Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets
P1528183

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SUMMARY OF PRODUCT CHARACTERISTICS

DOLUTEGRAVIR 50 mg, LAMIVUDINE 300 mg and TENOFOVIR DISOPROXIL FUMARATE 300 mg TABLETS

1. Name of the Finished Pharmaceutical Product

Dolutegravir 50 mg, Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg Tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains dolutegravir sodium equivalent to Dolutegravir 50 mg, Lamivudine USP 300 mg, Tenofovir Disoproxil fumarate 300 mg equivalent to 245 mg of Tenofovir disoproxil.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Dolutegravir 50 mg, Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg Tablets are Pink colored, Oval, biconvex, film coated tablets debossed with 'N33' on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Dolutegravir, Lamivudine and Tenofovir disoproxil fumarate is indicated alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients weighing 40 kg and above.

4.2 Posology and method of administration

Dolutegravir, Lamivudine and Tenofovir disoproxil fumarate Tablets should be prescribed by physicians experienced in the management of HIV infection.

Posology

Recommended Dose in Adults and Pediatric Patients aged 12 years and older and weighing 40 kg and above:
The recommended dose of dolutegravir, lamivudine and tenofovir disoproxil fumarate is one tablet (containing 50 mg of dolutegravir, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate) taken once daily orally with or without food.

Patients with Renal Impairment
Because dolutegravir, lamivudine and tenofovir disoproxil fumarate is a fixed-dose combination tablet, it is not recommended for patients with impaired renal function (creatinine clearance below 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis.

Pregnancy Testing before Initiation of Dolutegravir
Perform pregnancy testing before initiation of Dolutegravir in adolescents and adults of childbearing potential.

Method of administration
Oral use.

Dolutegravir, Lamivudine and Tenofovir disoproxil fumarate Tablets can be taken with or without food (see section 5.2).

4.3 Contraindications

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are contraindicated in patients:

- with a previous hypersensitivity reaction to dolutegravir and lamivudine *[see section (4.4)]*.
- receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Lactic Acidosis and Severe Hepatomegaly with Steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases also have been reported in patients with no known risk factors. Treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Patients with HIV-1, Hepatitis B and Hepatitis C virus Co-infection

Dolutegravir:
Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir. In some cases the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with dolutegravir are recommended in patients with underlying hepatic disease such as hepatitis B or C.

Lamivudine:

Posttreatment Exacerbations of Hepatitis:
Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from postmarketing experience after changes from lamivudine-containing HIV-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

Important Differences among Lamivudine-Containing Products:
Lamivudine tablets contain a higher dose of the same active ingredient (lamivudine) than EPIVIR-HBV tablets and EPIVIR-HBV oral solution. EPIVIR-HBV was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in EPIVIR-HBV are not appropriate for patients co-infected with HIV-1 and HBV. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV. If treatment with EPIVIR-HBV is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid emergence of HIV-1 resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV-1 treatment. If a decision is made to administer lamivudine to patients co-infected with HIV-1 and HBV, lamivudine tablets, lamivudine oral solution, or another product containing the higher dose of lamivudine should be used as part of an appropriate combination regimen.

Emergence of Lamivudine-Resistant HBV:
Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1 and HBV (see full prescribing information for EPIVIR-HBV). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

Tenofovir disoproxil fumarate:
Due to the risk of development of HIV-1 resistance, tenofovir disoproxil fumarate should only be used in HIV-1 and HBV coinfected patients as part of an appropriate antiretroviral combination regimen.

HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with tenofovir disoproxil fumarate. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with tenofovir disoproxil fumarate.

Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including dolutegravir, lamivudine and tenofovir disoproxil fumarate. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

Fat Redistribution
Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown.

Hypersensitivity Reactions
Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. Discontinue dolutegravir and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with dolutegravir or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. Dolutegravir is contraindicated in patients who have experienced a previous hypersensitivity reaction to Dolutegravir.

Use with Interferon- and Ribavirin-Based Regimens
In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients,hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of lamivudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6).

Pancreatitis
In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine should be used with caution. Treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur.

Exacerbation of Hepatitis after Discontinuation of Treatment
Discontinuation of anti-HBV therapy, including tenofovir disoproxil fumarate, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue tenofovir disoproxil fumarate should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

New Onset or Worsening Renal Impairment
Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir disoproxil fumarate.

It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with tenofovir disoproxil fumarate. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving HEPSERA®, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of tenofovir disoproxil fumarate, and periodically during tenofovir disoproxil fumarate therapy.

Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent [e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)] *(see section 4.5)*. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir DF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients.

Coadministration with Other Products
Dolutegravir, lamivudine and tenofovir disoproxil fumarate should not be used in combination with the fixed-dose combination products ATRIPLA (efavirenz/emtricitabine/ tenofovir disoproxil fumarate), COMPLERA (emtricitabine, rilpivirine, and tenofovir), STRIBILD (cobicistat, elvitegravir, emtricitabine, and tenofovir), or TRUVADA(emtricitabine and tenofovir disoproxil fumarate) since tenofovir disoproxil fumarate is a component of these products.

Dolutegravir, lamivudine and tenofovir disoproxil fumarate should not be administered in combination with HEPSERA (adefovir dipivoxil) *(see section 4.5)*.

Bone Effects
Bone Mineral Density:
In clinical trials in HIV-1 infected adults, tenofovir disoproxil fumarate was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving tenofovir disoproxil fumarate.

Clinical trials evaluating tenofovir disoproxil fumarate in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the tenofovir disoproxil fumarate-treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected.

The effects of tenofovir disoproxil fumarate-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adults and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Mineralization Defects:
Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of tenofovir disoproxil fumarate. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF *(see section 4.4)*.

Early Virologic Failure
Clinical trials in HIV-infected subjects have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance substitutions have been reported. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

Embryo-Fetal Toxicity
Preliminary data from an observational study showed that Dolutegravir was associated with increased risk of neural tube defects when administered at the time of conception and in early pregnancy. As there is limited understanding of reported types of neural tube defects associated with Dolutegravir use and because the date of conception may not be determined with precision, avoid use of Dolutegravir at the time of conception through the first trimester of pregnancy.

If there are plans to become pregnant or if pregnancy is confirmed within the first trimester while on Dolutegravir, if possible, switch to an alternative regimen.

Perform pregnancy testing before initiation of Dolutegravir in adolescents and adults of childbearing potential to exclude use of Dolutegravir during the first trimester of pregnancy.

Advise adolescents and adults of childbearing potential to consistently use effective contraception.

4.5 Interaction with other medicinal products and other forms of interaction

Dolutegravir
Effect of Dolutegravir on the Pharmacokinetics of Other Agents:
In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC_{50} = 1.93 μM) and multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 μM). *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (metformin, Table 1) (see section 4.5).

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC_{50} = 2.12 μM) and OAT3 (IC_{50} = 1.97 μM). However, *in vivo*, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

In vitro, dolutegravir did not inhibit (IC_{50} greater than 50 μM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1), UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4.

In drug interaction trials, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following drugs: daclatasvir, tenofovir, methadone, midazolam, rilpivirine, and oral contraceptives containing norgestimate and ethinyl estradiol. Using cross-study comparisons to historical pharmacokinetic data for each interacting drug, dolutegravir did not appear to affect the pharmacokinetics of the following drugs: atazanavir, darunavir, efavirenz, etravirine, fosamprenavir, lopinavir, ritonavir, and boceprevir.

Effect of Other Agents on the Pharmacokinetics of Dolutegravir:
Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp *in vitro*. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir.

Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentration.

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir (Table 1) *(see section 4.5)*.

In vitro, dolutegravir was not a substrate of OATP1B1, or OATP1B3.

Darunavir/ritonavir, lopinavir/ritonavir, rilpivirine, tenofovir, boceprevir, daclatasvir, prednisone, rifabutin, and omeprazole had no clinically significant effect on the pharmacokinetics of dolutegravir.

Established and Other Potentially Significant Drug Interactions
Table 1 provides clinical recommendations as a result of drug interactions with dolutegravir. These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 1. Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir and/or Concomitant Drug	Clinical Comment
HIV-1 Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirine	↓Dolutegravir	Use of dolutegravir with etravirine without coadministration of atazanavir/ritonavir, darunavir/ ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz	↓Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily. Use alternative combinations that do not include metabolic inducers where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[a]
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	Avoid coadministration with nevirapine because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir Tipranavir/ritonavir	↓Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily. Use alternative combinations that do not include metabolic inducers where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[a]
Other Agents		
Carbamazepine	↓Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily in treatment-naïve or treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily. Use alternative treatment that does not include carbamazepine where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[a]
Oxcarbazepine Phenytoin, Phenobarbital St. John's wort (*Hypericum perforatum*)	↓Dolutegravir	Avoid coadministration with dolutegravir because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer dolutegravir 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron	↓Dolutegravir	Administer dolutegravir 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, dolutegravir and supplements containing calcium or iron can be taken together with food.
Metformin	↑Metformin	With concomitant use, limit the total daily dose of metformin to 1,000 mg either when starting metformin or dolutegravir. When stopping dolutegravir, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of dolutegravir is recommended.
Rifampin	↓Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily. Use alternatives to rifampin where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[a]

[a] The lower dolutegravir exposures observed in INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance upon coadministration with certain inducers may result in loss of therapeutic effect and development of resistance to dolutegravir or other coadministered antiretroviral agents.

Lamivudine
Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim) *(see section 5.2)*. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

Tenofovir disoproxil fumarate
This section describes clinically relevant drug interactions with tenofovir disoproxil fumarate.

Didanosine
Coadministration of tenofovir disoproxil fumarate and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions.

When administered with tenofovir disoproxil fumarate, C_{max} and AUC of didanosine increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of $CD4^+$ cell counts has been observed in patients receiving tenofovir disoproxil fumarate with didanosine 400 mg daily.

In patients weighing greater than 60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered with tenofovir disoproxil fumarate. In patients weighing less than 60 kg, the didanosine dose should be reduced to 200 mg once daily when it is coadministered with tenofovir disoproxil fumarate. When coadministered, tenofovir disoproxil fumarate and didanosine EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).

HIV-1 Protease Inhibitors
Tenofovir disoproxil fumarate decreases the AUC and C_{min} of atazanavir. When coadministered with tenofovir disoproxil fumarate, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Tenofovir disoproxil fumarate should not be coadministered with atazanavir without ritonavir.

Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations. Tenofovir disoproxil fumarate is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir disoproxil fumarate is coadministered with an inhibitor of these transporters, an increase in absorption may be observed. Patients receiving tenofovir disoproxil fumarate concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir should be monitored for tenofovir disoproxil fumarate-associated adverse reactions. Tenofovir disoproxil fumarate should be discontinued in patients who develop tenofovir disoproxil fumarate-associated adverse reactions.

Hepatitis C Antiviral Agents
Coadministration of tenofovir disoproxil fumarate and HARVONI (ledipasvir/sofosbuvir) has been shown to increase tenofovir exposure.

In patients receiving tenofovir disoproxil fumarate concomitantly with HARVONI without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, monitor for adverse reactions associated with tenofovir disoproxil Fumarate.

In patients receiving tenofovir disoproxil fumarate concomitantly with HARVONI and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofovir concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

Drugs Affecting Renal Function
Since tenofovir is primarily eliminated by the kidneys *(see section 5.2)*, coadministration of tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to, cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs.

In the treatment of chronic hepatitis B, tenofovir disoproxil fumarate should not be administered in combination with HEPSERA (adefovir dipivoxil).

4.6 Fertility, pregnancy and lactation

Pregnancy
Dolutegravir:
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 (see section 5.3). Dolutegravir should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.

Lamivudine:
No increased risk of birth defects has been reported for Lamivudine. However, risks to the fetus cannot be ruled out.

Tenofovir Disoproxil Fumarate:
Animal studies do not indicate direct or indirect harmful effects of Tenofovir Disoproxil Fumarate with respect to pregnancy, foetal development, parturition or postnatal development (see section 5.3). In humans, the safety of Tenofovir in pregnancy has not been fully established. Sufficient numbers of first trimester exposures have been monitored, however, to detect at least a twofold increase in the risk of overall birth defects. No increase in birth defects was seen.

Risk Summary
Preliminary data from an observational study has identified a possible increased risk of neural tube defects when Dolutegravir is administered at the time of conception compared with non-Dolutegravir -containing antiretroviral regimens. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to Dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk. In addition, 2 of the 4 birth defects (encephalocele and iniencephaly), which have been observed with Dolutegravir use, although often termed neural tube defects, may occur post-neural tube closure, the time period of which may be later than 6 weeks of gestation, but within the first trimester. Due to the limited understanding of the types of reported neural tube defects associated with Dolutegravir use and because the date of conception may not be determined with precision, avoid use of Dolutegravir at the time of conception through the first trimester of pregnancy. No neural tube defects have been reported in infants born to mothers who have started Dolutegravir after the first trimester of pregnancy.

If there are plans to become pregnant or if pregnancy is confirmed while on Dolutegravir during the first trimester, if possible, switch to an alternative regimen. Advise pregnant adolescents and adults of the potential risk to the embryo exposed to Dolutegravir from the time of conception through the first trimester of pregnancy.

There are insufficient human data on the use of Dolutegravir during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. The background risk for major birth defects for the indicated population is unknown.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with Dolutegravir at systemic exposures (AUC) less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD) of Dolutegravir .

DETACH BEFORE DISPENSING

PACKAGE LEAFLET

DOLUTEGRAVIR 50 mg, LAMIVUDINE 300 mg and TENOFOVIR DISOPROXIL FUMARATE 300 mg TABLETS

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. See section 4.

In this leaflet
1. What Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is and what it is used for
2. Before you take Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets
3. How to take Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets
4. Possible side effects
5. How to store Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets
6. Further information

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets
Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tabletscontains the active ingredient dolutegravir, lamivudine & tenofovir disoproxil fumarate. Dolutegravir belongs to a group of anti-retroviral medicines called *integrase inhibitors (INIs)*. Lamivudine and Tenofovir is a nucleo(t)side reverse transcriptase inhibitor.

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 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.

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are 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.

Perform pregnancy testing before initiation of Dolutegravir in adolescents and adults of childbearing potential to exclude use of Dolutegravir during the first trimester of pregnancy.

If there are plans to become pregnant or if pregnancy is confirmed within the first trimester while on Dolutegravir, if possible, switch to an alternative regimen.

The Marketing Authorisation Holder for **Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is:**
M/s Aurobindo Pharma Ltd.,
Plot No.: 2, Maitrivihar
Ameerpet, Hyderabad-500 038
India.

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are manufactured by:
AUROBINDO PHARMA LTD.,
Unit VII, SEZ, TSIIC, Plot. No.SI,
Survey No's: 411/P, 425/P, 434/P, 435/P & 458/P,
Green Industrial Park, Polepally Village,
Jedcherla Mandal, Mahaboobnagar District,
Telangana State, India.

1. What Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tabletsare and what it is used for

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are a prescription medicine that are used together with other antiretroviral medicines to treat Human Immunodeficiency Virus (HIV-1) infection.

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets contains the active ingredient dolutegravir, lamivudine & tenofovir disoproxil fumarate. Dolutegravir belongs to a group of anti-retroviral medicines called *integrase inhibitors (INIs)*. Lamivudine and Tenofovir is a nucleo(t)side reverse transcriptase inhibitor.

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 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.

2. Before you take Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets

Do not take Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets:
- have ever had an allergic reaction to a medicine that contains Dolutegravir.
- take dofetilide. Taking Dolutegravir and Dofetilide can cause side effects that may be serious or life-threatening.
- are allergic to lamivudine or any of the ingredients in dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. See the end of this patient information leaflet for a complete list of ingredients in dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.
- if you are currently taking St. John's wort (Hypericum perforatum) (a herbal remedy used for depression and anxiety) or voriconazole (a drug used against fungal infections).
- If there are plans to become pregnant or if pregnancy is confirmed while on Dolutegravir during the first trimester, if possible, switch to an alternative regimen.

Before you take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, tell your doctor if you:
- have ever had an allergic reaction to dolutegravir.
- If you are taking another medicine called dofetilide (to treat heart conditions).
- have had liver problems, including hepatitis B or C infection.
- have kidney problems
- have bone problems
- have any other medical condition. Including HIV infection.
- are pregnant or plan to become pregnant. Preliminary data from an observational study showed that Dolutegravir was associated with increased risk of neural tube defects when administered at the time of conception and in early pregnancy.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.**
- you should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby. Talk with your doctor about the best way to feed your baby.

Tell your doctor about the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines interact with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine. You can ask your product for a list of medicines that interact with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.

Over-the-counter medicines that interact with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets include:
- St. John's wort (*Hypericum perforatum*). Avoid use of St. John's wort with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.
- antacids, laxatives, or other medicines that contain aluminum, magnesium, sucralfate, or buffered medicines. Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should be taken at least 2 hours before or 6 hours after you take antacids, laxatives, or other medicines that contain aluminum, magnesium, sucralfate, or buffered medicines.
- iron or calcium supplements taken by mouth. Supplements containing calcium or iron may be taken at the same time with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets if taken with food. Otherwise, dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should be taken at least 2 hours before or 6 hours after you take these medicines.
- other medicines that contain tenofovir
- adefovir

Especially tell your doctor if you take the following medications.
- didanosine
- atazanavir
- darunavir
- lopinavir with ritonavir
- ledipasvir with sofosbuvir

Do not start taking a new medicine without telling your doctor. Your doctor can tell you if it is safe to take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets with other medicines.

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, lamivudine and tenofovir disoproxil fumarate tablets.

Preliminary data from an observational study has identified a possible increased risk of neural tube defects when Dolutegravir is administered at the time of conception compared with non-Dolutegravir -containing antiretroviral regimens.

Perform pregnancy testing before initiation of Dolutegravir in adolescents and adults of childbearing potential to exclude use of Dolutegravir during the first trimester of pregnancy.

If there are plans to become pregnant or if pregnancy is confirmed within the first trimester while on Dolutegravir, if possible, switch to an alternative regimen.

Breast-feeding
Women who are HIV-positive must not breast feed because HIV infection can be passed on to the baby in breast milk.

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

Driving and using machines
Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets 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, lamivudine and tenofovir disoproxil fumarate tablets

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. See possible side effects, section 4 before you take Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.

- **Take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets exactly as your doctor tells you to take them.**
- If you miss a dose of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, take it as soon as you remember. Do not take 2 doses at the same time or take more than what your doctor tells you to take.
- Stay under the care of a doctor during treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.
- Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets may be taken with or without food.
- Do not run out of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your doctor or pharmacy.
- If you take too much dolutegravir, lamivudine and tenofovir disoproxil fumarate, call your doctor or go to the nearest hospital emergency room right away.

Use in children and adolescents
Dolutegravir: Safety and efficacy of dolutegravir have not been established in pediatric patients weighing less than 30 kg or in any pediatric patients who are INSTI-experienced.

Lamivudine: The safety and effectiveness of lamivudine in combination with other antiretroviral agents have been established in pediatric patients aged 3 months and older.

Tenofovir disoproxil fumarate: Safety and effectiveness of tenofovir disoproxil fumarate in pediatric patients younger than 2 years of age with HIV-1 infection have not been established.

If you take more Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets than you should
If you take too many tablets of Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, **contact your doctor or pharmacist for advice**. If possible, show them the Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets pack.

If you forget to take Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets
If you miss a dose, take it as soon as you remember.

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

Don't stop taking Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets without advice from your doctor
Take Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 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.
- **Dolutegravir, lamivudine and tenofovir disoproxil fumarate**

A/s: 480 x 740 mm ■ Black

AUROBINDO Packaging Development	Product Name	Component	Item Code	Date & Time
	DLT TABLETS	Leaflet	P1528183	11.08.2021 & 12:00 pm
	Customer / Country	Version No.	Reason Of Issue	Reviewed / Approved by
	PUN_UNIT-7	01	Commercial	
Team Leader: Lovaraju	Dimensions	No. of Colours : 01		
Initiator: Subramanyam	480 x 740 mm			
Artist: SCD	Pharmacode	28183		
	28183			
Additional Information : Supersede code: P1525327				Sign / Date

Females and Males of Reproductive Potential

Pregnancy Testing

Perform pregnancy testing in adolescents and adults of childbearing potential before initiation of Dolutegravir.

Contraception

Adolescents and adults of childbearing potential should avoid use of Dolutegravir at the time of conception through the first trimester of pregnancy because of the potential risk of neural tube defects.

Advise adolescents and adults of childbearing potential who are taking Dolutegravir to consistently use effective contraception.

Breast-feeding

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of both the potential for HIV-1 transmission and serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving dolutegravir, lamivudine and tenofovir disoproxil fumarate.

It is not known whether dolutegravir is present in human breast milk, affects human milk production, or has effects on the breastfed infant. Available toxicological data in animals has shown excretion of dolutegravir in milk (see section 5.3). In animal studies it has been shown that Tenofovir is excreted into milk. It is not known whether Tenofovir is excreted in human milk. Lamivudine is excreted into the breast milk of lactating mothers.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, dizziness has been reported during treatment with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and operating machinery.

4.8 Undesirable effects

The following serious adverse drug reactions are discussed in section 4.4 Special warnings and precautions for use:

- Lactic acidosis and severe hepatomegaly with steatosis.
- Patients with HIV-1, hepatitis B and hepatitis C virus co-infection.
- Immune reconstitution syndrome.
- Fat redistribution.
- Hypersensitivity reactions.
- Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C.
- Pancreatitis.
- Severe Acute Exacerbation of Hepatitis.
- New Onset or Worsening Renal Impairment.
- Bone Effects.

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Dolutegravir: There is no known specific treatment for overdose with dolutegravir. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Lamivudine: There is no known specific treatment for overdose with lamivudine. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

Tenofovir disoproxil fumarate: Limited clinical experience at doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available. In a Study, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil fumarate, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of action

Dolutegravir:

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

Lamivudine:

Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue.

Tenofovir disoproxil fumarate:

Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV reverse transcriptase by competing with the natural substrate deoxyadenosine 5′-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Pharmacodynamic effects

Dolutegravir:

In a randomized, dose-ranging trial, HIV-1-infected subjects treated with dolutegravir monotherapy demonstrated rapid and dose-dependent antiviral activity with mean declines from baseline to Day 11 in HIV-1 RNA of 1.5, 2.0, and 2.5 log_{10} for dolutegravir 2 mg, 10 mg, and 50 mg once daily, respectively. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

Effects on Electrocardiogram:

In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single-dose oral administrations of placebo, dolutegravir 250 mg suspension (exposures approximately 3–fold of the 50 mg once-daily dose at steady state), and moxifloxacin 400 mg (active control) in random sequence. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) for dolutegravir was 2.4 msec (1-sided 95% upper CI: 4.9 msec). Dolutegravir did not prolong the QTc interval over 24 hours postdose.

Effects on Renal Function:

The effect of dolutegravir on renal function was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled trial in healthy subjects (n = 37) who received dolutegravir 50 mg once daily (n = 12), dolutegravir 50 mg twice daily (n = 13), or placebo once daily (n = 12) for 14 days. A decrease in creatinine clearance, as determined by 24-hour urine collection, was observed with both doses of dolutegravir after 14 days of treatment in subjects who received 50 mg once daily (9% decrease) and 50 mg twice daily (13% decrease). Neither dose of dolutegravir had a significant effect on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol) or effective renal plasma flow (determined by the clearance of probe drug, para-amino hippurate) compared with the placebo.

Lamivudine & Tenofovir disoproxil fumarate:

Lamivudine, the negative enantiomer of 2'-deoxy-3'-thiacytidine, is a dideoxynucleoside analogue. Tenofovir Disoproxil Fumarate is converted *in vivo* to Tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate.

Lamivudine and Tenofovir are phosphorylated by cellular enzymes to form Lamivudine triphosphate and Tenofovir diphosphate, respectively. Lamivudine triphosphate and Tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase (RT), resulting in DNA chain termination. Both substances are active against HIV-1 and HIV-2, as well as against hepatitis B virus.

5.2 Pharmacokinetic properties

Dolutegravir:

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.

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.

Lamivudine:

Absorption and Bioavailability

Lamivudine is rapidly absorbed following oral administration. Bioavailability is between 80 and 85%. Co-administration of Lamivudine with food results in a delay of tmax and a lower C max (decreased by 47%). However, the extent (based on the AUC) of Lamivudine absorbed is not influenced.

Distribution

Intravenous studies with Lamivudine showed that the mean apparent volume of distribution is 1.3 l/kg. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 36% serum albumin *in vitro*).

Metabolism

Metabolism of Lamivudine is a minor route of elimination. Lamivudine is predominantly cleared unchanged by renal excretion. The likelihood of metabolic drug interactions with Lamivudine is low due to the small extent of hepatic metabolism (5 - 10%) and low plasma protein binding.

Elimination

The observed Lamivudine half-life of elimination is 5 to 7 hours. The half-life of intracellular Lamivudine triphosphate has been estimated to approximately 22 hours. The mean systemic clearance of Lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70%), including tubular secretion through the organic cationic transport system.

Special populations

Renal impairment: Studies in patients with renal impairment show that Lamivudine elimination is affected by renal dysfunction. Dose reduction is recommended for patients with creatinine clearance ≤50 ml/min (see section 4.2).

Tenofovir Disoproxil Fumarate:

Tenofovir Disoproxil Fumarate is a water-soluble ester prodrug, which is rapidly converted *in vivo* to Tenofovir and formaldehyde. Tenofovir is converted intracellularly to Tenofovir monophosphate and to the active component, Tenofovir diphosphate.

Absorption

Following oral administration of Tenofovir Disoproxil Fumarate to HIV infected patients, Tenofovir Disoproxil Fumarate is rapidly absorbed and converted to Tenofovir. The oral bioavailability of Tenofovir from Tenofovir Disoproxil Fumarate in fasted patients was approximately 25%. Administration of Tenofovir Disoproxil Fumarate with a high fat meal enhanced the oral bioavailability, with an increase in Tenofovir AUC by approximately 40% and Cmax by approximately 14%.

Following single dose administration of one tablet of Efavirenz 600 mg, Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg Tablets in healthy volunteers, the mean (±SD) Tenofovir Cmax value was 277 (±79) ng/ml and the corresponding value for AUC was 2358 (±627) ng.h/ml. The mean (±SD) Tenofovir tmax value was 1.17 (±0.57) hours.

Distribution

Following intravenous administration the steady-state volume of distribution of Tenofovir was estimated to be approximately 800 ml/kg. *In vitro* protein binding of Tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the Tenofovir concentration range 0.01 to 25 μg/ml.

Elimination

Tenofovir is primarily excreted by the kidney, both by filtration and an active tubular transport system with approximately 70-80% of the dose excreted unchanged in urine following intravenous administration. Total clearance has been estimated to be approximately 230 ml/h/kg (approximately 300 ml/min). Renal clearance has been estimated to be approximately 160 ml/h/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of Tenofovir. Following oral administration the terminal half-life of Tenofovir is approximately 12 to 18 hours.

Studies have established the pathway of active tubular secretion of Tenofovir to be influx into proximal tubule cell by the human organic anion transporters (hOAT) 1 and 3 and efflux into the urine by the multidrug resistant protein 4 (MRP 4). *In vitro* studies have determined that neither Tenofovir Disoproxil Fumarate nor Tenofovir are substrates for the CYP450 enzymes.

Age and gender

Limited data on the pharmacokinetics of Tenofovir in women indicate no major gender effect.

Tenofovir exposure achieved in adolescent patients receiving oral daily doses of Tenofovir 300 mg was similar to exposures achieved in adults receiving once-daily doses of Tenofovir 300 mg.

Pharmacokinetic studies have not been performed in children or in the elderly (over 65 years).

Pharmacokinetics have not been specifically studied in different ethnic groups.

Renal impairment

Pharmacokinetic parameters of Tenofovir were determined following administration of a single dose of Tenofovir Disoproxil Fumarate 300 mg to 40 non-HIV, non-HBV infected patients with varying degrees of renal impairment defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl > 80 ml/min; mild with CrCl = 50-79 ml/min; moderate with CrCl = 30-49 ml/min and severe with CrCl = 10-29 ml/min). Compared with patients with normal renal function, the mean (%CV) Tenofovir exposure increased from 2,185 (12%) ng·h/ml in subjects with CrCl > 80 ml/min to respectively 3,064 (30%) ng·h/ml, 6,009 (42%) ng·h/ml and 15,985 (45%) ng·h/ml in patients with mild, moderate and severe renal impairment. The dosing recommendations in patients with renal impairment, with increased dosing interval, are expected to result in higher peak plasma concentrations and lower Cmin levels in patients with renal impairment compared with patients with normal renal function. The clinical implications of this are unknown.

In patients with end-stage renal disease (ESRD) (CrCl < 10 ml/min) requiring haemodialysis, between dialysis Tenofovir concentrations substantially increased over 48 hours achieving a mean Cmax of 1,032 ng/ml and a mean AUC0-48h of 42,857 ng·h/ml. It is recommended that the dosing interval for Tenofovir Disoproxil Fumarate 300 mg is modified in patients with creatinine clearance < 50 ml/min or in patients who already have ESRD and require dialysis (see section 4.2).

The pharmacokinetics of Tenofovir in non-haemodialysis patients with creatinine clearance < 10 ml/min and in patients with ESRD managed by peritoneal or other forms of dialysis have not been studied.

Hepatic impairment

A single 300 mg dose of Tenofovir Disoproxil Fumarate was administered to non-HIV, non-HBV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetic parameters were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) Tenofovir Cmax and AUC0-∞ values were 223 (34.8%) ng/ml and 2,050 (50.8%) ng·h/ml, respectively, in normal subjects compared with 289 (46.0%) ng/ml and 2,31 (43.5%) ng·h/ml in subjects with moderate hepatic impairment, and 305 (24.8%) ng/ml and 2,740 (44.0%) ng·h/ml in subjects with severe hepatic impairment.

Intracellular pharmacokinetics

Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs).

5.3 Preclinical safety data

Dolutegravir:

Dolutegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *invivo* 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).

In a juvenile toxicity study in rats, dolutegravir administration resulted in two preweanling deaths at 75 mg/kg/day. There were no new target organs identified in juveniles compared to adults. In the rat pre/post-natal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 27 timeshuman exposure at the maximum recommended human dose).

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

Lamivudine:

Administration of Lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. Lamivudine was not mutagenic in bacterial tests, but showed activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic *in vitro* at doses that gave plasma concentrations around 40-50 times higher than the anticipated clinical plasma levels. As the *in vitro* mutagenic activity of Lamivudine could not be confirmed in *in vivo* tests, it is concluded that Lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans.

Tenofovir Disoproxil Fumarate:

Preclinical studies conducted in rats, dogs and monkeys revealed target organ effects in gastrointestinal tract, kidney, bone and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (rats and dogs). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in bone mineral density. However, no conclusion could be drawn on the mechanism(s) underlying these toxicities.

Reproductive studies were conducted in rats and rabbits. There were no effects on mating or fertility parameters or on any pregnancy or foetal parameter. There were no gross foetal alterations of soft or skeletal tissues. Tenofovir Disoproxil Fumarate reduced the viability index and weight of pups in peri-post natal toxicity studies.

Genotoxicity studies have shown that Tenofovir Disoproxil Fumarate was negative in the *in vivo* mouse bone marrow micronucleus assay but was positive for inducing forward mutations in the *in vitro* L5178Y mouse lymphoma cell assay in the presence or absence of S9 metabolic activation. Tenofovir Disoproxil Fumarate was positive in the Ames test (strain TA 1535) in two out of three studies, once in the presence of S9 mix (6.2- to 6.8-fold increase) and once without S9 mix. Tenofovir Disoproxil Fumarate was also weakly positive in an *in vivo / in vitro* unscheduled DNA synthesis test in primary rat hepatocytes.

Tenofovir Disoproxil Fumarate did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high local concentrations of Tenofovir Disoproxil Fumarate in the gastrointestinal tract at a dose of 600 mg/kg/day. While the mechanism of tumour formation is uncertain, the findings are unlikely to be of relevance to humans.

6. Pharmaceutical particulars

6.1 List of excipients

*Tablet Cor*e:

Mannitol, Microcrystalline Cellulose, Povidone, Ferric Oxide Red, Sodium Starch Glycolate, Sodium Stearyl Fumarate, Croscarmellose sodium, Hypromellose, Magnesium stearate, Colloidal Silicon Dioxide.

Film-coating:

Polyvinyl alcohol, Titanium dioxide, Polyethylene Glycol, Talc, Iron oxide red and Iron oxide black.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer outer package for expiry date.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

HDPE container containing 30 & 90 tablets.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Limited,
India.

8. DATE OF PREPARATION OF THE TEXT: 14.09.2020

NDC 59651-062-30
NDC 59651-062-90
POM

TFDA Reg. No.: TZ 19 H 0157
Botswana Reg. No.: BOT1803254
ZAMBIA Reg. No.: 127/087
NAFDAC Reg. No.: A4-100011

RWANDA Reg. NO.: 1075/Rwanda FDA/2019

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DETACH BEFORE DISPENSING

antiretroviral medicines and are also being treated for hepatitis C with interferon with or without ribavirin. If you are taking dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets and interferon with or without ribavirin, tell your doctor if you have any new symptoms.

- **Talk to your doctor about taking an HIV test before starting treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets for chronic hepatitis B. You should also get a test for HBV if you are taking dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets for treatment of HIV.**

The most common side effects of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets include:

• trouble sleeping • tiredness • headache • nausea • generally not feeling well • nasal signs and symptoms • itching • dizziness	• diarrhea • cough • rash • pain • depression • weakness • vomiting • fever

Tell your doctor about any side effect that bothers you or that does not go away.
These are not all the possible side effects of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. Call your doctor for medical advice about side effects.

5. How to store Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets

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

- Do not store above 30°C. Store in the original package.
- Keep dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets in the original container.
- Do not use dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets if the seal over the bottle opening is broken or missing.
- Keep the bottle tightly closed. Protect from moisture.
- The bottle contains a desiccant packet to help keep your medicine dry (protect it from moisture). Keep the desiccant packet in the bottle. Do not remove the desiccant packet.

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, Lamivudine and Tenofovir Disoproxil Fumarate Tablets contains

- The active substance is Dolutegravir, lamivudine and tenofovir disoproxil fumarate. Each film coated tablet contains Dolutegravir sodium equivalent to 50 mg Dolutegravir, Lamivudine USP 300 mg, Tenofovir disoproxil fumarate 300 mg equivalent to 245 mg of tenofovir disoproxil .
- The other ingredients in the tablet core are Mannitol, Microcrystalline Cellulose, Povidone, Ferric Oxide Red, Sodium Starch Glycolate, Sodium Stearyl Fumarate, Croscarmellose sodium, Hypromellose, Magnesium stearate, Colloidal Silicon Dioxide.
- The other ingredients in the tablet film coating are Polyvinyl alcohol, Ttanium dioxide, Polyethylene Glycol, Talc, Iron oxide red and Iron oxide black.

What Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets looks like and contents of the pack

Dolutegravir, lamivudine and tenofovir disoproxil fumarate Tablets are Pink colored, Oval, biconvex, film coated tablets debossed with 'N33' on one side and plain on the other side.

The film-coated tablets are provided in bottles containing 30 & 90 tablets.

Reporting of side effects

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

"If you notice any side effect (s) with the use of this drug, please report it immediately via internet to the following e-mail address: pharmacovigilance@aurobindo.com".

tablets can cause serious side effects including:

- **Changes in liver tests.** People with a history of hepatitis B or C virus may have an increased risk of developing new or worsening changes in certain liver tests during treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. Your doctormay do tests to check your liver function before and during treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.
- **Risk of inflammation of the pancreas (pancreatitis).** Children may be at risk for developing pancreatitis during treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets if they:

• have taken nucleoside analogue medicines in the past	• have a history of pancreatitis • have other risk factors for pancreatitis

Call your doctor right away if your child develops signs and symptoms of pancreatitis including severe upper stomach-area pain, with or without nausea and vomiting. Your doctor may tell you to stop giving dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets to your child if their symptoms and blood test results show that your child may have pancreatitis.

- **Changes in body fat can happen in people who take HIV-1 medicines.** These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these problems are not known.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your doctor right away if you start having new symptoms after you start taking dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.
- **New or worse kidney problems, including kidney failure**, can happen in some people who take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. Your doctor should do blood tests to check your kidneys before you start treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. If you have had kidney problems in the past or need to take another medicine that can cause kidney problems, your doctor may need to do blood tests to check your kidneys during your treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.
- **Bone problems** can happen in some people who take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. Bone problems include bone pain, softening or thinning (which may lead to fractures). Your doctor may need to do additional tests to check your bones.
- **Build-up of an acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. Lactic acidosis is a serious medical emergency that can cause death.
- Lactic acidosis can be hard to identify early, because the symptoms could seem like symptoms of other health problems. **Call your doctor right away if you get any of the following symptoms which could be signs of lactic acidosis:**
  - feel very weak or tired
  - have unusual (not normal) muscle pain
  - have trouble breathing
  - have stomach pain with
    - nausea (feel sick to your stomach)
    - vomiting
  - feel cold, especially in your arms and legs
  - feel dizzy or light-headed
  - have a fast or irregular heartbeat
- **Severe liver problems.** Severe liver problems can happen in people who take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets or similar medicines. In some cases these liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis).

Talk to your doctor right away if you get any of the following signs or symptoms of liver problems:

• your skin or the white part of your eyes turns yellow (jaundice) • dark or "tea-colored" urine • light-colored stools (bowel movements)	• loss of appetite for several days or longer • nausea • pain, aching, or tenderness on the right side of your stomach area

You may be more likely to get lactic acidosis or severe liver problems if you are female, very overweight (obese), or have been taking dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets or a similar medicine for a long time.

- **Allergic reactions.** Talk to your doctor right away if you develop a rash with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. **Stop taking dolutegravir,lamivudine and tenofovir disoproxil fumarate tablets and get medical help right away if you:**
- **develop a rash with any of the following signs or symptoms:**

• fever	• blisters or peeling of the skin
• generally ill feeling	• redness or swelling of the eyes
• extreme tiredness	• swelling of the mouth, face, lips, or tongue
• muscle or joint aches	• problems breathing
• blisters or sores in mouth	

- **Worsening of hepatitis B virus in people who have HIV-1 infection.** If you have HIV-1 (Human Immunodeficiency Virus type 1) and hepatitis B virus (HBV) infection, your HBV may get worse (flare-up) if you stop taking dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. A "flare-up" is when your HBV infection suddenly returns in a worse way than before. Worsening liver disease can be serious and may lead to death.
- Do not run out of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. Refill your prescription or talk to your doctor before your dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are all gone.
- Do not stop dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets without first talking to your healthcare provider.
- If you stop taking dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, your doctor will need to check your health often and do blood tests regularly for several months to check your liver. Tell your doctor about any new or unusual symptoms you may have after you stop taking dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.
- **Resistant Hepatitis B Virus (HBV).** If you have HIV-1 and hepatitis B, the hepatitis B virus can change (mutate) during your treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets and become harder to treat (resistant).
- **Use with interferon and ribavirin-based regimens.** Worsening of liver disease that has caused death has happened in people infected with both HIV-1 and hepatitis C virus who are taking