4.3).

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 medical products in which excretion is dependent upon OAT3.

Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in Table 1.

Interaction table

Interactions between dolutegravir and co-administered medicinal products are listed in Table 1 (*increase* is indicated as "↑", decrease as "↓", no change as "↔", area under the concentration versus time curve as "AUC", maximum observed concentration as "C_{max}", concentration at end of dosing interval as "C").

Table 1: 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	Dolutegravir ↓ AUC ↓ 71% C_{max} ↓ 52% C ↓ 88% Etravirine ↔ (Induction of UGT1A1 and CYP3A enzymes)	Etravirine decreased plasma dolutegravir concentration, which may result in loss of virologic response and possible resistance to dolutegravir. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ ritonavir, darunavir/ritonavir or lopinavir/ritonavir (see further below in table).
Efavirenz	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% C ↓ 75% Efavirenz ↔ (historical controls) (Induction of UGT1A1 and CYP3A enzymes)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. 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 dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. 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% C ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitors		
Tenofovir	Dolutegravir ↔ AUC ↑ 1% C_{max} ↓ 3% C ↓ 8% Tenofovir ↔	No dose adjustment is necessary.
Protease Inhibitors		
Atazanavir	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% C ↑ 180% Atazanavir ↔ (historical controls) (Inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Atazanavir/Ritonavir	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 34% C ↑ 121% Atazanavir ↔ Ritonavir ↔ (Inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Tipranavir/Ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ 59% C_{max} ↓ 47% C ↓ 76% (Induction of UGT1A1 and CYP3A enzymes)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir the absence of integrase class resistance. 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% C ↓ 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.
Nelfinavir	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary.
Darunavir/Ritonavir	Dolutegravir ↓ AUC ↓ 32% C_{max} ↓ 11% C24 ↓ 38% (Induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Lopinavir/Ritonavir	Dolutegravir ↔ AUC ↓ 3% C_{max} ↔ 0% C24 ↓ 6%	No dose adjustment is necessary.
Protease Inhibitors and Non-nucleoside Reverse Transcriptase Inhibitors Combinations		
Lopinavir/Ritonavir + Etravirine	Dolutegravir ↔ AUC ↑ 10% C_{max} ↑ 7% C ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/Ritonavir + Etravirine	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% C ↓ 37% DRV ↔ RTV ↔	No dose adjustment is necessary.
Other Antiviral Agents		
Telaprevir	Dolutegravir ↑ AUC ↑ 25% C_{max} ↑ 19% C ↑ 37% Telaprevir ↔ (Historical controls) (Inhibition of CYP3A enzyme)	No dose adjustment is necessary.
Boceprevir	Dolutegravir ↔ AUC ↑ 7% C_{max} ↑ 5% C ↑ 8% Boceprevir ↔ (Historical controls)	No dose adjustment is necessary.
Other Agents		
Antiarrhythmics		
Dofetilide	Dofetilide ↑ (Not studied, potential increase via inhibition of OCT2 transporter)	Dolutegravir and dofetilide co-administration is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration (see section 4.3).
Anticonvulsants		
Oxcarbamazepine Phenytoin Phenobarbital Carbamazepine	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes)	Co-administration with these enzyme inducers should be avoided.
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)	Co-administration with St. John's Wort is strongly discouraged.
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% C24 ↓ 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% C24 ↓ 56% (Complex binding to polyvalent ions)	
Multivitamin	Dolutegravir ↓ AUC ↓ 33% C_{max} ↓ 35% C24 ↓ 32% (Complex binding to polyvalent ions)	
Corticosteroids		
Prednisone	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 6% C ↑ 17%	No dose adjustment is necessary.
Antidiabetics		
Metformin	Metformin ↑ Dolutegravir ↔ (Not studied. Increase of metformin expected, due to inhibition of OCT-2 transporter)	Close monitoring of metformin efficacy and safety is recommended when starting or stopping dolutegravir in patients receiving metformin. A dose adjustment of metformin may be necessary.
Antimycobacterials		
Rifampicin	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 43% C ↓72% (Induction of UGT1A1 and CYP3A enzymes)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin in the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided (see section 4.4).
Rifabutin	Dolutegravir ↔ AUC ↓ 5% C_{max} ↑ 16% C ↓ 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% C ↓ 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
There are limited amount of data from the use of dolutegravir in pregnant women. The effect of dolutegravir on human pregnancy is unknown. In reproductive toxicity studies in animals, dolutegravir was shown to cross the placenta. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Dolutegravir should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.

Breast-feeding
It is unknown whether dolutegravir is excreted in human milk. Available toxicological data in animals has shown excretion of dolutegravir in milk. In lactating rats that received a single oral dose of 50 mg/kg at 10 days postpartum, dolutegravir was detected in milk at concentrations typically higher than blood. It is recommended that HIV infected women do not breast-feed their infants under any circumstances 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.

4.7 Effects on abilily to drive and use machines
There have been no studies to investigate the effect of dolutegravir on driving performance or the ability to operate machines. However, 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 safety profile is based on pooled data from Phase IIb and Phase III clinical studies in 1222 previously untreated patients, 357 previously treated patients unexposed to integrase inhibitors and 264 patients with prior treatment failure that included an integrase inhibitor (including integrase class resistance). The most severe adverse reaction, seen in an individual patient, was a hypersensitivity reaction that included rash and severe liver effects (see section 4.4). The most commonly seen treatment emergent adverse reactions were nausea (13%), diarrhoea (18%) and headache (13%).

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

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

Table 2: 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
Nervous system disorders	Very common	Headache
	Common	Dizziness
Gastrointestinal disorders	Very common	Nausea
	Very common	Diarrhoea
	Common	Vomiting
	Common	Flatulence
	Common	Upper abdominal pain
	Common	Abdominal pain
	Common	Abdominal discomfort
Hepatobiliary disorders	Uncommon	Hepatitis
Skin and subcutaneous tissue disorders	Common	Rash
	Common	Pruritus
General disorders and administration site conditions	Common	Fatigue
Investigations	Common	Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations
	Common	Creatine phosphokinase (CPK) elevations

** see below under Description of selected adverse reactions.

Description of selected adverse reactions
Changes in laboratory biochemistries
Increases in serum creatinine occurred within the first week of treatment with 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 response syndrome
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

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AUROBINDO Packaging Development		Product Name	Component	Item Code	Date & Time
		Dolutegravir Tablets 50 mg	Leaflet	P1521328	02.7.2019 & 11.00 am
		Country	Version No.	Reason of Issue	Reviewed / Approved by
		Philippines	04	Commercial	
Team Leader	Pratap Sahu	Dimensions (mm)	Colours: 01	UNIT_7	
Initiator	Subramanyam	280 x 580 mm			
Artist	Sree Designers	Pharma Code: 21328			
Additional Information:			21328		

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

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: J05AX12

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 IC50 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 IC50s 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 IC50 value was 0.2 nM (range 0.02-2.14). The mean IC50 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 told shift was 7S fold, resulting in protein adjusted IC90 of 0.064 ug/mL.

Resistance
Resistance in vitro
In a study of evolution of resistance *in vitro* serial passage is used. When the lab-strain HIV-1 IIIB is used 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.

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 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): L74I,/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 E157Q (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).

Effects on electrocardiogram
No relevant effects were reported on the QTc interval, with doses exceeding the clinical dose by approximately threefold.

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 48 week data from an open-label, randomized and active-controlled study FLAMINGO (ING114915).

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 (DTG + ABC/3TC) or fixed-dose efavirenz-tenofovir-emtricitabine (EFV/TDF/FTC). At baseline, median patient age was 35 years, 16% were female, 32% non-white, 7% had hepatitis C co-infection and 4% were CDC Class C, these characteristics were similar between treatment groups.

The primary endpoint and other week 48 outcomes (including outcomes by key baseline covariates) for SPRING-2 and SINGLE are shown in Table 3.

Table 3: 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/ mm3)				
<200	43 / 55 (78%)	34 / 50 (68%)	45 / 57 (79%)	48 / 62 (77%)
200 to <350	128 / 144 (89%)	118 / 139 (85%)	143 / 163 (88%)	126 / 159 (79%)
≥350	190 / 212 (90%)	199 / 222 (90%)	176 / 194 (91%)	164 / 198 (83%)
NRTI Backbone				
ABC/3TC	145 / 169 (86%)	142 / 164 (87%)	N/A	N/A
	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 3 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/mm3, 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 a median change in CD4 count of 325 vs 281 cells/ mm3, respectively.

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.

Treatment emergent resistance in previously untreated patients failing therapy
Through 96 weeks in SPRING-2 and SINGLE, and through 48 weeks of therapy in the FLAMINGO study, no cases of treatment emergent 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.

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 4.

Table 4: 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/ mm3)		
<50	33 / 62 (53%)	30 / 59 (51%)
50 to <200	77 / 111 (69%)	76 / 125 (61%)
200 to <350	64 / 82 (78%)	53 / 79 (67%)
≥350	77 / 99 (78%)	71 / 98 (72%)
Background Regimen		
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/mm3)	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 dolutegravir tablets 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 dolutegravir tablets (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 dolutegravir tablets 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/mm3, 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; 82% had non-R5 virus.

Mean change from baseline in HIV RNA at day 8 (primary endpoint) was -1.4log10 copies/mL (95% CI -1.3 – -1.5log10, p<0.001). Response was associated with baseline INI mutation pathway, as shown in Table 5.

Table 5: 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	DTG 50 mg BID N=88*		
	n	Mean (SD) Plasma HIV-1 RNA log10 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 log10 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 6. 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 6: 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/mm3 at Week 24 and 110 cells/mm3 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. 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 log10 copies/mL (95% CI -1.5 - -0.8log10 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.

Paediatric population
In a Phase I/II 48 week multicentre, open-label study (P1093/ING112578), the pharmacokinetic parameters, safety, tolerability and efficacy of dolutegravir tablets will be evaluated in combination regimens in HIV-1 infected adolescents.

At 24 weeks, 16 of 23 (70%) adolescents (12 to less than 18 years of age) treated with dolutegravir tablets once daily (35 mg n=4, 50 mg n=19) plus OBR achieved viral load <50 copies/mL. Four subjects had virologic failure none of which had INI resistance at the time of virologic failure.

The European Medicines Agency has deferred the obligation to submit the results of studies with dolutegravir tablets in paediatric patients aged 4 weeks to below 12 years with HIV infection (see section 4.2 for information on paediatric use).

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 from 30 to 65% across studies. The between-subject PK variability of dolutegravir was higher in HIV infected subjects than healthy subjects. Within-subject variability (CVw%) is lower than between-subject variability.

Absorption
Dolutegravir is rapidly absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for tablet formulation.

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-∞) by 33%, 41%, and 66%, increased C_{max} by 46%, 52%, and 67%, prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively.

These increases may be clinically relevant in the presence of certain integrase class resistance. Therefore, dolutegravir tablets 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 P450 (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 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 tablet formulation. With 50 mg twice daily, the exposure over 24 hours was approximately doubled compared to 50 mg 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 log10 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 group.

Special patient populations
Children
The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 to <18 years of age) showed that dolutegravir tablets 50 mg once daily oral dosage resulted in dolutegravir exposure comparable to that observed in adults who received dolutegravir tablets 50 mg orally once daily.

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

Pharmacokinetic data for dolutegravir in subjects >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 dolutegravir 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. Dolutegravir tablets has not been studied in patients on dialysis.

Hepatic impairment
Dolutegravir is primarily metabolized and eliminated by the liver. A single dose of 50 mg of dolutegravir 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 dolutegravir tablets 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.

6. Pharmaceutical particulars
6.1 List of excipients
Tablet Core:
Mannitol, Microcrystalline Cellulose, Povidone, Sodium Starch Glycolate, Sodium Stearyl Fumarate.

Film-coating:
Polyvinyl Alcohol, Macrogol 3350, Titanium dioxide, Talc, Iron oxide red.

6.2 Incompatibilities
Not applicable.

6.3 Shelf-life
Please refer outer package for expiry date.

6.4 Storage Condition
Store at temperatures not exceeding 30°C.

6.5 Nature and contents of container
By 30's in a white opaque round 60cc HW HDPE Container with 33mm neck finish close with 33mm white opaque polypropylene stock ribbed closure with wad having induction sealing liner (Box of 1's)

6.6 Instructions for use and handling
No special requirements.

7. Caution
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
"For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph"
Please seek medical attention immediately at the first sign of any adverse drug reaction.

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