Rx **DOLUTEGRAVIR + LAMIVUDINE + TENOFOVIR DISOPROXIL FUMARATE**
50 mg/300 mg/300 mg film-coated tablet
Antiviral Combination

DOLUTEGRAVIR + LAMIVUDINE + TENOFOVIR DISOPROXIL FUMARATE

50 mg/300 mg/300 mg film-coated tablet

Antiviral Combination

Rx

FORMULATION: Each film-coated tablet contains 50 mg of dolutegravir (equivalent to 52.6 mg of dolutegravir sodium), 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DOLUTEGRAVIR, LAMIVUDINE and TENOFOVIR DISOPROXIL FUMARATE TABLETS safely and effectively. See full prescribing information for DOLUTEGRAVIR, LAMIVUDINE and TENOFOVIR DISOPROXIL FUMARATE TABLETS.

DOLUTEGRAVIR, LAMIVUDINE and TENOFOVIR DISOPROXIL FUMARATE tablets, for oral use

WARNING: LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATIONS OF HEPATITIS B

See full prescribing information for complete boxed warning.

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.1)**
- **Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and human immunodeficiency virus (HIV-1) and have discontinued anti-hepatitis B therapy, including lamivudine and tenofovir disoproxil fumarate, two components of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)**

INDICATIONS AND USAGE

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, a combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), lamivudine, and tenofovir disoproxil fumarate (both nucleoside reverse transcriptase inhibitors), are indicated for use alone as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing 40 kg or greater. (1)

Limitations of Use:

- Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets alone are not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is insufficient in these subpopulations. See the dolutegravir prescribing information. (1)

DOSAGE AND ADMINISTRATION

- Recommended dose in adults and pediatric patients (12 years of age and older weighing at least 40 kg): One tablet once daily taken orally without food. (2.1)
- If dosing with certain UGT1A or CYP3A inducers, then the recommended dolutegravir dosage regimen is 50 mg twice daily. An additional 50-mg dose of dolutegravir, separated by 12 hours from dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, should be taken. (2.2)
- Because dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are a fixed-dose tablet and cannot be dose adjusted, dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are not recommended in patients requiring dosage adjustment or patients with renal impairment. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablet: 50 mg of dolutegravir, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate (3)

CONTRAINDICATIONS

- Previous hypersensitivity reaction to dolutegravir, lamivudine, or tenofovir disoproxil fumarate. (4)
- Coadministration with dofetilide. (4)

WARNINGS AND PRECAUTIONS

- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.1)
- Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is recommended in patients with underlying hepatic disease such as hepatitis B or C. (5.2)
- Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported. Discontinue dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop, as a delay in stopping treatment may result in a life-threatening reaction. (5.3)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.4)
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance before initiating treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. In patients at risk for renal dysfunction, assess estimated creatinine clearance, serum phosphorus, urine glucose and urine protein before initiating treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets and periodically during treatment. Avoid administering dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets with concurrent or recent use of nephrotoxic drugs. (5.5)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving interferon and ribavirin-based regimens. Monitor for treatment-associated toxicities. Discontinue dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.6)
- Administration of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets is not recommended in patients receiving other products containing lamivudine, emtricitabine, tenofovir disoproxil fumarate, or tenofovir alafenamide (5.7). Do not administer in combination with adefovir dipivoxil (HEPSERA). (5.2)
- Decreases in bone mineral density (BMD): Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.8)
- Redistribution/accumulation of body fat and immune reconstitution syndrome have been reported in patients treated with combination antiretroviral therapy. (5.9, 5.10)

ADVERSE REACTIONS

- In adult subjects: The most common adverse reactions (in those receiving dolutegravir, lamivudine and tenofovir disoproxil fumarate) are insomnia, fatigue, and headache, nausea, nasal signs and symptoms, diarrhea, cough, rash, pain, depression, and asthenia. (6.1)
- In pediatric subjects: The most common adverse reactions (in those receiving lamivudine) are fever and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Coadministration of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets with other drugs can alter the concentration of other drugs and other drugs may alter the concentrations of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets. The potential drug-drug interactions must be considered prior to and during therapy. (4, 7, 12.3)
- Dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets should not be administered with other antiretroviral medications for the treatment of HIV-1 infection.

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Breastfeeding is not recommended due to the potential for HIV transmission. (8.3)
- Dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets are not recommended in patients with creatinine clearance less than 50 mL per min. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATIONS OF HEPATITIS B

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. Discontinue dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[see Warnings and Precautions (5.1)]*.

Exacerbations of Hepatitis B: Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and human immunodeficiency virus (HIV-1) and have discontinued anti-hepatitis B therapy, including lamivudine or tenofovir disoproxil fumarate. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are indicated for use alone as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing 40 kg or greater.

Limitation of Use:

- Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets alone are not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is insufficient in these subpopulations. See the dolutegravir prescribing information.

2 DOSAGE AND ADMINISTRATION

2.1 Adults and Pediatric Patients Weighing 40 kg (88 lbs) or Greater

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are a fixed-dose combination product containing 50 mg of dolutegravir, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate. The recommended dosage regimen of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets in adults and pediatric patients weighing 40 kg (88 lbs) or greater is one tablet once daily orally without food.

2.2 Dosage Recommendation with Certain Concomitant Medications

The dolutegravir dose (50 mg) in dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is insufficient when coadministered with medications listed in Table 1 that may decrease dolutegravir concentrations; the following dolutegravir dosage regimen is recommended.

Table 1. Dosing Recommendations for Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets with Coadministered Medications

Coadministered Drug	Dosing Recommendation
Efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, carbamazepine, or rifampin	The recommended dolutegravir dosage regimen is 50 mg twice daily. An additional dolutegravir 50-mg tablet, separated by 12 hours from dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, should be taken.

2.3 Not Recommended Due to Lack of Dosage Adjustment

Because dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are fixed-dose combination tablets and cannot be dose adjusted, dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are not recommended in patients requiring dosage adjustment or patients with renal impairment (estimated creatinine clearance below 50 mL/min).

3 DOSAGE FORMS AND STRENGTHS

Dolutegravir, Lamivudine and Tenofovir disoproxil fumarate tablets, 50 mg/300 mg/300 mg are orange colored, modified capsule shaped, biconvex film coated tablets debossed with 'H' on one side and 'D 17' on the other side. Each tablet contains 50 mg of Dolutegravir (equivalent to 52.6 mg of dolutegravir sodium), 300 mg of Lamivudine USP, and 300 mg of Tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).

4 CONTRAINDICATIONS

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

- with prior hypersensitivity reaction to dolutegravir *[see Warnings and Precautions (5.3)]*, lamivudine, or tenofovir disoproxil fumarate.
- receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events with concomitant use of dolutegravir *[see Drug Interactions (7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 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. Female sex and obesity may be risk factors for the development of lactic acidosis and severe hepatomegaly with steatosis in patients treated with antiretroviral nucleoside analogues. See full prescribing information for lamivudine and tenofovir disoproxil fumarate. Treatment with dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets 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).

5.2 Patients with Hepatitis B Virus Co-infection

It is recommended that all patients with HIV-1 be tested for the presence of chronic HBV before initiating antiretroviral therapy. Dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets are not approved for the treatment of chronic HBV infection, and the safety and efficacy of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets have not been established in patients coinfected with HBV and HIV-1.

Dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets should not be administered with HEPSERA® (adefovir dipivoxil) *[see Drug Interactions (7.7)]*.

Effects on Serum Liver Biochemistries: Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets *[see Adverse Reactions (6.1)]*. See full prescribing information for 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. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver failure have been reported in patients receiving a dolutegravir-containing regimen without pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with a combination product of abacavir, dolutegravir and lamivudine. Monitoring for hepatotoxicity is recommended.

Posttreatment Exacerbations of Hepatitis: Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine or tenofovir disoproxil fumarate. See full prescribing information for lamivudine and tenofovir disoproxil fumarate. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

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. 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. See full prescribing information for lamivudine.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of subjects receiving dolutegravir in Phase 3 clinical trials. Discontinue dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets 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, lamivudine, and tenofovir disoproxil fumarate tablets or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

5.4 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, dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets should be used with caution. Treatment with dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur *[see Adverse Reactions (6.1)]*.

5.5 New Onset or Worsening Renal Impairment

Because dose interval adjustment requirement for tenofovir disoproxil fumarate for patients with CrCL below 50 mL/min and dose adjustments of lamivudine cannot be achieved with dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets, patients with estimated creatinine clearance below 50 mL/min should not receive dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets.

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 *[see Adverse Reactions (6.2)]*.

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

Dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets 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 Drug Interactions (7.7)]*. 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.

5.6 Use with Interferon- and Ribavirin-Based Regimens

Patients receiving interferon alfa with or without ribavirin and dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets should be closely monitored for treatment associated toxicities, especially hepatic decompensation. See full prescribing information for lamivudine. Discontinuation of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets 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) (see full prescribing information for interferon and ribavirin).

5.7 Related Products that are Not Recommended

Dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets contains fixed doses of an INSTI (dolutegravir) and 2 nucleoside analogue reverse transcriptase inhibitors (lamivudine and tenofovir disoproxil fumarate); concomitant administration of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets with other products containing lamivudine, emtricitabine, tenofovir disoproxil fumarate, or tenofovir alafenamide is not recommended.

5.8 Bone Effects of Tenofovir Disoproxil Fumarate

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. For more information, consult the tenofovir disoproxil fumarate prescribing information.

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 *[see Adverse Reactions (6.2)]*. 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 disoproxil fumarate *[see Warnings and Precautions (5.5)]*.

5.9 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. A causal relationship has not been established.

5.10 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. 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.

5.11 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of dolutegravir and other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4), Drug Interactions (7.3)]*:

- Loss of therapeutic effect of dolutegravir and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

For concomitant drugs for which the interaction can be mitigated, please see Table 5 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with dolutegravir; review concomitant medications during therapy with dolutegravir; and monitor for the adverse reactions associated with the concomitant drugs.

6 ADVERSE REACTIONS

The following serious adverse drug reactions are discussed in other sections of the labeling:

- Lactic Acidosis and Severe Hepatomegaly with Steatosis *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Effects on Serum Liver Biochemistries in Patients with Hepatitis B or C Co-infection *[see Warnings and Precautions (5.2)]*.
- Severe Acute Exacerbation of Hepatitis *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*.
- Pancreatitis *[see Warnings and Precautions (5.4)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.5)]*.
- Hepatic Decompensation in Patients Co-infected with HIV-1 and Hepatitis C *[see Warnings and Precautions (5.6)]*.
- Bone Effects of Tenofovir Disoproxil Fumarate *[see Warnings and Precautions (5.8)]*.
- Fat Redistribution *[see Warnings and Precautions (5.9)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.10)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Dolutegravir, Lamivudine, Tenofovir Disoproxil Fumarate

Serious Dolutegravir Hypersensitivity Reactions: In clinical trials, hypersensitivity reactions have occurred with dolutegravir, a component of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets *[see Warnings and Precautions (5.3)]*. These hypersensitivity reactions have been characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury.

Treatment-Naïve Subjects: In SINGLE, 833 adult subjects were randomized and received at least one dose of either dolutegravir 50 mg with fixed-dose abacavir sulfate and lamivudine once daily (n = 414) or fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate once daily (n = 419) (study treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rate of adverse events leading to discontinuation was 4% in subjects receiving dolutegravir + fixed-dose abacavir sulfate and lamivudine and 14% in subjects receiving fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate once daily.

Treatment–emergent ADRs of moderate to severe intensity observed in at least 2% of subjects in either treatment arm of SINGLE are provided in Table 2.

Table 2. Treatment–Emergent Adverse Drug Reactions of at Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment–Naïve Subjects in SINGLE (Week 144 Analysis)

Adverse Reaction	Dolutegravir + Abacavir Sulfate and Lamivudine Once Daily (n = 414)	Efavirenz/Emtricitabine/ Tenofovir Disoproxil Fumarate Once Daily (n = 419)
Psychiatric		
Insomnia	3%	3%
Depression	1%	2%
Abnormal dreams	<1%	2%
Nervous System		
Dizziness	<1%	5%
Headache	2%	2%
Gastrointestinal		
Nausea	<1%	3%
Diarrhea	<1%	2%
General Disorders		
Fatigue	2%	2%
Skin and Subcutaneous Tissue		
Rash[a]	<1%	6%
Ear and Labyrinth		
Vertigo	0	2%

[a]Includes pooled terms: rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and drug eruption.

Treatment-Experienced Subjects: SAILING is an international, double-blind trial in INSTI-naïve, antiretroviral treatment-experienced adult subjects. Subjects were randomized and received either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rate of adverse events leading to discontinuation was consistent with that seen in the overall treatment-naïve patient population. See full prescribing information for dolutegravir.

The ADRs observed in the subset of subjects who received dolutegravir + fixed-dose abacavir sulfate and lamivudine were generally consistent with those seen in the overall treatment-naïve patient population.

Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials: The following ADRs occurred in less than 2% of treatment-naïve or treatment-experienced subjects receiving dolutegravir in a combination regimen in any one trial. These events have been included because of their seriousness and assessment of potential causal relationship.

Gastrointestinal Disorders: Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting.

Hepatobiliary Disorders: Hepatitis.

Musculoskeletal Disorders: Myositis.

Psychiatric Disorders: Suicidal ideation, attempt, behavior, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness.

Renal and Urinary Disorders: Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus.

Laboratory Abnormalities: *Treatment-Naïve Subjects:* Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects in SINGLE are presented in Table 3. The mean change from baseline observed for selected lipid values is presented in Table 4.

Table 3. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment–Naïve Subjects in SINGLE (Week 144 Analysis)

Laboratory Abnormality	Dolutegravir + Abacavir Sulfate and Lamivudine Once Daily (n = 414)	Efavirenz/Emtricitabine/ Tenofovir Disoproxil Fumarate Once Daily (n = 419)
ALT		
Grade 2 (>2.5 to 5.0 x ULN)	3%	5%
Grade 3 to 4 (>5.0 x ULN)	1%	<1%
AST		
Grade 2 (>2.5 to 5.0 x ULN)	3%	4%
Grade 3 to 4 (>5.0 x ULN)	1%	3%
Creatine kinase		
Grade 2 (6.0 to 9.9 x ULN)	5%	3%
Grade 3 to 4 (≥10.0 x ULN)	7%	8%
Hyperglycemia		
Grade 2 (126 to 250 mg/dL)	9%	6%
Grade 3 (>250 mg/dL)	2%	<1%
Lipase		
Grade 2 (>1.5 to 3.0 x ULN)	11%	11%
Grade 3 to 4 (>3.0 ULN)	5%	4%
Total neutrophils		
Grade 2 (0.75 to 0.99 x 10^9)	4%	5%
Grade 3 to 4 (<0.75 x 10^9)	3%	3%

ULN = Upper limit of normal.

Table 4. Mean Change from Baseline in Fasted Lipid Values in Treatment–Naïve Subjects in SINGLE (Week 144 Analysis[a])

Lipid	Dolutegravir + Abacavir Sulfate and Lamivudine Once Daily (n = 414)	Efavirenz/Emtricitabine/ Tenofovir Disoproxil Fumarate Once Daily (n = 419)
Cholesterol (mg/dL)	24.0	26.7
HDL cholesterol (mg/dL)	5.4	7.2
LDL cholesterol (mg/dL)	16.0	14.6
Triglycerides (mg/dL)	13.6	31.9

[a]Subjects on lipid-lowering agents at baseline were excluded from these analyses (dolutegravir + fixed-dose abacavir sulfate and lamivudine n = 30 and fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate n = 27). Seventy-two subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless if they discontinued the agent (dolutegravir + fixed-dose abacavir sulfate and lamivudine n = 36 and fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate n = 36).

Treatment-Experienced Subjects: Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naïve trials.

Hepatitis B and/or Hepatitis C Virus Co-infection: In Phase 3 trials, subjects with hepatitis B and/or C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal. Overall, the safety profile in subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects 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 virus co-infection for all treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected compared with HIV mono-infected subjects receiving dolutegravir were observed in 18% vs. 3% with the 50 mg once-daily dose and 13% vs. 8% with the 50 mg twice-daily dose. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C at the start of therapy with dolutegravir, particularly in the setting where anti-hepatitis therapy was withdrawn *[see Warnings and Precautions (5.2)]*.

Changes in Serum Creatinine: Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function *[see Clinical Pharmacology (12.2)]*. Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 96 weeks. In treatment-naïve subjects, a mean change from baseline of 0.15 mg per dL (range: -0.32 mg per dL to 0.65 mg per dL) was observed after 96 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced subjects.

Clinical Trials Experience in Pediatric Subjects: IMPAACT P1093 is an ongoing multicenter, open-label, non-comparative trial of approximately 160 HIV-1-infected pediatric subjects aged 4 weeks to less than 18 years, of which 46 treatment-experienced, INSTI-naïve subjects aged 6 to less than 18 years have been enrolled *[see Use in Specific Populations (8.4), Clinical Studies (14.2)]*.

The adverse reaction profile was similar to that for adults. Grade 2 ADRs reported by more than one subject were decreased neutrophil count (n = 3) and diarrhea (n = 2). There were no Grade 3 or 4 drug-related ADRs reported. No ADRs led to discontinuation.

The Grade 3 or 4 laboratory abnormalities reported in more than one subject were elevated total bilirubin (n = 3) and decreased neutrophil count (n = 2). The changes in mean serum creatinine were similar to those observed in adults.

Pancreatitis: Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric subjects receiving lamivudine alone or in combination with other antiretroviral agents. In an open-label dose-escalation trial (NUCA2002), 14 subjects (14%) developed pancreatitis while receiving monotherapy with lamivudine. Three of these subjects died of complications of pancreatitis. In a second open-label trial (NUCA2005), 12 subjects (18%) developed pancreatitis. In Trial ACTG300, pancreatitis was not observed in 236 subjects randomized to lamivudine plus zidovudine. Pancreatitis was observed in 1 subject in this trial who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy *[see Warnings and Precautions (5.4)]*.

Tenofovir Disoproxil Fumarate: ***Clinical Trials in Adult Patients with HIV-1 Infection:*** More than 12,000 subjects have been treated with tenofovir disoproxil fumarate alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in clinical trials and expanded access programs. A total of 1,544 subjects have received tenofovir disoproxil fumarate 300 mg once daily in clinical trials; over 11,000 subjects have received tenofovir disoproxil fumarate in expanded access programs.

The most common adverse reactions (incidence greater than or equal to 10%, Grades 2 to 4) identified from any of the 3 large controlled clinical trials include rash, diarrhea, headache, pain, depression, asthenia, and nausea.

Changes in Bone Mineral Density: In HIV-1 infected adult subjects in Study 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving tenofovir disoproxil fumarate + lamivudine + efavirenz (-2.2% ± 3.9) compared with subjects receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6) through 144 weeks. Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the tenofovir disoproxil fumarate group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24 to 48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of tenofovir disoproxil fumarate-treated subjects vs. 21% of the stavudine-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the tenofovir disoproxil fumarate group and 6 subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide) and higher serum parathyroid hormone levels and 1,25 Vitamin D levels in the tenofovir disoproxil fumarate group relative to the stavudine group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range *[see Warnings and Precautions (5.8)]*.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use for each of the individual components of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dolutegravir

Hepatobiliary Disorders: Acute liver failure, hepatotoxicity
Musculoskeletal: Arthralgia, myalgia.
Psychiatric: Anxiety

Lamivudine

Body as a Whole: Redistribution/accumulation of body fat *[see Warnings and Precautions (5.9)]*.

Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

Hemic and Lymphatic: Anemia (including pure red cell aplasia and severe anemias progressing on therapy).

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis *[see Warnings and Precautions (5.1)]*, posttreatment exacerbations of hepatitis B *[see Warnings and Precautions (5.2)]*.

Hypersensitivity: Anaphylaxis, urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Skin: Alopecia, pruritus.

Tenofovir Disoproxil Fumarate

Immune System Disorders: allergic reaction, including angioedema.

Metabolism and Nutrition Disorders: lactic acidosis, hypokalemia, hypophosphatemia.

Respiratory, Thoracic, and Mediastinal Disorders: dyspnea.

Gastrointestinal Disorders: pancreatitis, increased amylase, abdominal pain.

Hepatobiliary Disorders: hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT).

Skin and Subcutaneous Tissue Disorders: rash.

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy.

Renal and Urinary Disorders: acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria.

General Disorders and Administration Site Conditions: asthenia.

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

7 DRUG INTERACTIONS

7.1 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 (dofetilide and metformin, Table 5) *[see Contraindications (4), Drug Interactions (7.3)]*.

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. Based on these data and the results of drug interaction trials, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

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.

7.2 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 5) *[see Drug Interactions (7.3), Clinical Pharmacology (12.3)]*.

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.

7.3 Established and Other Potentially Significant Drug Interactions

There were no drug-drug interaction trials conducted with the dolutegravir, lamivudine, and tenofovir disoproxil fumarate fixed-dose combination tablets.

Table 5 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. *[See Clinical Pharmacology (12.3).]*

Table 5. Established and Other Potentially Significant Drug Interactions for Dolutegravir: 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[a]	↓Dolutegravir	Use of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50 mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	Avoid coadministration with dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir[a] Tipranavir/ritonavir[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50 mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets.
Other Agents		
Dofetilide	↑Dofetilide	Coadministration is contraindicated with dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets *[see Contraindications (4)]*.
Carbamazepine[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50 mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets.
Oxcarbazepine Phenytoin Phenobarbital St. John's wort (*Hypericum perforatum*)	↓Dolutegravir	Avoid coadministration with dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron[a]	↓Dolutegravir	Administer dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets 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 1000 mg either when starting metformin or dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets. When stopping dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets is recommended.
Rifampin[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50 mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets.

[a]*See Clinical Pharmacology (12.3) Table 8 or Table 9 for magnitude of interaction.*

7.4 Didanosine

Coadministration of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets 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 tenofovir disoproxil fumarate was administered with didanosine, C_{max} and AUC of didanosine increased significantly *[see Clinical Pharmacology (12.3)]*. 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 dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. Data are not available to recommend a dose adjustment of didanosine for adult of pediatric patients weighing less than 60 kg. When coadministered, dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets and didanosine EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).

7.5 HIV-1 Protease Inhibitors

Tenofovir disoproxil fumarate decreases the AUC and C_{min} of atazanavir *[see Clinical Pharmacology (12.3)]*. When coadministered with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets 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 *[see Clinical Pharmacology (12.3)].* 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 dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir should be monitored for tenofovir disoproxil fumarate-associated adverse reactions. Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should be discontinued in patients who develop tenofovir disoproxil fumarate-associated adverse reactions.

7.6 Hepatitis C Antiviral Agents

Coadministration of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets and ledipasvir/sofosbuvir (HARVONI) or sofosbuvir/velpatasvir (EPCLUSA) has been shown to increase tenofovir exposure *[see Clinical Pharmacology (12.3)]*.

In patients receiving dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets concomitantly with sofosbuvir/velpatasvir, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

In patients receiving dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets concomitantly with ledipasvir/sofosbuvir 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 dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets concomitantly with ledispasvir/sofosbuvir 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.

7.7 Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys *[see Clinical Pharmacology (12.3)]*, coadministration of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets 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, adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[see Warnings and Precautions (5.5)].*

7.8 Drugs Inhibiting Organic Cation Transporters

Lamivudine, a component of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, 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 Clinical Pharmacology (12.3)]*. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

7.9 Sorbitol

Coadministration of single doses of lamivudine and sorbitol resulted in a sorbitol dose-dependent reduction in lamivudine exposures. When possible, avoid use of sorbitol-containing medicines with lamivudine *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well controlled trials in pregnant women. Reproduction studies with the components of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets have been performed in animals (see Dolutegravir, Abacavir, and Lamivudine sections below). Animal reproduction studies are not always predictive of human response. Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should be used during pregnancy only if the potential benefit outweigh the risks.

Animal Data

Dolutegravir: Reproduction studies performed in rats and rabbits at doses up to 50 times the human dose of 50 mg once daily have revealed no evidence of impaired fertility or harm to the fetus due to dolutegravir.

Oral administration of dolutegravir to pregnant rats at doses up to 1,000 mg per kg daily, approximately 50 times the 50 mg once-daily human clinical exposure based on AUC, from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity, or teratogenicity.

Oral administration of dolutegravir to pregnant rabbits at doses up to 1,000 mg per kg daily, approximately 0.74 times the 50 mg once-daily human clinical exposure based on AUC, from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity. In rabbits, maternal toxicity (decreased food consumption, scant/no feces/urine, suppressed body weight gain) was observed at 1,000 mg per kg.

Lamivudine: Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses producing plasma levels up to approximately 32 times the human exposure for a dose of 300 mg. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at plasma levels up to 32 times those in humans.

Tenofovir Disoproxil Fumarate: Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

8.3 Nursing Mothers

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 the potential for serious adverse reactions in nursing infants, instruct mothers not to breastfeed.

Dolutegravir

Studies in lactating rats and their offspring indicate that dolutegravir was present in rat milk. It is not known whether dolutegravir is excreted in human breast milk.

Lamivudine

Lamivudine is excreted in human breast milk.

Tenofovir Disoproxil Fumarate

Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is secreted in human milk

8.4 Pediatric Use

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should only be administered to patients with a body weight of at least 40 kg.

8.5 Geriatric Use

Clinical trials of dolutegravir, lamivudine, or tenofovir disoproxil fumarate did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Patients with Impaired Renal Function

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are not recommended for patients with creatinine clearance less than 50 mL per min because dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine or tenofovir disoproxil fumarate, two components of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, is required for patients with creatinine clearance less than 50 mL per min, then the individual components should be used *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Impaired Hepatic Function

Dolutegravir

No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and matching healthy subjects were observed. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied. Therefore, dolutegravir is not recommended for use in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no known specific treatment for overdose with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required.

Dolutegravir

As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Lamivudine

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

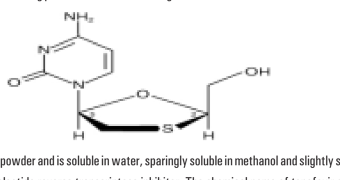
Limited clinical experience at doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available. In Study 901, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are 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 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

11 DESCRIPTION

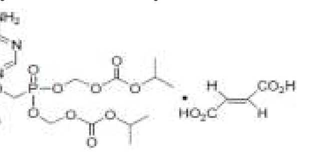
Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are for oral administration. Each film coated tablet contains 50 mg of Dolutegravir (equivalent to 52.6 mg of dolutegravir sodium), 300 mg of Lamivudine USP, and 300 mg of Tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil). In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, and sodium stearyl fumarate. The tablets have an orange film coat which contains iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Dolutegravir, as dolutegravir sodium, an HIV INSTI. The chemical name of dolutegravir sodium is Sodium (4R, 12as)-9-{[(2,4-difluorobenzyl)carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1', 2': 4, 5] pyrazino [2,1-b] [1,3]oxazin -7-olate. The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.37 g per mol. It has the following structural formula:



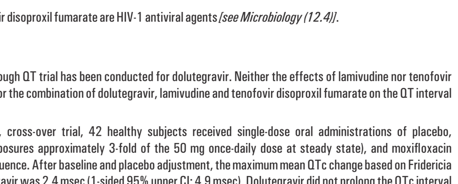
Dolutegravir sodium is an off-white or white to light yellow color powder and is very slightly soluble in methanol and practically insoluble in water.

Lamivudine (also known as 3TC) is a synthetic nucleoside analogue with activity against HIV-1 and HBV. The chemical name of lamivudine USP is 2(1H) - Pyrimidinone, 4-amino-1-[2- (hydroxy methyl)-1,3-oxathio-lan-5-yl], (2R-cis)-. Lamivudine is the (-) enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)-2'-deoxy-3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.26 g per mol. It has the following structural formula:



Lamivudine is a white or almost white powder and is soluble in water, sparingly soluble in methanol and slightly soluble in ethanol.

Tenofovir disoproxil fumarate is a nucleotide reverse transcriptase inhibitor. The chemical name of tenofovir disoproxil fumarate is 9-[(R)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy] phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$ and a molecular weight of 635.51. It has the following structural formula:



Tenofovir disoproxil fumarate is a white to an off-white crystalline powder. Sparingly soluble in ethanol and in methanol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dolutegravir, lamivudine, and tenofovir disoproxil fumarate are HIV-1 antiviral agents *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Dolutegravir

Effects on Electrocardiogram: A thorough QT trial has been conducted for dolutegravir. Neither the effects of lamivudine nor tenofovir disoproxil fumarate as single entities or the combination of dolutegravir, lamivudine and tenofovir disoproxil fumarate on the QT interval have been evaluated.

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.

12.3 Pharmacokinetics

Pharmacokinetics in Adults

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets

The mean systemic exposures of dolutegravir, lamivudine and tenofovir disoproxil fumarate from the Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets were comparable to that from TIVICAY tablets of ViiV USA (containing dolutegravir 50 mg), EPIVIR tablets of ViiV USA (containing lamivudine 300 mg), and VIREAD tablets of Gilead Sciences, Inc. USA (containing tenofovir disoproxil fumarate 300 mg), respectively, when single doses were administered to healthy subjects under fasted conditions.

Dolutegravir: Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours postdose. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and C_{24h} ranging from 1.2 to 1.5. Dolutegravir is a P-glycoprotein substrate *in vitro*. The absolute bioavailability of dolutegravir has not been established. Dolutegravir is highly bound (greater than or equal to 98.9%) to human plasma proteins based on *in vivo* data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50-mg once-daily administration is estimated at 17.4 L based on a population pharmacokinetic analysis.

Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A. After a single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose is excreted unchanged in the feces. Thirty-one percent of the total oral dose is excreted in the urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was less than 1% of

Patient Information

DOLUTEGRAVIR + LAMIVUDINE + TENOFOVIR DISOPROXIL FUMARATE

50 mg/300 mg/300 mg film-coated tablet

Antiviral Combination

Read this Patient Information before you start taking dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets?

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets can cause serious side effects, including:

- **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. **Call your healthcare provider right away if you get any of the following symptoms that could be signs of lactic acidosis:**
    - feel very weak or tired
    - unusual (not normal) muscle pain
    - trouble breathing
    - stomach pain with nausea and vomiting
    - feel cold, especially in your arms and legs
    - feel dizzy or light-headed
    - have a fast or irregular heartbeat
- **Serious liver problems** can happen in people who take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. In some cases these serious liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis). **Call your healthcare provider 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 serious liver problems if you are female, very overweight (obese), or have been taking nucleoside analog medicines for a long time.

- **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 healthcare provider 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 healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver. Tell your healthcare provider 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).
- **Allergic reactions.** Call your healthcare provider 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
        - generally ill feeling
        - extreme tiredness
        - muscle or joint aches
        - blisters or sores in mouth
        - blisters or peeling of the skin
        - redness or swelling of the eyes
        - swelling of the mouth, face, lips, or tongue
        - problems breathing
- **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 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 healthcare provider if you have any new symptoms.

What are dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets?

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are a prescription medicine that is used alone as a complete regimen to treat Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and children who weigh 88 pounds (40 kg) or more.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS). Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets contain 3 prescription medicines, dolutegravir, lamivudine and tenofovir disoproxil fumarate.

- Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are not for use by themselves in people who have or have had resistance to dolutegravir, lamivudine, or tenofovir disoproxil fumarate.

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets may reduce the amount of HIV in your blood (called "viral load"). Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets may also help to increase the number of CD4 (T) cells in your blood which help fight off other infections. Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your immune system. This may reduce your risk of death or infections that can happen when your immune system is weak (opportunistic infections).

It is not known if dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are safe and effective in children who weigh less than 88 pounds or in children who have received certain types of medicine for HIV-1 infection.

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets do not cure HIV infection or AIDS.

You must keep taking HIV-1 medicines to control HIV-1 infection and decrease HIV-related illnesses.

Avoid doing things that can spread HIV-1 infection to others.

- Do not share or re-use needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.

Ask your healthcare provider if you have any questions about how to prevent passing HIV to other people.

Who should not take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets?

Do not take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets if you:

- take dofetilide (TIKOSYN). Taking dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets and dofetilide (TIKOSYN) can cause side effects that may be serious or life-threatening.
- are allergic to dolutegravir 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.

What should I tell my healthcare provider before taking dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets?

Before you take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, tell your healthcare provider if you:

- have had liver problems, including hepatitis B or C infection.
- have kidney problems.
- have bone problems.
- have any other medical condition.
- are pregnant or plan to become pregnant. It is not known if dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets will harm your unborn baby. Tell your healthcare provider if you become pregnant.
- 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 healthcare provider about the best way to feed your baby.

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

Some medicines interact with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. Keep a list of your medicines and show it to your healthcare provider and pharmacist. You can ask your healthcare provider or pharmacist for a list of medicines that interact with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets with other medicines.

You should not take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets if you also take:

- abacavir
- lamivudine
- emtricitabine
- tenofovir
- adefovir

Tell your healthcare provider if you take:

- 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 these medicines.
- anti-seizure medicines:
    - oxcarbazepine
    - phenytoin
    - phenobarbital
    - carbamazepine
- any other medicine to treat HIV–1
- 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.
- medicines used to treat hepatitis virus infections, such as interferon or ribavirin
- a medicine that contains metformin
- rifampin
- St. John's wort (*Hypericum perforatum*)
- didanosine
- atazanavir
- darunavir
- lopinavir with ritonavir
- ledipasvir with sofosbuvir

How should I take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets?

- See **"What is the most important information I should know about dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets?"**
- **Take dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets exactly as your healthcare provider tells you to take it.**
- For adults and children weighing 40 kg (88 lbs) or more, the usual dose of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is one tablet each day. An extra dose of dolutegravir only may be necessary for certain populations. Your healthcare provider will inform you if you need to take the extra dolutegravir dose
- 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 healthcare provider tells you to take.
- Stay under the care of a healthcare provider during treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.
- Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should be taken 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 healthcare provider or pharmacy.
- If you take too many dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets?

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets can cause serious side effects including:

- **See "What is the most important information I should know about dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets?"**
- **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 healthcare provider may do tests to check your liver function before and during treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.

Dimensions: 450 x 850 mm
Colour: Black

- **Risk of inflammation of the pancreas (pancreatitis).** Children may be at risk for developing pancreatitis during treatment with lamivudine if they:
  - have taken nucleoside analogue medicines in the past
  - have a history of pancreatitis
  - have other risk factors for pancreatitis

Call your healthcare provider right away if your child develops signs and symptoms of pancreatitis including severe upper stomach-area pain, with or without nausea and vomiting. Your healthcare provider 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.

- **New or worse kidney problems, including kidney failure,** can happen in some people who take 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 healthcare provider 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 healthcare provider may need to do additional tests to check your bones.
- **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 healthcare provider right away if you start having new symptoms after you start taking dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.

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

- trouble sleeping
- nausea
- diarrhea
- pain
- depression
- tiredness
- generally not feeling well
- cough
- weakness
- headache
- nasal signs and symptoms
- rash

The most common side effects of dolutegravir, lamivudine and tenofovir disoproxil fumarate tables in children include fever and cough.

Tell your healthcare provider 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. You may report side effects to FDA at 1-800-FDA-1088.

How should I store dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets?

- Store dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets below 30°C (86°F).
- Keep dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets in the original container.
- Keep the bottle tightly closed. Do not remove desiccant.

Keep dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets and all medicines out of the reach of children.

General information about the safe and effective use of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets for a condition for which they were not prescribed. Do not give dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets to other people, even if they have the same symptoms you have. They may harm them.

This leaflet summarizes the most important information about dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets that is written for health professionals.

What are the ingredients in dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets?

Active ingredient: dolutegravir sodium, lamivudine, and tenofovir disoproxil fumarate

Inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, and sodium stearyl fumarate

Tablet Coating: iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

The brands listed are trademarks of their respective owners.

Manufactured by:
HETERO LABS LIMITED
Unit III Formulation Plot No-110 IDA, Jeedimetla,
Hyderabad 500 055, Telangana, India

Imported and Distributed by:
CAMBER PHARMACEUTICALS, INC.
Unit 503-A ITC Bldg., 337 Sen. Gil Puyat Avenue,
Bel-Air, Makati City, Philippines.

the dose. Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L per hour based on population pharmacokinetic analyses.

The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1-infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1-infected subjects.

Table 6. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV-1-Infected Adults

Parameter	50 mg Once Daily Geometric Mean (%CV)
$AUC_{(0-24)}$ (mcg· h/mL)	53.6 (27)
C_{max} (mcg/mL)	3.67 (20)
C_{min} (mcg/mL)	1.11 (46)

Cerebrospinal Fluid (CSF): In 12 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 13.2 ng per mL (range: 3.74 ng per mL to 18.3 ng per mL) 2 to 6 hours postdose after 16 weeks of treatment. The clinical relevance of this finding has not been established.

Polymorphisms in Drug-Metabolizing Enzymes: In a meta-analysis of healthy subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41).

Lamivudine: After multiple dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy subjects, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 mcg per mL (mean ±SD) and the 24 hour steady state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg· hour per mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine by active organic cationic secretion. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans sulfoxide metabolite (approximately 5% of an oral dose after 12 hours). In most single-dose trials in HIV-1–infected subjects, HBV-infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours. In HIV-1–infected subjects, total clearance was 398.5 ± 69.1 mL per min (mean ± SD).

Tenofovir Disoproxil Fumarate: The pharmacokinetic properties of tenofovir disoproxil fumarate are summarized in Table 7. Following oral administration of tenofovir disoproxil fumarate, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. Less than 0.7% of tenofovir binds to human plasma proteins *in vitro* and the binding is independent of concentration over the range of 0.01 to 25 mcg /mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg. Approximately 70 to 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of tenofovir disoproxil fumarate, the terminal elimination half-life of tenofovir is approximately 17 hours.

Table 7. Single Dose Pharmacokinetic Parameters for Tenofovir in Adults

	Tenofovir
Fasted Oral Bioavailability[b] (%)	25 (NC[a] to 45.0)
Plasma Terminal Elimination Half-Life[b] (hr)	17 (12.0 to 25.7)
C_{max}[c] (mcg/mL)	0.30±0.09
$AUC_{0-\infty}$[c] (mcg·hr/mL)	2.29±0.69
CL/F[c] (mL/min)	1043±115
CL_{renal}[c] (mL/min)	243±33

a. NC = Not calculated
b. Median (range)
c. Mean (±SD)

Effects of Food on Oral Absorption of Dolutegravir, lamivudine and tenofovir disoproxil fumarate: The effect of food on dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets has not been evaluated.

Specific Populations

Patients with Hepatic Impairment: Dolutegravir: Dolutegravir is primarily metabolized and eliminated by the liver. In a trial comparing 8 subjects with moderate hepatic impairment (Child-Pugh Score B) with 8 matched healthy controls, exposure of dolutegravir from a single 50 mg dose was similar between the 2 groups. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied. Therefore, dolutegravir is not recommended for use in patients with severe hepatic impairment.

Lamivudine: The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Tenofovir Disoproxil Fumarate: The pharmacokinetics of tenofovir following a 300 mg single dose of tenofovir disoproxil fumarate have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. No change in tenofovir disoproxil fumarate dosing is required in patients with hepatic impairment.

HBV/HCV Co-infection: Dolutegravir: Population analyses using pooled pharmacokinetic data from adult trials indicated no clinically relevant effect of HCV co-infection on the pharmacokinetics of dolutegravir. There were limited data on HBV co-infection.

Patients with Renal Impairment: Because dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are a fixed-dose tablet and cannot be dose adjusted, dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are not recommended in patients requiring dosage adjustment or patients with renal impairment *[see Dosage and Administration (2.3)]*.

Male and Female Patients: There are no significant or clinically relevant gender differences in the pharmacokinetics of the individual components (dolutegravir, lamivudine or tenofovir disoproxil fumarate) based on the available information that was analyzed for each of the individual components.

Racial Groups: Dolutegravir and Lamivudine: There are no significant or clinically relevant racial differences in the pharmacokinetics of dolutegravir or lamivudine based on the available information that was analyzed for each of the individual components.

Tenofovir Disoproxil Fumarate: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Geriatric Patients: Dolutegravir: Population analyses using pooled pharmacokinetic data from adult trials indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir.

Lamivudine and Tenofovir Disoproxil Fumarate: The pharmacokinetics of lamivudine or tenofovir disoproxil fumarate have not been studied in subjects older than 65 years.

Pediatric Patients: Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should not be administered to pediatric patients weighing less than 40 kg (88 lbs).

Dolutegravir and Lamivudine: The pharmacokinetics of the combination of dolutegravir and lamivudine in pediatric subjects have not been established.

Tenofovir Disoproxil Fumarate: Steady-state pharmacokinetics of tenofovir were evaluated in 8 HIV-1 infected pediatric subjects (12 to less than 18 years). Mean ± SD C_{max} and AUC_{tau} are 0.38 ± 0.13 mcg/mL and 3.39 ± 1.22 mcg· hr/mL, respectively. Tenofovir exposure achieved in these pediatric subjects receiving oral daily doses of tenofovir disoproxil fumarate 300 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil fumarate 300 mg.

Assessment of Drug Interactions:

The drug interaction trials described were conducted with dolutegravir, lamivudine, and/or tenofovir disoproxil fumarate as single entities; no drug interaction trials have been conducted using the combination of dolutegravir, lamivudine, and tenofovir disoproxil fumarate. No clinically significant drug interactions are expected between dolutegravir and lamivudine.

Dosing recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir are provided in Section 7.3 *[see Drug Interactions (7)]*.

Table 8. Summary of Effect of Dolutegravir on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
			C_{max}	AUC	$C_τ$ or C_{24}
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Elbasvir 50 mg once daily	50 mg single dose	12	0.97 (0.89, 1.05)	0.98 (0.93, 1.04)	0.98 (0.93, 1.03)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	12	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin 500 mg twice daily	50 mg once daily	15[c]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	-
Metformin 500 mg twice daily	50 mg twice daily	15[c]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	-
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0.94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	-	0.95 (0.79 to 1.15)	-
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Sofosbuvir 400 mg once daily	50 mg once daily	24	0.88 (0.80, 0.98)	0.92 (0.85, 0.99)	NA
Metabolite (GS-331007)			1.01 (0.93, 1.10)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)
Velpatasvir 100 mg once daily	50 mg once daily	24	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)

[c]The number of subjects represents the maximum number of subjects that were evaluated.

Table 9. Summary of Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	$C_τ$ or C_{24}
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300 mg/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/ritonavir 600 mg/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Elbasvir/grazoprevir 50/200 mg once daily	50 mg single dose	12	1.22 (1.05, 1.40)	1.16 (1.00, 1.34)	1.14 (0.95, 1.36)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/ritonavir 200 mg + 600 mg/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400 mg/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)
Fosamprenavir/ritonavir 700 mg/100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400 mg/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Tipranavir/ritonavir 500 mg/200 mg twice daily	50 mg once daily	14	0.54 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Antacid (Maalox®) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (Maalox®) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Calcium carbonate 1200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16[c]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day®) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[a] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

[a]Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.
[b]Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.
[c]The number of subjects represents the maximum number of subjects that were evaluated.

Lamivudine:

Based on *in vitro* study results, lamivudine at therapeutic drug exposures is not expected to affect the pharmacokinetics of drugs that are substrates of the following transporters: organic anion transporter polypeptide 1B1/3 (OATP1B1/3), breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K, organic cation transporter 1 (OCT1), OCT2, or OCT3. Effect of Other Agents on the Pharmacokinetics of Lamivudine: Lamivudine is a substrate of MATE1, MATE2-K, and OCT2 *in vitro*. Lamivudine is a substrate of P-gp and BCRP; however, considering its absolute bioavailability (87%), it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore, coadministration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Interferon Alfa: There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a trial of 19 healthy male subjects *[see Warnings and Precautions (5.6)]*.

Ribavirin: *In vitro* data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects *[see Warnings and Precautions (5.6)]*.

Sorbitol (Excipient): Lamivudine and sorbitol solutions were coadministered to 16 healthy adult subjects in an open-label, randomized sequence, 4-period, crossover trial. Each subject received a single 300-mg dose of lamivudine oral solution alone or coadministered with a single dose of 3.2 grams, 10.2 grams, or 13.4 grams of sorbitol in solution. Coadministration of lamivudine with sorbitol resulted in dose-dependent decreases of 20%, 39%, and 44% in the $AUC_{(0-24)}$, 14%, 32%, and 36% in the $AUC_{(\infty)}$, and 28%, 52%, and 55% in the C_{max} of lamivudine.

Trimethoprim/Sulfamethoxazole: Lamivudine and TMP/SMX were coadministered to 14 HIV-1-positive subjects in a single-center, open-label, randomized, crossover trial. Each subject received treatment with a single 300 mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of 43% ± 23% (mean ± SD) in lamivudine AUC∞, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used in treat PCP.

Tenofovir Disoproxil Fumarate: At concentrations substantially higher (~300-fold) than those observed *in vivo*, tenofovir did not inhibit *in vitro* drug metabolism mediated by any of the following human CYP isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP mediated interactions involving tenofovir with other medicinal products is low.

Tenofovir disoproxil fumarate has been evaluated in healthy volunteers in combination with other antiretroviral and potential concomitant drugs. Tables 10 and 11 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of tenofovir disoproxil fumarate on the pharmacokinetics of coadministered drug. Coadministration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Concomitant dosing of tenofovir disoproxil fumarate with didanosine significantly increases the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions (Table 11). The mechanism of this interaction is unknown.

No clinically significant drug interactions have been observed between tenofovir disoproxil fumarate and efavirenz, methadone, nelfinavir, oral contraceptives, ribavirin, or sofosbuvir.

Table 10. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[a] in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[b] (90% CI)		
			C_{max}	AUC	C_{min}
Atazanavir[c]	400 once daily × 14 days	33	↑14 (↑8 to ↑20)	↑24 (↑21 to ↑28)	↑22 (↑15 to ↑30)
Atazanavir/ Ritonavir[c]	300/100 once daily	12	↑34 (↑20 to ↑51)	↑37 (↑30 to ↑45)	↑29 (↑21 to ↑36)
Darunavir/ Ritonavir[d]	300/100 twice daily	12	↑24 (↑8 to ↑42)	↑22 (↑10 to ↑35)	↑37 (↑19 to ↑57)
Indinavir	800 three times daily × 7 days	13	↑14 (↓3 to ↑33)	↔	↔
Ledipasvir/ Sofosbuvir[e,f]	90/400 once daily x 10 days	24	↑47 (↑37 to ↑58)	↑35 (↑29 to ↑42)	↑47 (↑38 to ↑57)
Ledipasvir/ Sofosbuvir[e,g]		23	↑64 (↑54 to ↑74)	↑50 (↑42 to ↑59)	↑59 (↑49 to ↑70)
Ledipasvir/ Sofosbuvir[h]	90/400 once daily x 14 days	15	↑79 (↑56 to ↑104)	↑98 (↑77 to ↑123)	↑163 (↑132 to ↑197)
Ledipasvir/ Sofosbuvir[i]	90/400 once daily x 10 days	14	↑32 (↑25 to ↑39)	↑40 (↑31 to ↑50)	↑91 (↑74 to ↑110)
Ledipasvir/ Sofosbuvir[j]	90/400 once daily x 10 days	29	↑61 (↑51 to ↑72)	↑65 (↑59 to ↑71)	↑115 (↑105 to ↑126)
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	24	↔	↑32 (↑25 to ↑38)	↑51 (↑37 to ↑66)
Saquinavir/ Ritonavir	1000/100 twice daily × 14 days	35	↔	↔	↑23 (↑16 to ↑30)
Sofosbuvir[k]	400 single dose	16	↑25 (↑8 to ↑45)	↔	↔
Sofosbuvir/ Velpatasvir[l]	400/100 once daily	24	↑55 (↑43 to ↑68)	↑30 (↑24 to ↑36)	↑39 (↑31 to ↑48)
Sofosbuvir/ Velpatasvir[m]	400/100 once daily	29	↑55 (↑45 to ↑66)	↑39 (↑33 to ↑44)	↑52 (↑45 to ↑59)
Sofosbuvir/ Velpatasvir[n]	400/100 once daily	15	↑77 (↑53 to ↑104)	↑81 (↑68 to ↑94)	↑121 (↑100 to ↑143)
Sofosbuvir/ Velpatasvir[o]	400/100 once daily	24	↑36 (↑25 to ↑47)	↑35 (↑29 to ↑42)	↑45 (↑39 to ↑51)
Sofosbuvir/ Velpatasvir[p]	400/100 once daily	24	↑44 (↑33 to ↑55)	↑40 (↑34 to ↑46)	↑84 (↑76 to ↑92)
Sofosbuvir/ Velpatasvir[q]	400/100 once daily	30	↑46 (↑39 to ↑54)	↑40 (↑34 to ↑45)	↑70 (↑61 to ↑79)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑13 (↑1 to ↑27)	↔	↔
Tipranavir/ Ritonavir[r]	500/100 twice daily	22	↓23 (↓32 to ↓13)	↓2 (↓9 to ↑5)	↑7 (↓2 to ↑17)
	750/200 twice daily (23 doses)	20	↓38 (↓46 to ↓29)	↑2 (↓6 to ↑10)	↑14 (↑1 to ↑27)

[a]Subjects received tenofovir disoproxil fumarate 300 mg once daily.
[b]Increase = ↑; Decrease = ↓; No Effect = ↔; NC = Not Calculated
[c]Reyataz (atazanavir) Prescribing Information
[d]Prezista (darunavir) Prescribing Information
[e]Data generated from simultaneous dosing with HARVONI (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provide similar results.
[f]Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF.
[g]Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.
[h]Study conducted with ATRIPLA (efavirenz/emtricitabine/tenofovir DF) coadministered with HARVONI.
[i]Study conducted with COMPLERA (emtricitabine/rilpivirine/tenofovir DF) coadministered with HARVONI.
[j]Study conducted with TRUVADA (emtricitabine/tenofovir DF) + dolutegravir coadministered with HARVONI.
[k]Study conducted with ATRIPLA coadministered with SOVALDI (sofosbuvir).
[l]Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF.
[m]Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.
[n]Study conducted with ATRIPLA coadministered with EPCLUSA (sofosbuvir/velpatasvir).
[o]Study conducted with STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir DF) coadministered with EPCLUSA.
[p]Study conducted with COMPLERA coadministered with EPCLUSA.
[q]Administered as raltegravir + emtricitabine/tenofovir DF.
[r]Aptivus Prescribing Information.

No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with tenofovir disoproxil fumarate: abacavir, didanosine (buffered tablets), emtricitabine, entecavir and lamivudine.

Table 11. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir Disoproxil Fumarate

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[a] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑12 (↓1 to ↑26)	↔	NA
Atazanavir[b]	400 once daily × 14 days	34	↓21 (↓27 to ↓14)	↓25 (↓30 to ↓19)	↓40 (↓48 to ↓32)
Atazanavir[b]	Atazanavir/Ritonavir 300/100 once daily × 42 days	10	↓28 (↓50 to ↑5)	↓25[c] (↓42 to ↓3)	↓23[c] (↓46 to ↑10)
Darunavir[d]	Darunavir/Ritonavir 300/100 once daily	12	↑16 (↓6 to ↑42)	↑21 (↓5 to ↑54)	↑24 (↓10 to ↑69)
		33		↔[g]	
Emtricitabine	200 once daily × 7 days	17	↔	↔	↑20 (↑12 to ↑29)
Entecavir	1 mg once daily x 10 days	28	↔	↑13 (↑11 to ↑15)	↔
Indinavir	800 three times daily × 7 days	12	↓11 (↓30 to ↑12)	↔	↔
		15		↔	↔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	↔	↔	↔
			↔	↔	↔
Saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑22 (↑6 to ↑41)	↑29[h] (↑12 to ↑48)	↑47[h] (↑23 to ↑76)
			↔	↔	↑23 (↑3 to ↑46)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↔	↔	↔
Tipranavir[i]	Tipranavir/Ritonavir 500/100 twice daily	22	↓17 (↓26 to ↓6)	↓18 (↓25 to ↓9)	↓21 (↓30 to ↓10)
	Tipranavir/Ritonavir 750/200 twice daily (23 doses)	20	↓11 (↓16 to ↓4)	↓9 (↓15 to ↓3)	↓12 (↓22 to 0)

[a]Increase = ↑; Decrease = ↓; No Effect = ↔; NA = Not Applicable
[b]Reyataz (atazanavir) Prescribing Information
[c]In HIV-infected subjects, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
[d]Prezista (darunavir) Prescribing Information
[e]Videx (didanosine) EC Prescribing Information. Subjects received didanosine enteric-coated capsules.
[f]373 kcal, 8.2 g fat
[g]Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions.
[h]Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.
[i]Aptivus (tipranavir) Prescribing Information

Coadministration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Concomitant dosing of tenofovir disoproxil fumarate with didanosine enteric-coated capsules significantly increases the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown. See Drug Interactions (7.4) regarding use of didanosine with tenofovir disoproxil fumarate.

12.4 Microbiology

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 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.

Antiviral Activity in Cell Culture: *Dolutegravir:* Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV−1 clinical isolates with median EC_{50} values of 0.18 nM (n = 3, range: 0.09 to 0.5 nM), 0.08 nM (n = 5, range: 0.05 to 2.14 nM) 0.12 nM (n = 4, range: 0.05 to 0.51 nM), 0.17 nM (n = 3, range: 0.16 to 0.35 nM), 0.24 nM (n = 3, range: 0.09 to 0.32 nM), 0.17 nM (range: 0.07 to 0.44 nM), 0.2 nM (n = 3, range: 0.02 to 0.87 nM), and 0.42 nM (n = 3, range: 0.41 to 1.79 nM) for clades A, B, C, D, E, F, and G, and group O viruses, respectively. Dolutegravir EC_{50} values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC_{50} values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B) respectively. The EC_{50} values against HIV-2 isolates (n = 4) ranged from 0.003 to 0.120 microM in PBMCs. Lamivudine was not antagonistic to all tested anti-HIV agents. Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

Tenofovir Disoproxil Fumarate: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} (50% effective concentration) values for tenofovir were in the range of 0.04 μM to 8.5 μM. In drug combination studies, tenofovir was not antagonistic with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir). Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5 μM to 2.2 μM) and strain specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 5.5 μM).

Antiviral Activity in Combination with Other Antiviral Agents: Neither dolutegravir nor lamivudine were antagonistic to all tested anti-HIV agents. See full prescribing information for dolutegravir and lamivudine.

Resistance in Cell Culture: *Dolutegravir:* Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold.

Lamivudine: Lamivudine-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either valine or isoleucine (M184V/I).

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from subjects. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In subjects receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most subjects became phenotypically and genotypically resistant to lamivudine within 12 weeks.

Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in reverse transcriptase and showed a 2- to 4-fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir.

In Study 903 of treatment-naïve subjects (tenofovir disoproxil fumarate + lamivudine + efavirenz versus stavudine + lamivudine + efavirenz), genotypic analyses of isolates from subjects with virologic failure through Week 144 showed development of efavirenz and lamivudine resistance-associated substitutions to occur most frequently and with no difference between the treatment arms. The K65R substitution occurred in 8/47 (17%) of analyzed patient isolates in the tenofovir disoproxil fumarate arm and in 2/49 (4%) of analyzed patient isolates in the stavudine arm. Of the eight subjects whose virus developed K65R in the tenofovir disoproxil fumarate arm through 144 weeks, seven occurred in the first 48 weeks of treatment and one at Week 96. One patient in the tenofovir disoproxil fumarate arm developed the K70E substitution in the virus. Other substitutions resulting in resistance to tenofovir disoproxil fumarate were not identified in this trial.

In Study 934 of treatment-naïve subjects (tenofovir disoproxil fumarate + EMTRIVA + efavirenz versus zidovudine (AZT)/lamivudine (3TC) + efavirenz), genotypic analysis performed on HIV-1 isolates from all confirmed virologic failure subjects with greater than 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation showed development of efavirenz resistance-associated substitutions occurred most frequently and was similar between the two treatment arms. The M184V substitution, associated with resistance to EMTRIVA and lamivudine, was observed in 2/19 analyzed subject isolates in the tenofovir disoproxil fumarate + EMTRIVA group and in 10/29 analyzed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no subjects have developed a detectable K65R substitution in their HIV-1 as analyzed through standard genotypic analysis.

Cross-Resistance: *Dolutegravir:* The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

Lamivudine: Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors (NRTIs). Lamivudine-resistant HIV-1 mutants were cross-resistant in cell culture to didanosine (ddI). Cross-resistance is also expected with abacavir and emtricitabine as these select M184V substitutions.

Tenofovir Disoproxil Fumarate: Cross-resistance among certain reverse transcriptase inhibitors has been recognized. The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1 infected subjects treated with abacavir or didanosine. HIV-1 isolates with this substitution also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R or K70E substitution. HIV-1 isolates from subjects (N = 20) whose HIV-1 expressed a mean of three zidovudine-associated reverse transcriptase substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), showed a 3.1-fold decrease in the susceptibility to tenofovir.

In Studies 902 and 907 conducted in treatment-experienced subjects (tenofovir disoproxil fumarate + Standard Background Therapy (SBT) compared to Placebo + SBT), 14/304 (5%) of the tenofovir disoproxil fumarate-treated subjects with virologic failure through Week 96 had greater than 1.4-fold (median 2.7-fold) reduced susceptibility to tenofovir. Genotypic analysis of the baseline and failure isolates showed the development of the K65R substitution in the HIV-1 reverse transcriptase gene.

The virologic response to tenofovir disoproxil fumarate therapy has been evaluated with respect to baseline viral genotype (N = 222) in treatment-experienced subjects participating in Studies 902 and 907. In these clinical trials, 94% of the participants evaluated had baseline HIV-1 isolates expressing at least one NRTI substitution. Virologic responses for subjects in the genotype substudy were similar to the overall trial results.

Several exploratory analyses were conducted to evaluate the effect of specific substitutions and substitutional patterns on virologic outcome. Because of the large number of potential comparisons, statistical testing was not conducted. Varying degrees of cross-resistance of tenofovir disoproxil fumarate to preexisting zidovudine resistance-associated substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) were observed and appeared to depend on the type and number of specific substitutions. Tenofovir disoproxil fumarate-treated subjects whose HIV-1 expressed three or more zidovudine resistance-associated substitutions that included either the M41L or L210W reverse transcriptase substitution showed reduced responses to tenofovir disoproxil fumarate therapy; however, these responses were still improved compared with placebo. The presence of the D67N, K70R, T215Y/F, or K219Q/E/N substitution did not appear to affect responses to tenofovir disoproxil fumarate therapy. Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N = 8) had reduced response to tenofovir disoproxil fumarate. Limited data are available for subjects whose virus expressed a Y115F substitution (N = 3), Q151M substitution (N = 2), or T69 insertion (N = 4), all of whom had a reduced response.

In the protocol defined analyses, virologic response to tenofovir disoproxil fumarate was not reduced in subjects with HIV-1 that expressed the abacavir/emtricitabine/lamivudine resistance-associated M184V substitution. HIV-1 RNA responses among these subjects were durable through Week 48.

Studies 902 and 907 Phenotypic Analyses: Phenotypic analysis of baseline HIV-1 from treatment-experienced subjects (N = 100) demonstrated a correlation between baseline susceptibility to tenofovir disoproxil fumarate and response to tenofovir disoproxil fumarate therapy. Table 12 summarizes the HIV-1 RNA response by baseline tenofovir disoproxil fumarate susceptibility.

Table 12. HIV-1 RNA Response at Week 24 by Baseline Tenofovir Disoproxil Fumarate Susceptibility (Intent-To-Treat)[a]

Baseline Tenofovir Disoproxil Fumarate Susceptibility[b]	Change in HIV-1 RNA[c] (N)
< 1	-0.74 (35)
> 1 and ≤ 3	-0.56 (49)
> 3 and ≤ 4	-0.3 (7)
> 4	-0.12 (9)

[a]Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram assay (Virco).
[b]Fold change in susceptibility from wild-type.
[c]Average HIV-1 RNA change from baseline through Week 24 ($DAVG_{24}$) in log_{10} copies/mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: *Dolutegravir:* Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg per kg, and rats were administered doses of up to 50 mg per kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 14-fold higher than those in humans at the recommended dose of 50 mg twice daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 10-fold and 15-fold higher in males and females, respectively, than those in humans at the recommended dose of 50 mg twice daily.

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 12 times (mice) and 57 times (rats) the human exposures at the recommended dose of 300 mg.

Tenofovir Disoproxil Fumarate: Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Mutagenesis: *Dolutegravir:* Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the *in vivo* rodent micronucleus assay.

Lamivudine: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Tenofovir Disoproxil Fumarate: Tenofovir disoproxil fumarate was mutagenic in the *in vitro* mouse lymphoma assay and negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice.

Impairment of Fertility: *Dolutegravir and Lamivudine:* Dolutegravir or lamivudine did not affect male or female fertility in rats at doses associated with exposures approximately 44 or 112 times (respectively) higher than the exposures in humans at the doses of 50 mg and 300 mg (respectively).

Tenofovir Disoproxil Fumarate: There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

13.2 Animal Toxicology and/or Pharmacology

Tenofovir Disoproxil Fumarate: Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2 to 20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

14 CLINICAL STUDIES

14.1 Adult Subjects

Treatment-Naïve Subjects

In SINGLE, 833 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily with fixed-dose abacavir sulfate and lamivudine or fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate. At baseline, the median age of subjects was 35 years, 16% female, 32% non-white, 7% had hepatitis C co-infection (hepatitis B virus co-infection was excluded), 4% were CDC Class C (AIDS), 32% had HIV-1 RNA greater than 100,000 copies per mL, and 53% had CD4+ cell count less than 350 cells per mm³; these characteristics were similar between treatment groups.

Week 144 (open-label-phase analysis which followed the Week 96 double-blind phase) outcomes for SINGLE are provided in Table 13.

Table 13. Virologic Outcomes of Randomized Treatment in SINGLE at 144 Weeks (Snapshot Algorithm)

	Dolutegravir + Abacavir Sulfate and Lamivudine Once Daily (n = 414)	Efavirenz, Emtricitabine, and Tenofovir DF Once Daily (n = 419)
HIV−1 RNA < 50 copies/mL	71%	63%
Treatment difference[a]	8.3% (95% CI: 2.0%, 14.6%)[d]	
Virologic nonresponse	10%	7%
Data in window not < 50 copies/mL	4%	< 1%
Discontinued for lack of efficacy	3%	3%
Discontinued for other reasons while not suppressed	3%	4%
No virologic data	18%	30%
Reasons		
Discontinued study/study drug due to adverse event or death[b]	4%	14%
Discontinued study/study drug for other reasons[c]	12%	13%
Missing data during window but on study	2%	3%
Proportion (%) of Subjects with HIV−1 RNA < 50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤100,000	73%	64%
>100,000	69%	61%
Gender		
Male	72%	66%
Female	69%	48%
Race		
White	72%	71%
African-American/African Heritage/Other	71%	47%

[a] Adjusted for pre-specified stratification factors.
[b] Includes subjects who discontinued due to an adverse event or death at any time point if this resulted in no virologic data on treatment during the analysis window.
[c] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.
[d] The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving dolutegravir and 81% in the fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate group, with a treatment difference of 7.4% and 95% CI of (2.5%, 12.3%).

Treatment differences were maintained across baseline characteristics including baseline viral load, CD4+ cell count, age, gender, and race. The adjusted mean changes in CD4+ cell counts from baseline were 378 cells per mm³ in the group receiving dolutegravir + fixed-dose abacavir sulfate and lamivudine and 332 cells per mm³ for the fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate group at 144 weeks. The adjusted difference between treatment arms and 95% CI was 46.9 cells per mm³ (15.6 cells per mm³, 78.2 cells per mm³) (adjusted for pre-specified stratification factors: baseline HIV−1 RNA, and baseline CD4+ cell count).

Treatment-Experienced

In SAILING, there were 715 subjects included in the efficacy and safety analyses (see full prescribing information for dolutegravir). At Week 48, 71% of subjects randomized to dolutegravir plus background regimen versus 64% of subjects randomized to raltegravir plus background regimen had HIV−1 RNA less than 50 copies per mL (treatment difference and 95% CI: 7.4% [0.7%, 14.2%]).

14.2 Pediatric Subjects

Dolutegravir: IMPAACT P1093 is a Phase 1/2, 48-week, multicenter, open-label trial to evaluate the pharmacokinetic parameters, safety, tolerability, and efficacy of dolutegravir in combination treatment regimens in HIV-1-infected infants, children, and adolescents. Subjects were stratified by age, enrolling adolescents first (Cohort 1: aged 12 to less than 18 years) and then younger children (Cohort 2A: aged 6 to less than 12 years). All subjects received a weight-based dose of dolutegravir.

These 46 subjects had a mean age of 12 years (range: 6 to 17), were 54% female and 52% black. At baseline, mean plasma HIV-1 RNA was 4.6 log_{10} copies per mL, median CD4+ cell count was 639 cells per mm³ (range: 9 to 1,700), and median CD4+% was 23% (range: 1% to 44%). Overall, 39% had baseline plasma HIV-1 RNA greater than 50,000 copies per mL and 33% had a CDC HIV clinical classification of category C. Most subjects had previously used at least 1 NNRTI (50%) or 1 PI (70%).

At Week 24, the proportion of subjects with HIV-1 RNA less than 50 copies per mL in Cohort 1 and Cohort 2A was 70% (16/23) and 61% (14/23), respectively. At Week 48, the proportion of subjects from Cohort 1 with HIV-1 RNA less than 50 copies per mL was 61% (14/23). Virologic outcomes were also evaluated based on body weight. Across both cohorts, virologic suppression (HIV-1 RNA less than 50 copies per mL) at Week 24 was achieved in 75% (18/24) of subjects weighing at least 40 kg and 55% (6/11) of subjects in the 30 to less than 40 kg weight-band. At Week 48, 63% (12/19) of the subjects in Cohort 1 weighing at least 40 kg were virologically suppressed.

The median CD4+ cell count increase from baseline to Week 48 was 84 cells per mm³ in Cohort 1. For Cohort 2A, the median CD4+ cell count increase from baseline to Week 24 was 209 cells per mm³.

Lamivudine: *Clinical Endpoint Trial:* ACTG300 was a multicenter, randomized, double-blind trial that provided for comparison of lamivudine plus zidovudine with didanosine monotherapy. A total of 471 symptomatic, HIV-1-infected therapy-naive (less than or equal to 56 days of antiretroviral therapy) pediatric subjects were enrolled in these 2 treatment arms. The median age was 2.7 years (range: 6 weeks to 14 years), 58% were female, and 86% were non-white. The mean baseline CD4+ cell count was 868 cells per mm³ (mean: 1,060 cells per mm³ and range: 0 to 4,650 cells per mm³ for subjects aged less than or equal to 5 years; mean: 419 cells per mm³ and range: 0 to 1,555 cells per mm³ for subjects aged over 5 years) and the mean baseline plasma HIV-1 RNA was 5.0 log_{10} copies per mL. The median duration on trial was 10.1 months for the subjects receiving lamivudine plus zidovudine and 9.2 months for subjects receiving didanosine monotherapy. Results are summarized in Table 14.

Table 14. Number of Subjects (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
HIV-1 disease progression or death (total)	15 (6.4%)	37 (15.7%)
Physical growth failure	7 (3.0%)	6 (2.6%)
Central nervous system deterioration	4 (1.7%)	12 (5.1%)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (0.8%)	11 (4.7%)

Once-Daily Dosing

ARROW (COL105677) was a 5-year randomized, multicenter trial which evaluated multiple aspects of clinical management of HIV-1 infection in pediatric subjects. HIV−1-infected, treatment-naïve subjects aged 3 months to 17 years were enrolled and treated with a first-line regimen containing lamivudine and abacavir, dosed twice daily according to World Health Organization recommendations. After a minimum of 36 weeks on treatment, subjects were given the option to participate in Randomization 3 of the ARROW trial, comparing the safety and efficacy of once-daily dosing with twice-daily dosing of lamivudine and abacavir, in combination with a third antiretroviral drug, for an additional 96 weeks. Of the 1,206 original ARROW subjects, 669 participated in Randomization 3. Virologic suppression was not a requirement for participation: at baseline for Randomization 3 (following a minimum of 36 weeks of twice-daily treatment), 75% of subjects in the twice-daily cohort were virologically suppressed, compared with 71% of subjects in the once-daily cohort.

The proportion of subjects with HIV-1 RNA of less than 80 copies per mL through 96 weeks is shown in Table 15. The differences between virologic responses in the two treatment arms were comparable across baseline characteristics for gender and age.

Table 15. Virologic Outcome of Randomized Treatment at Week 96[a] (ARROW Randomization 3)

Outcome	Lamivudine plus Abacavir Twice-Daily Dosing (n = 333)	Lamivudine plus Abacavir Once-Daily Dosing (n = 336)
HIV-1 RNA < 80 copies/mL[b]	70%	67%
HIV-1 RNA 80 copies/mL[c]	28%	31%
No virologic data		
Discontinued due to adverse event or death	1%	< 1%
Discontinued study for other reasons[d]	0%	< 1%
Missing data during window but on study	1%	1%

[a] Analyses were based on the last observed viral load data within the Week 96 window.
[b] Predicted difference (95% CI) of response rate is -4.5% (-11% to 2%) at Week 96.
[c] Includes subjects who discontinued due to lack or loss of efficacy or for reasons other than an adverse event or death, and had a viral load value of greater than or equal to 80 copies per mL, or subjects who had a switch in background regimen that was not permitted by the protocol.
[d] Other includes reasons such as withdrew consent, loss to follow-up, etc. and the last available HIV-1 RNA less than 80 copies per mL (or missing).

Analyses by formulation demonstrated the proportion of subjects with HIV-1 RNA of less than 80 copies per mL at randomization and Week 96 was higher in subjects who had received tablet formulations (75% [458/610] and 72% [434/601]) than in those who had received any solution formulations at any time (52% [29/56] and 54% [30/56]), respectively. These differences were observed in each different age group evaluated.

16 HOW SUPPLIED/STORAGE AND HANDLING

Dolutegravir, Lamivudine and Tenofovir disoproxil fumarate tablets, 50 mg/300 mg /300 mg are orange colored, modified capsule shaped, biconvex film coated tablets debossed with 'H' on one side and 'D 17' on the other side. They are supplied in HDPE bottles of 30, 60, 90, 100 or 750 tablets with desiccant, induction seals and child-resistant closures as follows:

Bottle of 30 tablets
Bottle of 60 tablets
Bottle of 90 tablets
Bottle of 100 tablets
Bottle of 750 tablets

Store below 30°C.

To protect from moisture, dispense the packages of 30, 60 and 90 tablets in their original bottles. Do not remove desiccant.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Drug Interactions: Do not coadminister dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets with dofetilide because the interaction between dofetilide and dolutegravir can result in potentially life-threatening adverse events *[see Contraindications (4)]*. Patients should be advised to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products.

Lactic Acidosis/Hepatomegaly: Inform patients that some HIV medicines, including dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) *[see Boxed Warning, Warnings and Precautions (5.1)]*.

Patients with Hepatitis B or C Co-infection: Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets and advise patients to have laboratory testing before and during therapy *[see Warnings and Precautions (5.2)]*.

Advise patients co−infected with HIV−1 and HBV that worsening of liver disease has occurred in some cases when treatment with lamivudine or disoproxil fumarate were discontinued. Advise patients to discuss any changes in regimen with their physician *[see Warnings and Precautions (5.2)]*.

Inform patients with HIV−1/HCV co-infection that 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 *[see Warnings and Precautions (5.6)]*.

Effects on Serum Liver Biochemistries in Patients with Hepatitis B or C Co-infection: Advise patients that it is recommended to have laboratory testing before and during therapy as patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir *[see Warnings and Precautions (5.2)]*.

Inform patients co-infected with HIV-1 and HBV that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Advise patients to discuss any changes in regimen with their healthcare provider *[see Warnings and Precautions (5.2)]*.

Inform patients with HIV-1/HCV co-infection that 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 *[see Warnings and Precautions (5.6)]*.

Severe acute exacerbations of hepatitis have been reported in patients who are infected with HBV or coinfected with HBV and HIV-1 and have discontinued tenofovir disoproxil fumarate *[see Warnings and Precautions (5.2)]*.

Patients with HIV-1 should be tested for Hepatitis B virus (HBV) before initiating antiretroviral therapy *[see Warnings and Precautions (5.2)]*.

In patients with chronic hepatitis B, it is important to obtain HIV antibody testing prior to initiating tenofovir disoproxil fumarate *[see Warnings and Precautions (5.2)]*.

Risk of Pancreatitis: Advise parents or guardians to monitor pediatric patients for signs and symptoms of pancreatitis *[see Warnings and Precautions (5.4)]*.

Renal Impairment: Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of tenofovir disoproxil fumarate. Dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) *[see Warnings and Precautions (5.5)]*. Dosing interval of tenofovir disoproxil fumarate may need adjustment in patients with renal impairment; however, because dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are fixed-dose tablets and cannot be dose adjusted, dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are not recommended in patients requiring dosage adjustment or patients with renal impairment *[see Dosage and Administration (2.2)]*.

Coadministration with Other Products: Do not use with other products containing lamivudine, emtricitabine, tenofovir disoproxil fumarate, or tenofovir alafenamide *[see Warnings and Precautions (5.7)]*. Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should not be administered in combination with adefovir dipivoxil (HEPSERA) *[see Warnings and Precautions (5.5)]*.

Bone Effects: Decreases in bone mineral density have been observed with the use of tenofovir disoproxil fumarate. Bone mineral density monitoring should be considered in patients who have a history of pathologic bone fracture or at risk for osteopenia *[see Warnings and Precautions (5.8)]*.

Fat Redistribution: Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.9)]*.

Immune Reconstitution Syndrome: In some patients with advanced HIV infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection *[see Warnings and Precautions (5.10)]*.

Information about HIV-1 Infection; Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. Inform patients that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death.

Advise patients to remain under the care of a physician when using dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.

Advise patients to take all HIV medications exactly as prescribed.

Advise patients to avoid doing things that can spread HIV-1 infection to others.

Advise patients not to re-use or share needles or other injection equipment.

Advise patients not to share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.

Advise patients to always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Female patients should be advised not to breastfeed because it is not known if dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets can be passed to your baby in your breast milk and whether it could harm your baby. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Instruct patients to read the Patient Information before starting dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets and to reread it each time the prescription is renewed.

Instruct patients to inform their physician or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Instruct patients that if they miss a dose, they should take it as soon as they remember. If they do not remember until it is within 4 hours of the time for the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Instruct patients to store dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

STORAGE CONDITION: Store at temperatures not exceeding 30°C.

AVAILABILITY:

100 cc opaque white HDPE container (with a 38 mm neck and child-resistant plastic cap with pulp liner) x 30's (box of 30's)

Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription

ADR REPORTING STATEMENT: For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Please seek medical attention immediately at the first sign of any adverse drug reaction.

This product has been produced under a licence from the Medicines Patent Pool.

This product is not authorised for supply into the Private Market.

Any other use is not authorised.

Manufactured by:
HETERO LABS LIMITED
Unit III Formulation Plot No-110 IDA, Jeedimetla,
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Imported and Distributed by:
CAMBER PHARMACEUTICALS, INC.
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