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

HIGHLIGHTS OF PRESCRIBING INFORMATION **POM Schedule: S2 NS2 PP**

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.

Issued: August 2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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.

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.

Size: 500x950 mm
Pre Folding size: 45x60 mm
Pharma code: 6902