1. Name of the Medicinal Product

Dolutegravir Sodium Tablets 50 mg

2. Qualitative and Quantitative Composition

Each film coated tablet contains:
Dolutegravir sodium
equivalent to Dolutegravir 50 mg

For Excipients see point 6.1

3. Pharmaceutical Form

Film Coated Tablet

4. Clinical Particulars

4.1 Therapeutic indications

` Dolutegravir Sodium Tablets 50mg is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children above 6 years of age .

4.2 Posology and method of administration

Dolutegravir Sodium Tablets 50mg 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 Sodium Tablets 50mg should be administered twice daily in this population when co-administered with some medicines (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin).

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.

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.

The decision to use dolutegravir for such patients should be informed by the integrase resistance pattern.

Adolescents aged 12 and above

In adolescents (12 to less than 18 years of age 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. In the presence of integrase inhibitor resistance, there are insufficient data to recommend a dose for dolutegravir in adolescents.

Children 6 to less than 12 years of age

In patients infected with HIV-1 without resistance to the integrase class, the recommended dose of dolutegravir in children (6 to less than 12 years of age and weighing at least 15 kg) is determined according to the weight of the child.

In the presence of integrase inhibitor resistance, there are insufficient data to recommend a dose for dolutegravir in children. Dose recommendations according to weight are presented in table.

Table Paediatric dose recommendations

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

The specific dosage recommendation for the 10 mg tablet, as specified in above Table, should be followed. Therefore, the 50 mg once daily dose should not be given as five 10 mg tablets.

Missed doses

If the patient misses a dose of Dolutegravir Sodium Tablets 50mg, the patient should take Dolutegravir Sodium Tablets 50mg 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.

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.

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.

Paediatric population

The safety and efficacy of dolutegravir in children aged less than 6 years or weighing less than 15 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.

Method of administration

Oral use

Dolutegravir Sodium Tablets 50mg can be taken with or without food. In the presence of integrase class resistance, Dolutegravir Sodium Tablets 50mg should preferably be taken with food to enhance exposure (particularly in patients with Q148 mutations).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients .
- Dolutegravir Sodium Tablets must not be administered concurrently with medicinal products with narrow therapeutic windows that are substrates of organic cation transporter 2 (OCT2), including but not limited to fampridine (also known as dalfampridine)

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 harbouring Q148+≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I. 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.

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/ aluminiumcontaining 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 drugs).

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.

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, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. 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 . 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.

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. Co-administration of dolutegravir and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration.

The absorption of dolutegravir is reduced by certain anti-acid agents

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.

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).

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 below Table.

Interaction table

Interactions between dolutegravir and co-administered medicinal products are listed in Table (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 "Cr").

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	Dolutegravir ↓ AUC ↓ 71%	Etravirine without boosted protease inhibitors decreased plasma

inhibitors	C_{max} ↓ 52% $C\tau$ ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	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.
Lopinavir/ritonavir + etravirine	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% $C\tau$ ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% $C\tau$ ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary.
Efavirenz	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% $C\tau$ ↓ 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.
Nevirapine	Dolutegravir ↓ (Not studied, a similar reduction in exposure as observed with efavirenz is expected, due to induction)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance alternative combinations that do not include nevirapine should be considered.
Rilpivirine	Dolutegravir ↔ AUC ↑ 12% C_{max} ↑ 13% C_{τ} ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitors		
Tenofovir	Dolutegravir ↔ AUC ↑ 1% C_{max} ↓ 3% C_{τ} ↓ 8% Tenofovir ↔	No dose adjustment is necessary.
Protease Inhibitors		
Atazanavir	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% C_{τ} ↑ 180% Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. Dolutegravir should not be dosed higher than 50 mg twice daily in combination with atazanavir due to lack of data.
Atazanavir/ritonavir	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 34%	No dose adjustment is necessary. Dolutegravir should not be dosed higher than 50 mg twice daily in

	C_{τ} ↑ 121% Atazanavir ↔ Ritonavir ↔ (inhibition of UGT1A1 and CYP3A enzymes)	combination with atazanavir due to lack of data.
Tipranavir/ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ 59% C_{max} ↓ 47% C_{τ} ↓ 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.
Fosamprenavir/ ritonavir (FPV+RTV)	Dolutegravir ↓ AUC ↓ 35% C_{max} ↓ 24% C_{τ} ↓ 49% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary in the absence of integrase class resistance.In the presence of integrase class resistance alternative combinations that do not include fosamprenavir/ritonavir should be considered.
Darunavir/ritonavir	Dolutegravir ↓ AUC ↓ 22% C_{max} ↓ 11% C_{24} ↓ 38% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Lopinavir/ritonavir	Dolutegravir ↔ AUC ↓ 4% C_{max} ↔ 0% C_{24} ↓ 6%	No dose adjustment is necessary.
Other Antiviral agents		
Daclatasvir	Dolutegravir ↔ AUC ↑ 33% C_{max} ↑ 29%	Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent.

	C_{τ} ↑ 45% Daclatasvir ↔	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_{τ} ↓ 73%	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternatives to carbamazepine should be used where possible for INI resistant patients.
Oxcarbazepine Phenytoin Phenobarbital	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with these metabolic inducers. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include these metabolic inducers should be used where possible in INI-resistant patients.
Azole anti-fungal agents		

Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected.
Herbal products		
St. John's wort	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with St. John's wort. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include St. John's wort should be used where possible in INI-resistant patients.
Antacids and supplements		
Magnesium/ aluminium-containing antacid	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% (Complex binding to polyvalent ions)	Magnesium/ aluminium-containing antacid should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).
Calcium supplements	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 dolutegravir 50mg twice daily: Metformin AUC ↑ 145 % C_{max} ↑ 111%	A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when coadministered with dolutegravir, because of the increased risk for lactic acidosis in patients with moderate renal impairment due to increased metformin concentration .
Antimycobacterials		
Rifampicin	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 43% C_{τ} ↓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 .
Rifabutin	Dolutegravir ↔ AUC ↓ 5% C_{max} ↑ 16% $C\tau$ ↓ 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% $C\tau$ ↓ 1%	No dose adjustment is necessary of either agent.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Pregnancy and Lactation

Pregnancy

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 . 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.

Lactation

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.

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

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).

Immune system disorders	Uncommon	Hypersensitivity
	Uncommon	Immune Reconstitution Syndrome
Psychiatric disorders	Common	Insomnia
	Common	Abnormal dreams
	Common	Depression
	Common	Anxiety
	Uncommon	Suicidal ideation*, suicide attempt* *particularly in patients with a pre-existing history of depression or psychiatric illness.
Nervous system	Very common	Headache

disorders	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
	Rare	Acute hepatic failure
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	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.

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

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy.

Paediatric population

Based on limited available data in children and adolescents (6 to less than 18 years of age and weighing at least 15 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

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.

5.2 Pharmacokinetic properties

Absorption:

Dolutegravir is rapidly absorbed following oral administration, with median Tmax 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 $AUC_{(0-\infty)}$ 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.

These increases may be clinically relevant in the presence of certain integrase class resistance. Therefore, Dolutegravir Sodium Tablets 50 mg is recommended to be taken with food by patients infected with HIV with integrase class resistance.

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 17L to 20L 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 18ng/mL (comparable to unbound plasma concentration, and above the IC_{50}).

Dolutegravir is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue and vaginal tissue were 6-10% 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).

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.

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).

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).

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

Mannitol, Microcrystalline Cellulose (PH 101), Sodium Starch Glycolate (Type A), Povidone, Sodium Stearyl Fumarate, Opadry II Pink (85F540358), Purified Water

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C in dry place, protect from light.

6.5 Nature and contents of container

HDPE Container pack of 30's

6.6 Special Precaution for disposal

None

7. Supplier

Macleods Pharmaceuticals Ltd.
304, Atlanta Arcade, Marol Church Road,
Andheri (East), Mumbai- 400 059,
India
Phone: +91-22-66762800
Fax: +91-22-2821 6599
E-mail: exports@macleodsphara.com

8. Who Reference Number (Prequalification Programme)

9. Date of first Prequalification/ last renewal

10. Date of Revision of the Text:

References:

https://www.medicines.org.uk/emc/product/10057/smpc

PACKAGE LEAFLET: INFORMATION FOR THE USER

Dolutegravir Sodium Tablets 50 mg

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

What is in this leaflet

1. WHAT DOLUTEGRAVIR 50 mg ARE AND WHAT IT IS USED FOR
Dolutegravir belongs to a group of anti-retroviral medicines called *integrase inhibitors (INIs)*.

Dolutegravir 50 mg tablet is used to treat **HIV (human immunodeficiency virus) infection** in adults and adolescents over 12 years old.

Dolutegravir 50 mg tablet does not cure HIV infection; it reduces the amount of virus in your body, and keeps it at a low level. As a result of that, it also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cells that are important in helping your body to fight infection.

Not everyone responds to treatment with Dolutegravir 50 mg tablet in the same way. Your doctor will monitor the effectiveness of your treatment.

Dolutegravir 50mg tablet is always used in combination with other anti-retroviral medicines (*combination therapy*). To control your HIV infection, and to stop your illness from getting worse, you must keep taking all your medicines, unless your doctor tells you to stop taking any.

2. BEFORE YOU TAKE DOLUTEGRAVIR 50 mg TABLETS

Don't take Dolutegravir 50mg tablet:
- if you are allergic to dolutegravir or any of the other ingredients of this medicine.
- if you are taking another medicine called dofetilide (to treat heart conditions).

→If you think any of these apply to you, tell your doctor.

Warnings and precautions
Look out for important symptoms
Some people taking medicines for HIV infection develop other conditions, which can be serious. These include:
- symptoms of infections and inflammation
- joint pain, stiffness and bone problems

You need to know about important signs and symptoms to look out for while you're taking Dolutegravir 50mg tablet.

Protect other people
HIV infection is spread by sexual contact with someone who has the infection, or by transfer of infected blood (for example, by sharing injection needles). You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.

Children
Do not give this medicine to children under 12 years of age, weighing less than 40 kg or with HIV infection that is resistant to other medicines similar to Dolutegravir 50mg tablet. The use of Dolutegravir 50mg tablet in children under 12 has not yet been studied.

Other medicines and Dolutegravir 50 mg tablet
Tell your doctor if you are taking, have recently taken or are planning to take any other medicines. This includes herbal medicines and other medicines bought without a prescription.

Don't take Dolutegravir 50mg tablet with the following medicine:
- dofetilide, used to treat **heart conditions**

Some medicines can affect how Dolutegravir 50mg tablet works, or make it more likely that you will have side effects. Dolutegravir 50mg tablet can also affect how some other medicines work.
Tell your doctor if you are taking any of the medicines *in the following list*:
- metformin, to treat diabetes
- medicines called antacids, to treat indigestion and heartburn. Do not take an antacid during the 6 hours before you take Dolutegravir 50mg tablet, or for at least 2 hours after you take it.
- calcium supplements, iron supplements and multivitamins. **Do not take a calcium supplement, iron supplement or multivitamin** during the 6 hours before you take Dolutegravir 50mg tablet, or for at least 2 hours after you take it.
- etravirine, efavirenz, fosamprenavir/ritonavir, nevirapine or tipranavir/ritonavir, to treat **HIV infection**
- rifampicin, to treat tuberculosis (TB) and other **bacterial infections**
- phenytoin and phenobarbital, to treat **epilepsy**
- oxcarbazepine and carbamazepine, to treat **epilepsy** or **bipolar disorder**
- **St. John's wort** (*Hypericum perforatum*), a herbal remedy to treat **depression**

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

Pregnancy
If you are pregnant, if you become pregnant, or if you are planning to have a baby:
→ **Talk to your doctor** about the risks and benefits of taking Dolutegravir 50mg tablet.

Breast-feeding
Women who are HIV-positive must not breast feed because HIV infection can be passed on to the baby in breast milk.
It is not known whether the ingredients of Dolutegravir 50mg tablet can pass into your breast milk.

If you are breast-feeding, or thinking about breast-feeding:
→ **Talk to your doctor immediately.**

Driving and using machines
Dolutegravir 50mg tablet can make you dizzy and have other side effects that make you less alert.
→ Don't drive or operate machinery unless you are sure you're not affected.

3. HOW TO TAKE DOLUTEGRAVIR 50 mg
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
- The usual dose is one 50 mg tablet **once a day**; if you are taking certain other medicines, the dose is one 50 mg tablet twice a day; or
- **For the treatment of HIV that is resistant** to other medicines similar to Dolutegravir 50mg tablet, the usual dose of Dolutegravir 50mg tablet is one 50 mg tablet, **twice a day.**

Your doctor will decide on the correct dose of Dolutegravir 50mg tablet for you.

Swallow the tablet with some liquid. Dolutegravir 50mg tablet can be taken with or without food. When Dolutegravir 50mg tablet is taken twice a day, your doctor may advise you to take with food.

Use in children and adolescents
Children and adolescents aged between 12 and 17 years and weighing at least 40 kg can take the adult dose of one tablet (50 mg), once a day. Dolutegravir 50mg tablet should not be used in children and adolescents with **HIV infection that is resistant** to other medicines similar to Dolutegravir 50mg tablet.

Antacid medicines
Antacids, to treat indigestion and heartburn, can stop Dolutegravir being absorbed into your body and make it less effective.
Do not take an antacid during the 6 hours before you take Dolutegravir 50mg tablet, or for at least 2 hours after you take it. Other acid-lowering medicines like ranitidine and omeprazole can be taken at the same time as Dolutegravir 50mg tablet.

→ Talk to your doctor for further advice on taking acid-lowering medicines with Dolutegravir 50mg tablet.

Calcium supplements, iron supplements or multivitamins
Calcium supplements, iron supplements or multivitamins can stop Dolutegravir being absorbed into your body and make it less effective.
Do not take a calcium supplement, iron supplement or multivitamin during the 6 hours before you take Dolutegravir 50mg tablet, or for at least 2 hours after you take it.
→Talk to your doctor for further advice on taking calcium supplements, iron supplements or multivitamins with Dolutegravir 50mg tablet.
If you take more Dolutegravir 50mg tablet than you should
If you take too many tablets of Dolutegravir 50mg tablet, **contact your doctor or pharmacist for advice**. If possible, show them the Dolutegravir 50mg tablet pack.

If you forget to take Dolutegravir 50mg tablet
If you miss a dose, take it as soon as you remember. But if your next dose is due within 4 hours, skip the dose you missed and take the next one at the usual time. Then continue your treatment as before.
→ **Don't take a double dose** to make up for a missed dose.

Don't stop taking Dolutegravir 50mg tablet without advice from your doctor
Take Dolutegravir 50mg tablet for as long as your doctor recommends. Don't stop unless your doctor advises you to.

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

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

When you're being treated for HIV, it can be hard to tell whether a symptom is a side effect of Dolutegravir 50mg tablet or other medicines you are taking, or an effect of the HIV disease itself. **So it is very important to talk to your doctor about any changes in your health**.

Allergic reactions
These are uncommon in people taking Dolutegravir 50mg tablet. Signs include:
- skin rash
- a high temperature (*fever*)
- lack of energy (*fatigue*)
- swelling, sometimes of the face or mouth (*angioedema*), causing difficulty in breathing
- muscle or joint aches.

→ **See a doctor straight away.** Your doctor may decide to carry out tests on your liver, kidneys or blood, and may tell you to stop taking Dolutegravir 50mg tablet.

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

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

Uncommon side effects
These may affect **up to 1 in 100 people**:
- inflammation of the liver (*hepatitis*)
- suicidal thoughts and behaviours (particularly in patients who have had depression or mental health problems before)

If you get any side effects
→ **Talk to your doctor**. This includes any possible side effects not listed in this leaflet.

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

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

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

Joint pain, stiffness and bone problems
Some people taking combination therapy for HIV develop a condition called *osteonecrosis*. With this condition, parts of the bone tissue die because of reduced blood supply to the bone. People may be more likely to get this condition:
- if they have been taking combination therapy for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids
- if they drink alcohol
- if their immune systems are very weak
- if they are overweight.

Signs of osteonecrosis include:
- stiffness in the joints
- aches and pains in the joints (especially in the hip, knee or shoulder)
- difficulty moving.

If you notice any of these symptoms:
→ **Tell your doctor**.
Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. HOW TO STORE DOLUTEGRAVIR 50 mg
Store below 30°C in dry place, protect from light.
Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated after EXP on the carton and bottle.
This medicine does not require any special storage conditions.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. FURTHER INFORMATION
What Dolutegravir 50mg tablet contains
- The active substance is dolutegravir. Each tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir.
- The other ingredients are Mannitol, Microcrystalline cellulose, Povidone, Sodium starch glycolate, Sodium stearyl fumarate, Polyvinyl alcohol, Triacetin, Talc, Titanium Dioxide, Red Iron oxide

What Dolutegravir 50mg tablet looks like and contents of the pack
Dolutegravir 50mg tablet film-coated tablets are Pink coloured round , biconvex, film coated debossed “I77” on one side and plain on other side.
The film-coated tablets are provided in bottles containing 30 or 90 tablets.

Supplier
Macleods Pharmaceuticals Ltd.
304, Atlanta Arcade,
Marol Church Road,
Andheri (East)
Mumbai- 400 059,
India
Phone: +91-22-66762800
Fax: +91-22-2821 6599
E-mail: exports@macleodspharma.com

Manufacturer
Macleods Pharmaceuticals Limited
Plot No. 25-27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman - 396 210 (U.T.)
Off.: Atlanta Arcade, Marol Church Road, Andheri (E), Mumbai - 400 059.

PM02465301

NOTICE: INFORMATION POUR L'UTILISATEUR

Comprimés de Dolutegravir sodique 50 mg

Lisez attentivement cette brochure entièrement avant que vous commenciez à prendre ce médicament car elle contient des informations importantes pour vous.
- Gardez cette notice. Vous aurez peut-être besoin de la relire.
- Si vous avez d'autres questions, posez-les à votre médecin ou à votre pharmacien.
- Ce médicament a été prescrit pour vous uniquement. Ne le donnez pas à d'autres personnes. Il peut leur faire du mal, même si leurs symptômes sont les mêmes que les vôtres.
- Si vous obtenez des effets secondaires quelconques parlez-en à votre médecin ou votre pharmacien. Cela inclut les effets secondaires possibles, qui ne figurent pas dans cette notice.

Qu'y a-t-il dans cette notice

1. QU'EST-CE QUE C'EST QUE DOLUTEGRAVIR 50 mg ET À QUOI IL SERT
Dolutegravir appartient à un groupe de médicaments antirétroviraux, appelés *inhibiteurs de l'intégrase (INIs)*.

Dolutegravir 50 mg comprimés est utilisé pour traiter **l'infection par le VIH (virus de l'immunodéficience humaine)** chez les adultes et les adolescents âgés de plus de 12 ans.

Dolutegravir 50 mg comprimés ne guérit pas l'infection par le VIH; Il réduit la quantité de virus dans votre corps et le maintient à un niveau bas. À la suite de cela, il augmente aussi le comptage de cellules CD4 dans le sang. Les cellules CD4 sont un type de globules blancs qui sont importants pour aider votre corps à combattre l'infection.

Pas tout le monde réagit de la même manière au traitement avec Dolutegravir 50 mg comprimés. Votre médecin surveillera l'efficacité de votre traitement.

Dolutegravir 50mg comprimés est toujours utilisé en combinaison avec d'autres médicaments antirétroviraux (*traitement combiné*). Pour contrôler votre infection par le VIH et pour arrêter la progression de votre maladie, vous devez continuer à prendre tous vos médicaments, sauf si votre médecin vous dit d'arrêter de prendre l'un des médicaments.

2. AVANT DE PRENDRE DOLUTEGRAVIR 50 mg COMPRIMÉS

Ne prenez pas Dolutegravir 50mg comprimés:
- Si vous êtes allergique au dolutegravir ou à l'un des autres composants de ce médicament.
- Si vous prenez un autre médicament appelé dofétilide (pour traiter les troubles cardiaques).

→Si vous pensez qu'un de ceux-ci s'appliquent à vous, parlez-en à votre médecin.

Avertissements et précautions
Faite attention aux symptômes importants
Certaines personnes prenant des médicaments pour une infection au VIH développent d'autres conditions, qui peuvent être graves. Celles-ci
incluent:
- symptômes de l'infection et de l'inflammation
- douleurs articulaires, raideur et problèmes osseux

Vous devez connaître les signes et symptômes importants à surveiller pendant que vous prenez Dolutegravir 50mg comprimés.

Protéger d'autres personnes
L'infection par le VIH se transmet par contact sexuel avec une personne qui a l'infection, ou par transfert de sang infecté (par exemple, en partageant des aiguilles à injection). Vous pouvez toujours passer le VIH lors de la prise de ce médicament, même si le risque est réduit par un traitement antirétroviral efficace. Discutez avec votre médecin des précautions nécessaires pour éviter d'infecter d'autres personnes.

Enfants
Ne donnez pas ce médicament aux enfants moins de 12 ans, moins de 40 kg ou infectés par le VIH qui est résistant aux autres médicaments similaires à Dolutegravir 50mg comprimés. L'utilisation du Dolutegravir 50mg comprimés chez les enfants de moins de 12 n'a pas encore été étudiée.

Autres médicaments et Dolutegravir 50 mg comprimés
Prévenez votre médecin si vous prenez, si vous avez récemment pris ou si vous envisagez de prendre tout autre médicament. Cela inclut des médicaments à base de plantes et autres médicaments achetés sans ordonnance.

Ne prenez pas Dolutegravir 50mg comprimés avec les médicaments suivants:
- dofétilide, utilisé pour traiter les **troubles cardiaques**

Certains médicaments peuvent affecter le fonctionnement de Dolutegravir 50mg comprimés, ou rendre plus vraisemblable la possibilité que vous aillez des effets secondaires. Dolutegravir 50mg comprimés peut également affecter comment fonctionnent certains autres médicaments.
Prévenez votre médecin si vous prenez l'un des médicaments *de la liste suivante*:
- metformine, pour traiter le diabète
- les médicaments appelés antiacides, pour traiter les indigestions et brûlures d'estomac. Ne prenez pas un antiacide durant les 6 heures avant de prendre Dolutegravir 50mg comprimés, ou pendant au moins 2 heures après que vous le prenez.
- les suppléments de calcium, les suppléments de fer et les multivitamines. **Ne prenez pas de supplément de fer, de supplément de calcium ou de multivitamines** pendant les six heures avant de prendre Dolutegravir 50mg comprimés, ou pendant au moins 2 heures après que vous le prenez.
- étravirine, efavirenz, fosamprénavir/ritonavir, névirapine ou tipranavir/ritonavir, pour traiter **le VIH infection**
- rifampicine, pour traiter la tuberculose (TB) et autres **infections bactériennes**
- phénytoïne et phénobarbital, pour traiter **l'épilepsie**
- Oxcarbazepine et carbamazépine, pour traiter **l'épilepsie** ou le **trouble bipolaire**
- **Millepertuis** (*Hypericum perforatum*), une plante médicinale pour traiter la **dépression**

→ Parlez à votre médecin ou votre pharmacien si vous prenez l'un de ces médicaments. Votre médecin peut décider d'ajuster votre dose, ou que vous avez besoin d'examens supplémentaires.

Grossesse
Si vous êtes enceinte, si vous devenez enceinte ou si vous avez décidé d'avoir un bébé :
→Parlez à votre médecin des risques et des avantages de prendre Dolutegravir 50mg comprimés.

L'allaitement maternel
Les femmes qui sont séropositives ne doivent allaitez pas parce que l'infection par le VIH peut être transmise au bébé dans le lait maternel.
On ne sait pas si les composants du Dolutegravir 50mg comprimés peuvent passer dans le lait maternel.

Si vous allaitez au sein, ou pensez à l'allaitement au sein:
→ Consultez immédiatement votre médecin.

Conduite et utilisation de machines
Dolutegravir 50mg comprimés peut vous rendre étourdi et a d'autres effets secondaires qui vous rendent moins alerte.
→ne pas conduire ou utiliser des machines, sauf si vous êtes sûr que vous n'êtes pas concerné.

3. COMMENT PRENDRE DOLUTEGRAVIR 50 mg
Prenez toujours ce médicament exactement comme votre médecin vous l'a dit. Vérifiez auprès de votre médecin ou votre pharmacien si vous n'êtes pas sûr.
- La dose habituelle est d'un comprimé de 50 mg **une fois par jour**; Si vous prenez certains autres médicaments, la dose est d'un comprimé de 50 mg deux fois par jour; ou
- **Pour le traitement du VIH résistant** aux autres médicaments similaires au Dolutegravir 50mg comprimés, la dose habituelle de Dolutegravir 50mg comprimés est d'un comprimé de 50 mg, **deux fois par jour.**

Votre médecin décidera de la dose correcte de Dolutegravir 50mg comprimés qui vous convient.

Avalez le comprimé avec peu de liquide. Dolutegravir 50mg comprimés peut être pris avec ou sans nourriture. Lorsque Dolutegravir 50mg comprimés est pris deux fois par jour, votre médecin peut vous conseiller de le prendre avec des aliments.

Utilisation chez les enfants et les adolescents
Les enfants et les adolescents âgés de 12 à 17 ans et pesant au moins 40 kg peuvent prennent la dose adulte (50 mg) d'un comprimé une fois par jour. Dolutegravir 50mg comprimés ne doit pas être utilisé chez les enfants et adolescents atteints **d'infection par le VIH résistant** aux autres médicaments similaires à Dolutegravir 50mg comprimés.

Médicaments antiacides
Les antiacides, pour traiter les indigestions et les brûlures d'estomac, peuvent empêcher Dolutegravir d'être absorbé dans votre corps et le rende moins efficace.
Ne prenez pas un antiacide durant les 6 heures avant de prendre Dolutegravir 50mg comprimés, ou pendant au moins 2 heures après que vous le prenez. Les autres médicaments abaissant les acides comme la ranitidine et l'oméprazole peuvent être pris en même temps que Dolutegravir 50mg comprimés.

→ Parlez à votre médecin pour des conseils supplémentaires sur la prise de médicaments abaissant l'acide avec Dolutegravir 50mg comprimés.

Les suppléments de calcium, les suppléments de fer ou les multivitamines
Les suppléments de calcium, les suppléments de fer ou les multivitamines peuvent arrêter Dolutegravir d'être absorbé par votre organisme et le rendre moins efficace.
Ne prenez pas de supplément de calcium, de supplément de fer ou de multivitamines pendant les six heures avant de prendre Dolutegravir 50mg comprimés, ou pendant au moins 2 heures après vous le prenez.
→ Parlez à votre médecin pour des conseils supplémentaires sur la prise de suppléments de calcium, des suppléments de fer ou des multivitamines avec Dolutegravir 50mg comprimés.

Si vous prenez plus Dolutegravir 50mg comprimés que vous n'auriez dû prendre
Si vous prenez trop de comprimés de Dolutegravir 50mg comprimés, **contactez votre médecin ou votre pharmacien pour obtenir des conseils**. Si possible, leur montrer le pack de Dolutegravir 50mg comprimés.

Si vous oubliez de prendre Dolutegravir 50mg comprimés
Si vous manquez une dose, prenez-la dès que vous vous en souvenez. Mais si votre prochaine dose est due dans les 4 heures, sautez la dose oubliée et prenez la prochaine à l'heure habituelle. Continuez votre traitement comme avant.
→Ne prenez pas une double dose pour compenser une dose oubliée.

Ne cessez pas de prendre Dolutegravir 50mg comprimés sans l'avis de votre médecin
Prenez Dolutegravir 50mg comprimés pour aussi longtemps que votre médecin vous le recommande. N'arrêtez pas à moins que votre médecin vous le conseille.

Si vous avez d'autres questions sur l'utilisation de ce médicament, posez-les à votre médecin ou à votre pharmacien

4. EFFETS SECONDAIRES POSSIBLES
Comme tous les médicaments, ce médicament peut causer des effets secondaires, mais pas chez tout le monde.

Lorsque vous êtes traité pour le VIH, il peut être difficile de dire si un symptôme est un effet secondaire de Dolutegravir 50mg comprimés ou autres médicaments que vous prenez ou un effet de la maladie VIH elle-même. **Il est donc très important de parler à votre médecin de tout changement dans votre santé**.

Réactions allergiques
Celles-ci sont rares chez les personnes prenant des comprimés de Dolutegravir 50mg. Les signes comprennent:
- éruption cutanée
- température élevée (*fièvre*)
- manque d'énergie (*fatigue*)
- gonflement, parfois du visage ou la bouche (*œdème de Quincke*), causant des difficultés à respirer
- douleurs musculaires ou articulaires.

→ Voir un médecin tout de suite. Votre médecin peut décider de procéder à des tests sur votre foie, vos reins ou votre sang et peut vous dire d'arrêter de prendre les comprimés de Dolutegravir 50mg.

Effets indésirables très fréquents
Ceux-ci peuvent affecter **plus que 1 personne sur 10** :
- maux de tête
- diarrhée
- sentiment d'être malade (nausées).

Effets secondaires courants
Ceux-ci peuvent affecter **jusqu'à à 1 personne sur 10** :
- éruption cutanée
- démangeaison (prurit)
- être malade (vomissements)
- douleurs à l'estomac (douleurs abdominales)
- malaises à l'estomac (abdominale)
- insomnie
- vertige
- rêves anormaux
- dépression (sentiment de profonde tristesse et d'indignité)
- manque d'énergie (fatigue)
- vent (flatulences)
- augmentation du niveau des enzymes hépatiques
- augmentation du niveau des enzymes produites dans les muscles (*créatine phosphokinase*).

Effets secondaires peu fréquents
Ceux-ci peuvent affecter **jusqu'à 1 sur 100 personnes** :
- inflammation du foie (*hépatite*)
- les pensées et les comportements suicidaires (particulièrement chez les patients qui ont eu des dépressions ou problèmes de santé mentale au préalable)

Si vous obtenez des effets secondaires
→Parlez à votre médecin. Cela inclut les effets secondaires possibles, qui ne figurent pas dans cette notice.

Autres effets secondaires possibles
Les gens prenant la thérapie combinée pour le VIH peuvent obtenir d'autres effets secondaires
Symptômes de l'infection et de l'inflammation
Les personnes ayant une infection à VIH avancée (SIDA) ont un système immunitaire faible et sont plus susceptibles de développer des infections graves (*infections opportunistes*). Ces infections peuvent avoir été « silencieuses » et non détectés par le système immunitaire faible avant que traitement ai été commencé. Après avoir commencé le traitement, le système immunitaire se renforce et peut attaquer les infections qui peuvent causer des symptômes d'infection ou d'inflammation. Les symptômes comprennent habituellement la **fièvre**, ainsi que certains des éléments suivants:
- maux de tête
- mal de ventre
- difficulté à respirer

Dans de rares cas, comme le système immunitaire se renforce, il peut également attaquer les tissus sains *(maladies auto-immunes*). Les symptômes de troubles auto-immuns peuvent se développer plusieurs mois après que vous ayez commencé à prendre le médicament pour traiter votre infection par le VIH. Les symptômes peuvent inclure:
- palpitations (battements cardiaques rapides ou irréguliers) ou tremblements
- hyperactivité (agitations et mouvements excessifs)
- Faiblesse à partir des mains et des pieds et remontant vers le tronc du corps.

Si vous avez des symptômes de l'infection et de l'inflammation, ou si vous remarquez l'un des symptômes ci-dessus:
→ Prévenez votre médecin immédiatement. Ne pas prendre d'autres médicaments pour les infections sans avis de votre médecin.

Douleurs articulaires, raideur et problèmes osseux
Certaines personnes prenant la combinaison pour le VIH développent une maladie appelée *ostéonécrose*. Avec cette condition, des parties du tissu osseux meurent à cause de la circulation sanguine réduite à l'os. Les gens peuvent être plus susceptibles d'obtenir cette condition:
- s'ils ont suivi la thérapie combinée pendant une longue période
- s'ils prennent aussi des médicaments anti-inflammatoires appelés corticostéroïdes
- s'ils boivent de l'alcool
- si leur système immunitaire est très faible
- s'ils sont en surpoids.

Les signes de l'ostéonécrose comprennent:
- raideur dans les articulations
- douleurs dans les articulations (surtout dans la hanche, le genou ou l'épaule)
- difficultés à bouger.

Si vous remarquez l'un de ces symptômes:
→Prévenez votre médecin.
Signalement des effets secondaires
Si vous obtenez des effets secondaires, parlez-en à votre médecin ou votre pharmacien. Cela inclut les effets secondaires possibles, qui ne figurent pas dans cette notice.

5. COMMENT CONSERVER DOLUTEGRAVIR 50 mg
Conservez à une température inférieure à 30 °C en lieu sec, protégez de la lumière.
Gardez ce médicament hors de la vue et la portée des enfants.
N'utilisez pas ce médicament après la date de péremption qui est indiquée après EXP sur le carton et la bouteille.
Ce médicament ne nécessite pas de conditions particulières d'entreposage.
Ne jetez pas n'importe quel médicament via des eaux usées ou les ordures ménagères. Demandez à votre pharmacien comment jeter les médicaments que vous n'utilisez plus. Ces mesures contribueront à protéger l'environnement.

6. PLUS D'INFORMATIONS
Qu'est-ce que Dolutegravir 50mg comprimés contient
-La substance active est dolutegravir. Chaque comprimé contient dolutegravir sodique équivalant à 50 mg de dolutegravir.
-Les autres composants sont le Mannitol, la cellulose microcristalline, de la povidone, du glycolate sodique d'amidon, du stéaryl fumarate de sodium, de l'alcool polyvinylique, de la triacétine, du Talc, du dioxyde de titane, de l'oxyde de fer rouge
À quoi Dolutegravir 50mg comprimés ressemble et le contenu de l'emballage
Les comprimés pelliculés de Dolutegravir 50mg sont de couleur rose rond, biconvexe, enrobé en creux « I77 » d'un côté et lisse de l'autre côté.

Les comprimés pelliculés sont fournis dans des bouteilles contenant 30 ou 90 comprimés.

Fournisseur
Macleods Pharmaceuticals Ltd.
304, Atlanta Arcade,
Marol Church Road,
Andheri (East)
Mumbai- 400 059,
Inde
Téléphone: +91-22-66762800
Fax: +91-22-2821 6599
E-mail: exports@macleodspharma.com

Fabricant
Macleods Pharmaceuticals Limited
Plot No. 25-27, Survey No. 366,
Premier Industrial Estate, Kachigam,
Daman - 396 210 (U.T.)
Off.: Atlanta Arcade, Marol Church
Road, Andheri (E), Mumbai - 400 059.