CIPANEC Tablets (Dolutegravir + Lamivudine + Tenofovir Disoproxil Fumarate)

To be sold by retail on prescription of R. M.P. only

Black Box Warning

Exacerbations of Hepatitis B
Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis b virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued anti-hepatitis B treatment. monitor hepatic function closely in these patients and if appropriate, initiate anti-hepatitis B treatment.
Different formulations of lamivudine
Patients with HIV-1 infection should receive only dosage forms of lamivudine appropriate for the treatment of HIV-1.

Qualitative and Quantitative Composition

Each film coated tablet contains:

Dolutegravir sodium equivalent to

Dolutegravir.....50 mg

Lamivudine IP.....300 mg

Tenofovir Disoproxil Fumarate IP .....300 mg

equivalent to Tenofovir Disoproxil .....245 mg

Colors: Titanium Dioxide IP, Lake Brilliant Blue FCF, Indigo Carmine

Dosage Form and Strength

Oral, fixed-dose tablet

Dolutegravir 50 mg, Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg (equivalent to Tenofovir Disoproxil 245 mg)

Clinical Particulars

Therapeutic Indications

CIPANEC tablets are indicated for the management of Human Immunodeficiency Virus (HIV)

infections in adults weighing more than 40 kg.

Limitations of Use:

Dolutegravir/lamivudine/tenofovir disoproxil fumarate tablets should not be used in combination with efavirenz/emtricitabine/tenofovir disoproxil fumarate, zidovudine/ lamivudine, emtricitabine/rilpivirine/tenofovir disoproxil fumarate, lamivudine, lamivudine -HBV, abacavir/lamivudine, emtricitabine and tenofovir alafenamide, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine/rilpivirine/ tenofovir alafenamide, elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate, dolutegravir, abacavir/dolutegravir/lamivudine, emtricitabine/tenofovir disoproxil fumarate, tenofovir alafenamide or tenofovir disoproxil fumarate) **[see Special Warnings and Precautions for Use]**.

Posology and Method of Administration

Pregnancy Testing before Initiation of CIPANEC

Perform pregnancy testing before initiation of **CIPANEC** in adolescents and adults of childbearing potential **[see Special Warnings and Precautions for Use, Use in Special Populations].**

Recommended Dose in Adults

Dolutegravir/lamivudine/tenofovir disoproxil fumarate tablets may be taken with or without food.

The recommended dose of dolutegravir/lamivudine/tenofovir disoproxil fumarate tablet is one tablet daily. When coadministered with certain UGT1A or CYP3A inducers, dose adjustment may be required. **[see Special Warnings and Precautions for Use, Drug Interactions].**

Patients with Renal Impairment

The safety and efficacy of **CIPANEC** in patients with renal impairment has not yet been established.

Patients with Hepatic Impairment

The safety and efficacy of **CIPANEC** in patients with hepatic impairment has not yet been established.

Contraindications

CIPANEC is contraindicated in patients:

- with previous hypersensitivity reaction to dolutegravir, lamivudine or tenofovir disoproxil fumarate **[See Special Warnings and Precautions for Use**].
- receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events **[See Special Warnings and Precautions for Use, Drug Interactions].**

Special Warnings and Precautions for Use

Dolutegravir

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. Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablet is contraindicated in patients who have experienced a previous hypersensitivity reaction to dolutegravir.

Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen. 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 Undesirable Effects]**. 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 abacavir/dolutegravir/lamivudine. Monitoring for hepatotoxicity is recommended.

Embryo-Fetal Toxicity

Preliminary data from an observational study showed that dolutegravir was associated with increased risk of neural tube defects when administered at the time of conception and in early pregnancy. As there is limited understanding of reported types of neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, an alternative treatment to dolutegravir at the time of conception through the first trimester of pregnancy **[See Use in Special Populations]**.

Perform pregnancy testing before initiation of dolutegravir in adolescents and adults of childbearing potential to exclude the use of dolutegravir during the first trimester of pregnancy **[See Posology and Method of Administration].** Initiation of dolutegravir is not recommended in adolescents and adults actively trying to become pregnant unless there is no suitable alternative.

Advise adolescents and adults of childbearing potential to consistently use effective contraception **[See Use in Special Populations].**

In adolescents and adults of childbearing potential currently on dolutegravir who are actively trying to become pregnant, or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing dolutegravir versus switching to another antiretroviral regimen and consider switching to an alternative regimen [**see Use in Specific Populations**].

Dolutegravir may be considered during the second and third trimesters of pregnancy if the expected benefit justifies the potential risk to the pregnant woman and the fetus.

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, Drug Interactions]:**

• 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 **Drug Interactions** 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.

Lamivudine

Post-treatment Exacerbations of Hepatitis

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

Emergence of Lamivudine-Resistant HBV

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1 and HBV (see full prescribing information for Lamivudine-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.

Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised when administering lamivudine to any patient with known risk factors for liver disease; however, cases also have been reported in patients with no known risk factors. Treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate 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).

Pancreatitis

In patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine should be used with caution. Treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should be

stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur **[See Undesirable Effects].**

Tenofovir Disoproxil Fumarate

Severe Acute Exacerbation of Hepatitis B in Patients with HBV Infection

All patients should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating Tenofovir DF.

Discontinuation of anti-HBV therapy, including tenofovir DF, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue tenofovir DF should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since posttreatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

New Onset or Worsening Renal Impairment

Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir disoproxil **[See Undesirable Effects].**

Prior to initiation and during use of Tenofovir DF, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

Dosing interval adjustment of tenofovir disoproxil fumarate and close monitoring of renal function are recommended in all patients with creatinine clearance below 50 mL/min **[See Posology and Method of administration].** No safety or efficacy data are available in patients with renal impairment who received tenofovir disoproxil fumarate using these dosing guidelines, so the potential benefit of tenofovir disoproxil fumarate therapy should be assessed against the potential risk of renal toxicity.

Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)) **[Special Warnings and Precautions for Use- Drug Interactions].** 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 disoproxil fumarate. 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 of renal function.

Patients Coinfected with HIV-1 and HBV

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

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

hepatitis B before initiating treatment with tenofovir DF.

Bone Loss and Mineralization Defects

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 **[See Undesirable Effects].**

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 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 **[See Undesirable Effects]**. 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 Special Warnings and Precautions for Use].**

Immune Reconstitution Syndrome

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

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

Coadministration with Other products

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should not be used in combination with other drugs efavirenz/emtricitabine/tenofovir disoproxil fumarate, zidovudine/lamivudine, emtricitabine/rilpivirine/tenofovir disoproxil fumarate, lamivudine, lamivudine -HBV, abacavir/lamivudine, emtricitabine and tenofovir alafenamide, elvitegravir / cobicistat / emtricitabine/tenofovir alafenamide, emtricitabine/rilpivirine/ tenofovir alafenamide, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, dolutegravir, abacavir/dolutegravir/lamivudine, emtricitabine/tenofovir disoproxil fumarate, tenofovir alafenamide or tenofovir disoproxil fumarate). Tenofovir disoproxil fumarate should not be administered in combination with adefovir dipivoxil **[See Special Warnings and Precautions for Use - Drug**

Interactions].

Drug Interactions

Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC_{50} = 1.93 microM) and multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 microM). *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) [**See Contraindications, Special Warnings and Precautions for use, Drug Interactions**].

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC_{50} = 2.12 microM) and OAT3 (IC_{50} = 1.97 microM). 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 microM) 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.

Effect of Other Agents on the Pharmacokinetics of Dolutegravir

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

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

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir (Table 1) [**See Special Warnings and Precautions for Use, Drug Interactions**].

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

Established and Other Potentially Significant Drug Interactions

Table 1 provides clinical recommendations as a result of drug interactions with dolutegravir. These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy **[See Posology and Method of Administration**].

Table 1. Established and other potentially significant drug interactions: alterations in dose or regimen may be recommended based on drug interaction trials or predicted interactions [see posology and method of administration]

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 with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓ Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily for treatment-naïve and treatment-experienced, Integrase strand transfer inhibitors (INSTI)-naïve adult patients. Use alternative combinations that do not include metabolic inducers where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓ Dolutegravir	Avoid coadministration with nevirapine because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir[a] Tipranavir/ritonavir[a]	↓ Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. Use alternative combinations that do not include metabolic inducers where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]
Other Agents		
Dofetilide	↑ Dofetilide	Coadministration is contraindicated with dolutegravir **[See Contraindications]**
Carbamazepine[a]	↓ Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily in treatment-naïve or treatment-experienced, INSTI-naïve adult patients. Use alternative treatment that does not include carbamazepine where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]
Oxcarbazepine Phenytoin Phenobarbital St. John's wort (*Hypericum perforatum*)	↓ Dolutegravir	Avoid coadministration with dolutegravir because there are insufficient data to make dosing recommendations.

Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓ Dolutegravir	Administer dolutegravir 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron[a]	↓ Dolutegravir	Administer dolutegravir 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, dolutegravir and supplements containing calcium or iron can be taken together with food.
Potassium channel blocker: Dalfampridine	↑ Dalfampridine	Elevated levels of dalfampridine increase the risk of seizures. The potential benefits of taking dalfampridine concurrently with dolutegravir should be considered against the risk of seizures in these patients.
Metformin	↑ Metformin	With concomitant use, limit the total daily dose of metformin to 1,000 mg either when starting metformin or dolutegravir. When stopping dolutegravir, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of dolutegravir is recommended.
Rifampin[a]	↓ Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. Use alternatives to rifampin where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]

[a] *See Pharmacokinetics for magnitude of interaction*.

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

Drugs without Clinically Significant Interactions with Dolutegravir

Based on drug interaction trial results, the following drugs can be coadministered with dolutegravir without a dose adjustment: atazanavir/ritonavir, darunavir/ritonavir, daclatasvir, elbasvir/grazoprevir, methadone, midazolam, omeprazole, oral contraceptives containing norgestimate and ethinyl estradiol, prednisone, rifabutin, rilpivirine, sofosbuvir/velpatasvir, and tenofovir.

Drugs Inhibiting Organic Cation Transporters

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic

transport system (e.g., trimethoprim). No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

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.

Drugs Affecting Renal Function

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

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

Established and Significant Interactions

Table 2 provides a listing of established or clinically significant drug interactions. The drug interactions described are based on studies conducted with tenofovir disoproxil fumarate **[See PHARMACOLOGICAL PROPERTIES]**.

Table 2. Established and significanta drug interactions: Alteration in dose or regimen may be recommended based on drug interaction trials

Concomitant Drug Class: Drug Name	**Effect on Concentration[b]**	**Clinical Comment**

NRTI didanosine	↑ didanosine	Patients receiving tenofovir disoproxil fumarate and didanosine should be monitored closely for didanosine-associated adverse reactions. Discontinue didanosine in patients who develop didanosine associated adverse reactions. 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, reduce the didanosine dose to 250 mg when it is coadministered with tenofovir disoproxil fumarate. In patients weighing less than 60 kg, reduce the didanosine dose to 200 mg when it is coadministered with tenofovir disoproxil fumarate. When coadministered, tenofovir disoproxil fumarate and didanosine delayed-release capsules may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).
HIV-1 Protease Inhibitors: atazanavir lopinavir/ritonavir atazanavir/ritonavir darunavir/ritonavir	↓ atazanavir ↑ tenofovir	When coadministered with tenofovir disoproxil fumarate, atazanavir 300 mg should be given with ritonavir 100 mg. Monitor patients receiving tenofovir disoproxil fumarate, concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavirboosted darunavir for tenofovir disoproxil fumarate - associated adverse reactions. Discontinue tenofovir disoproxil fumarate, in patients who develop tenofovir disoproxil fumarate - associated adverse reactions.

Hepatitis C Antiviral Agents: sofosbuvir/velpatasvir sofosbuvir/velpatasvir/voxilaprevir ledipasvir/sofosbuvir	↑ tenofovir	Monitor patients receiving tenofovir disoproxil fumarate concomitantly with (sofosbuvir/velpatasvir) for adverse reactions associated with tenofovir disoproxil fumarate. Monitor patients receiving tenofovir disoproxil fumarate concomitantly with (ledipasvir/sofosbuvir) without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, for adverse reactions associated with tenofovir disoproxil fumarate. In patients receiving tenofovir disoproxil fumarate concomitantly with ledipasvir/sofosbuvir and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative hepatitis C virus (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.

[a.] This table is not all inclusive.

[b]. ↑=Increase, ↓=Decrease

Use in Special Populations

Patients with Renal Impairment

The safety and efficacy of **CIPANEC** in patients with renal impairment has not yet been established.

Dolutegravir

Dolutegravir plasma concentrations were decreased in subjects with severe renal impairment compared with those in matched healthy controls. However, no dosage adjustment is necessary for treatment-naïve or treatment-experienced and INSTI-naïve patients with mild, moderate, or severe renal impairment or for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance) with mild or moderate renal impairment. Caution is warranted for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance with severe renal impairment, as the decrease in dolutegravir concentrations may result in loss of therapeutic effect and development of resistance to dolutegravir or other coadministered antiretroviral agents. Dolutegravir has not been studied in patients on dialysis.

Lamivudine

Reduction of the dosage of lamivudine is recommended for patients with impaired renal function.

Tenofovir disoproxil fumarate

The dosing interval for tenofovir disoproxil fumarate should be modified in adult patients with estimated creatinine clearance below 50 mL/min or in patients with end stage renal disease requiring dialysis

Patients with Hepatic Impairment

The safety and efficacy of **CIPANEC** in patients with hepatic impairment has not yet been established.

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.

Pregnant Women

Risk Summary

Dolutegravir

Preliminary data from an observational study has identified a possible increased risk of neural tube defects when dolutegravir is administered at the time of conception compared with non-dolutegravir-containing antiretroviral regimens. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk. In addition, 2 of the 5 birth defects (encephalocele and iniencephaly), which have been observed with dolutegravir use, although often termed neural tube defects, may occur post-neural tube closure, the time period of which may be later than 6 weeks of gestation, but within the first trimester. Due to the limited understanding of the types of reported neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, an alternative treatment to dolutegravir should be considered at the time of conception through the first trimester of pregnancy. Initiation of dolutegravir is not recommended in adolescents and adults actively trying to become pregnant unless there is no suitable alternative **(See Data).**

If there are plans to become pregnant or if pregnancy is confirmed while on dolutegravir during the first trimester, if possible, assess the risks and benefits of continuing dolutegravir versus switching to another antiretroviral regimen and consider switching to an alternative regimen. Advise pregnant adolescents and adults of the potential risk to the embryo exposed to dolutegravir from the time of conception through the first trimester of pregnancy. A benefit-risk assessment should consider factors such as feasibility of switching, tolerability, ability to maintain viral suppression, and risk of transmission to the infant against the risk of neural tube defects.

There are insufficient human data on the use of dolutegravir during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and

15% to 20%, respectively.

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

Lamivudine

Available data from the Antiretroviral Pregnancy Registry (APR) show no difference in the risk of overall major birth defects for lamivudine compared with the background rate for major birth defects of 2.7% in the US reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) **(See Data***).*

In animal reproduction studies, oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryolethality at systemic exposure (AUC) similar to the recommended clinical dose; however, no adverse development effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (C_{max}) 35 times the recommended clinical dose **(See Data).**

Tenofovir disoproxil fumarate

Available data from the APR show no increase in the overall risk of major birth defects with first trimester exposure for tenofovir disoproxil fumarate (2.1%) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) **(See Data).**

Published studies in HBV-infected subjects do not report an increased risk of adverse pregnancy-related outcomes with the use of Tenofovir disoproxil fumarate during the third trimester of pregnancy **(See Data).**

In animal reproduction studies, no adverse developmental effects were observed when tenofovir disoproxil fumarate was administered at doses/exposures ≥ 14 (tenofovir disoproxil fumarate) and 2.7 (tenofovir) times those of the recommended daily dose of tenofovir disoproxil fumarate **(See Data).**

Data

Dolutegravir

Human Data:

In a birth outcome surveillance study in Botswana, there have been 5 cases of neural tube defects reported out of 1683 births (0.3%) to mothers who were exposed to dolutegravir-containing regimens at the time of conception. In comparison, the neural tube defect prevalence rates were 0.1% (15/14792) in the non-dolutegravir arm and 0.08% (70/89372) in the HIV-uninfected arm. Five cases reported with dolutegravir included one case each of encephalocele, anencephaly, iniencephaly and 2 cases of myelomeningocele. In the same study, one infant out of 3,840 (0.03%) deliveries to women who started dolutegravir during pregnancy had a neural tube defect, compared with 3 infants out of 5,952 (0.05%) deliveries to women who started non-dolutegravir-containing regimens during pregnancy.

Animal Data

Dolutegravir was administered orally at up to 1,000 mg per kg daily to pregnant rats and rabbits on gestation Days 6 to 17 and 6 to 18, respectively, and also to rats on gestation day 6 to lactation/post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/post-natal (rats) development were observed at up to the highest dose tested. During organogenesis systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the MRHD and in rats were approximately 27 times the exposure in humans at the MRHD. In the rat pre/post-natal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 27 times human exposure at the MRHD).

Lamivudine

Human Data

Based on prospective reports to the APR of over 11,000 exposures to lamivudine during pregnancy resulting in live births (including over 4,500 exposed in the first trimester), there was no difference between the overall risk of birth defects for lamivudine compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to lamivudine-containing regimens and 2.8% (95% CI: 2.5% to 3.3%) following second/third trimester exposure to lamivudine-containing regimens.

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks' gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks' gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks' gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of lamivudine were 3.9 (1.2 to 12.8)–fold greater compared with paired maternal serum concentration (n = 8).

Animal Data

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 35 times that for the recommended adult HIV dose. 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 exposure levels up to 35 times those in humans.

Tenofovir disoproxil fumarate

Human Data

Based on prospective reports from the APR exposures to tenofovir disoproxil fumarate containing regimens during pregnancy resulting in live births (including 3,342 exposed in the first trimester and 1,475 exposed in the second/third trimester), there was no increase in overall major birth defects with tenofovir disoproxil fumarate compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP. The prevalence of major birth defects in live births was 2.3% (95% CI: 1.8% to 2.8%) with first trimester exposure to tenofovir disoproxil fumarate

containing regimens, and 2.1% (95% CI: 1.4% to 3.0%) with the second/third trimester exposure to tenofovir disoproxil fumarate containing regimens.

Prospective reports from the APR of overall major birth defects in pregnancies exposed to tenofovir disoproxil fumarate are compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. Limitations of using an external comparator include differences in methodology and populations, as well as confounding due to the underlying disease.

In published data from three controlled clinical trials, a total of 327 pregnant women with chronic HBV infection were administered tenofovir disoproxil fumarate from 28 to 32 weeks gestation through 1 to 2 months postpartum and followed for up to 12 months after delivery. There were no new safety findings in pregnant women compared with the known safety profile of tenofovir disoproxil fumarate in HBV-infected adults. An increased risk of adverse pregnancy-related outcomes was not observed; 2 stillbirths were identified, and there was 1 major birth defect (talipes) and 1 occurrence of multiple congenital abnormalities (not further specified) in tenofovir disoproxil fumarate exposed infants. Infants were followed for up to 12 months after delivery; there were no clinically relevant drug-related safety findings in infants exposed to tenofovir disoproxil fumarate during late gestation.

Animal Data

Tenofovir disoproxil fumarate was administered orally to pregnant rats (at 0, 50, 150, or 450 mg/kg/day) and rabbits (at 0, 30, 100, or 300 mg/kg/day) through organogenesis (on gestation days 7 through 17, and 6 through 18, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with tenofovir disoproxil fumarate in rats at doses up to 14 times the human dose based on body surface area comparisons and in rabbits at doses up to 19 times the human dose based on body surface area comparisons. In a pre/postnatal development study in rats, tenofovir disoproxil fumarate was administered orally through lactation at doses up to 600 mg/kg/day; no adverse effects were observed in the offspring at tenofovir exposures of approximately 2.7 times higher than human exposures at the recommended daily dose of tenofovir disoproxil fumarate.

Lactating Women

Risk Summary

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 the potential for (1) HIV-1 transmission (in HIV-negative infants), and (2) developing viral resistance (in HIV-positive infants), instruct mothers not to breastfeed if they are receiving dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.

Dolutegravir

It is not known whether dolutegravir is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, dolutegravir was present in milk **(See Data).**

Tenofovir disoproxil fumarate

Based on published data, tenofovir has been shown to be present in human breast milk **(See Data).** It is not known if tenofovir affects milk production or has effects on the breastfed child.

Treatment of HIV-1 infection:
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.

Because of the potential for: (1) HIV transmission (in HIV-negative infants); (2) developing viral resistance (in HIV-positive infants); and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are taking tenofovir DF for the treatment of HIV-1.

Treatment of HBV infection: The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for tenofovir DF and any potential adverse effects on the breastfed infant from tenofovir DF or from the underlying maternal condition.

Data

Dolutegravir

Animal Data

Dolutegravir was the primary drug-related component excreted into the milk of lactating rats following a single oral dose of 50 mg per kg on lactation Day 10, with milk concentrations of up to approximately 1.3 times that of maternal plasma concentrations observed 8 hours postdose.

Tenofovir Disoproxil Fumarate

In a study of 50 HIV-uninfected, breastfeeding women on a tenofovir-containing regimen initiated between 1 and 24 weeks postpartum (median 13 weeks), tenofovir was undetectable in the plasma of most infants after 7 days of treatment in mothers. There were no serious adverse events in mothers or infants.

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

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

Pediatric Patients

CIPANEC is not indicated in paediatric patients.

Geriatric Patients

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.

Effects on Ability to Drive and Use Machines

Patients should be informed that dizziness has been reported during treatment with dolutegravir. The clinical status of the patient and the adverse reaction profile of **CIPANEC** should be borne in mind when considering the patient's ability to drive or operate machinery.

Undesirable Effects

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

- Hypersensitivity reactions **[See Special Warnings and Precautions for use].**
- Hepatotoxicity **[See Special Warnings and Precautions for Use].**
- Lactic acidosis and severe hepatomegaly with steatosis **[See Special Warnings and Precautions for Use].**
- Severe Acute Exacerbation of Hepatitis B in Patients with HBV Infection **[See Special Warnings and Precautions for Use]**
- Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C **[See Special Warnings and Precautions for Use].**
- Pancreatitis **[See Special Warnings and Precautions for use].**
- New Onset or Worsening Renal Impairment **[See Special Warnings and Precautions for Use].**
- Bone loss and Mineralization Defects **[See Special Warnings and Precautions for Use].**
- Fat Redistribution **[See Special Warnings and Precautions for Use].**
- Immune Reconstitution Syndrome **[See Special Warnings and Precautions for Use].**

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 practice.

Dolutegravir

Clinical Trials Experience in Adult Subjects

Treatment-Naïve Subjects:

The safety assessment of dolutegravir in HIV-1-infected treatment-naïve subjects is based on the analyses of data from 2 international, multicenter, double-blind trials, SPRING-2 (ING113086) and SINGLE (ING114467) and data from the international, multicenter, open-label FLAMINGO (ING114915) trial.

In SPRING-2, 822 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) treatment (either abacavir sulfate and lamivudine or emtricitabine / tenofovir). There were 808 subjects included in the efficacy and safety analyses. Through 96 weeks, the rate of adverse events leading to discontinuation was 2% in both treatment arms.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg with fixed-dose abacavir sulfate and lamivudine once daily or fixed-dose efavirenz/emtricitabine/tenofovir once daily (study treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rates of adverse events leading to discontinuation were 4% in subjects receiving dolutegravir 50 mg once daily + abacavir/lamivudine and 14% in subjects receiving efavirenz/emtricitabine/tenofovir once daily.

Treatment-emergent adverse reactions (ARs) of moderate to severe intensity observed in at least 2% of subjects in either treatment arm in SPRING-2 and SINGLE trials are provided in Table 3. Side-b--side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 3. Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis).

	SPRING-2		**SINGLE**	
System Organ Class/ Preferred Term	**Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)**	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**Dolutegravir 50 mg + Abacavir/lamivudine Once Daily (n = 414)**	**Efavirenz/emtricitabine/tenofovir disoproxil fumarate Once Daily (n = 419)**
Psychiatric				
Insomnia	<1%	<1%	3%	3%
Depression	<1%	<1%	1%	2%
Abnormal dreams	<1%	<1%	<1%	2%
Nervous System				
Dizziness	<1%	<1%	<1%	5%
Headache	<1%	<1%	2%	2%
Gastrointestinal				
Nausea	1%	1%	<1%	3%
Diarrhea	<1%	<1%	<1%	2%
Skin and Subcutaneous Tissue				
Rash[a]	0	<1%	<1%	6%
General Disorders				
Fatigue	<1%	<1%	2%	2%
Ear and Labyrinth				
Vertigo	0	<1%	0	2%

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

In addition, Grade 1 insomnia was reported by 1% and less than 1% of subjects receiving dolutegravir and raltegravir, respectively, in SPRING-2; whereas in SINGLE the rates were 7% and 4% for dolutegravir and efavirenz/emtricitabine/tenofovir disoproxil fumarate, respectively. These events were not treatment limiting.

In a multicenter, open-label trial (FLAMINGO), 243 subjects received dolutegravir 50 mg once daily versus 242 subjects who received darunavir 800 mg/ritonavir 100 mg once daily, both in combination with investigator-selected NRTI background regimen (either abacavir/lamivudine or emtricitabine/tenofovir disoproxil fumarate). There were 484 subjects included in the efficacy and safety analyses. Through 96 weeks, the rates of adverse events leading to discontinuation were 3%

in subjects receiving dolutegravir and 6% in subjects receiving darunavir/ritonavir. The ARs observed in FLAMINGO were generally consistent with those seen in SPRING-2 and SINGLE.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects:

In an international, multicenter, double-blind trial (ING111762, SAILING), 719 HIV-1-infected, antiretroviral treatment-experienced adults were randomized and received either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving dolutegravir 50 mg once daily + background regimen and 4% in subjects receiving raltegravir 400 mg twice daily + background regimen.

The only treatment-emergent AR of moderate to severe intensity with at least 2% frequency in either treatment group was diarrhea, 2% (6 of 354) in subjects receiving dolutegravir 50 mg once daily + background regimen and 1% (5 of 361) in subjects receiving raltegravir 400 mg twice daily + background regimen.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects:

In a multicenter, open-label, single-arm trial (ING112574, VIKING-3), 183 HIV-1-infected, antiretroviral treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received dolutegravir 50 mg twice daily with the current failing background regimen for 7 days and with optimized background therapy from Day 8. The rate of adverse events leading to discontinuation was 4% of subjects at Week 48.

Treatment-emergent ARs in VIKING-3 were generally similar compared with observations with the 50-mg once-daily dose in adult Phase 3 trials.

Virologically Suppressed Subjects: The ARs observed for dolutegravir plus rilpivirine in the Week 48 analysis of pooled data from 2 identical, international, multicenter, open-label trials (SWORD-1 and SWORD-2) of 513 HIV-1–infected, virologically suppressed subjects switching from their current antiretroviral regimen to dolutegravir plus rilpivirine, were consistent with the AR profiles and severities for the individual components when administered with other antiretroviral agents. There were no ARs (Grades 2 to 4) with an incidence of at least 2% in either treatment arm. The rates of adverse events leading to discontinuation were 4% in subjects receiving dolutegravir plus rilpivirine once daily and less than 1% in subjects who remained on their current antiretroviral regimen.

Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials:

The following ARs 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 are presented in Table 4. The mean change from baseline observed for selected lipid values is presented in Table 5. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 4. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

Laboratory Parameter Preferred Term	**SPRING-2**		**SINGLE**	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**Dolutegravir 50 mg + Abacavir/lamivudine Once Daily (n = 414)**	**Efavirenz/emtricitabine/tenofovir disoproxil fumarate Once Daily (n = 419)**
ALT				
Grade 2 (>2.5-5.0 x ULN)	4%	4%	3%	5%
Grade 3 to 4 (>5.0 x ULN)	2%	2%	1%	<1%
AST				
Grade 2 (>2.5-5.0 x ULN)	5%	3%	3%	4%
Grade 3 to 4 (>5.0 x ULN)	3%	2%	1%	3%
Total Bilirubin				
Grade 2 (1.6-2.5 x ULN)	3%	2%	<1%	<1%
Grade 3 to 4 (>2.5 x ULN)	<1%	<1%	<1%	<1%
Creatine kinase				
Grade 2 (6.0-9.9 x ULN)	2%	5%	5%	3%
Grade 3 to 4 (≥10.0 x ULN)	7%	4%	7%	8%
Hyperglycemia				
Grade 2 (126-250 mg/dL)	6%	6%	9%	6%
Grade 3 (>250 mg/dL)	<1%	2%	2%	<1%
Lipase				
Grade 2 (>1.5-3.0 x ULN)	7%	7%	11%	11%
Grade 3 to 4 (>3.0 x ULN)	2%	5%	5%	4%
Total neutrophils				
Grade 2 (0.75-0.99 x 10^9)	4%	3%	4%	5%

Grade 3 to 4 (<0.75 x 10^9)	2%	2%	3%	3%

ULN = Upper limit of normal.

Table 5. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysisa) and SINGLE Trials (Week 144 Analysisa)

Laboratory Parameter Preferred Term	**SPRING-2**		**SINGLE**	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**Dolutegravir 50 mg + abacavir/lamivudine Once Daily (n = 414)**	**Efavirenz/emtricitabine/tenofovir disoproxil fumarate Once Daily (n = 419)**
Cholesterol (mg/dL)	8.1	10.1	24.0	26.7
HDL cholesterol (mg/dL)	2.0	2.3	5.4	7.2
LDL cholesterol (mg/dL)	5.1	6.1	16.0	14.6
Triglycerides (mg/dL)	6.7	6.6	13.6	31.9

[a] Subjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SPRING-2, and in SINGLE: dolutegravir + abacavir/lamivudine n = 30 and efavirenz/emtricitabine/tenofovir disoproxil fumarate n = 27). Ninety-four 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 (SPRING-2: dolutegravir n = 9, raltegravir n = 13; SINGLE: dolutegravir + abacavir/lamivudine n = 36 and efavirenz/emtricitabine/tenofovir disoproxil fumarate: n = 36).

Laboratory abnormalities observed in the FLAMINGO trial were generally consistent with observations in SPRING-2 and SINGLE.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects:

Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naïve (SPRING-2 and SINGLE) trials.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects:

The most common treatment-emergent laboratory abnormalities (greater than 5% for Grades 2 to 4 combined) observed in VIKING-3 at Week 48 were elevated ALT (9%), AST (8%), cholesterol (10%), creatine kinase (6%), hyperglycemia (14%), and lipase (10%). Two percent (4 of 183) of subjects had a Grade 3 to 4 treatment-emergent hematology laboratory abnormality, with neutropenia (2% [3 of 183]) being the most frequently reported.

Virologically Suppressed Adults: Laboratory abnormalities observed in SWORD-1 and SWORD-2 were generally similar compared with observations seen in the other Phase 3 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 Special Warnings and Precautions for Use].**

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. 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.

Lamivudine

The safety profile of lamivudine in adults is primarily based on 3,568 HIV-1-infected subjects in 7 clinical trials.

The most common adverse reactions are headache, nausea, malaise, fatigue, nasal signs and symptoms, diarrhea, and cough.

Selected clinical adverse reactions in greater than or equal to 5% of subjects during therapy with lamivudine 150 mg twice daily plus zidovudine 200 mg 3 times daily for up to 24 weeks are listed in Table 6.

Table 6. Selected Clinical Adverse Reactions (Greater than or Equal to 5% Frequency) in Four Controlled Clinical Trials (NUCA3001, NUCA3002, NUCB3001, NUCB3002)

Adverse Reaction	**Lamivudine 150 mg Twice Daily plus zidovudine (n = 251)**	**zidovudine (n = 230)**
Body as a Whole		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
Digestive		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea & vomiting	13%	12%
Anorexia and/or decreased appetite	10%	7%
Abdominal pain	9%	11%
Abdominal cramps	6%	3%
Dyspepsia	5%	5%
Nervous system		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%

Respiratory		
Nasal signs & symptoms	20%	11%
Cough	18%	13%
Skin		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

[a] Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

Pancreatitis:

Pancreatitis was observed in 9 out of 2,613 adult subjects (0.3%) who received lamivudine in controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and NUCB3007 **[See Special Warnings and Precautions for Use].**

Lamivudine 300 mg Once Daily:

The types and frequencies of clinical adverse reactions reported in subjects receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) for 48 weeks were similar.

Selected laboratory abnormalities observed during therapy are summarized in Table 7.

Table 7. Frequencies of Selected Grade 3-4 Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Trials (NUCA3001, NUCA3002, NUCB3001, NUCB3002) and a Clinical Endpoint Trial (NUCB3007)

	24-Week Surrogate Endpoint Trials[a]		**Clinical Endpoint Trial[a]**	
Test (Threshold Level)	**Lamivudine plus zidovudine**	**Zidovudine[b]**	**Lamivudine plus Current Therapy[c]**	**Placebo plus Current Therapy[c]**
Absolute neutrophil count (<750/mm^3)	7.2%	5.4%	15%	13%
Hemoglobin (<8.0 g/dL)	2.9%	1.8%	2.2%	3.4%
Platelets (<50,000/mm^3)	0.4%	1.3%	2.8%	3.8%
ALT (>5.0 × ULN)	3.7%	3.6%	3.8%	1.9%
AST (>5.0 × ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (>2.5 × ULN)	0.8%	0.4%	ND	ND
Amylase (>2.0 × ULN)	4.2%	1.5%	2.2%	1.1%

[a] The median duration on study was 12 months.

[b] Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

[c] Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus zalcitabine.

ULN = Upper limit of normal.

ND = Not done.

The frequencies of selected laboratory abnormalities reported in subjects receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) were similar.

Tenofovir Disoproxil Fumarate

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 1544 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 2–4) identified from any of the 3 large controlled clinical trials include rash, diarrhea, headache, pain, depression, asthenia, and nausea.

Clinical Trials in Treatment-Naïve HIV-1 Infected Adult Subjects

Study 903 - Treatment-Emergent Adverse-Reactions: The most common adverse reactions seen in a double-blind comparative controlled trial in which 600 treatement-naïve subjects received tenofovir disoproxil fumarate (N=299) or stavudine (N=301) in combination with lamivudine and efavirenz for 144 weeks (Study 903) were mild to moderate gastrointestinal events and dizziness.

Mild adverse reactions (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea, and nausea. Selected treatment-emergent moderate to severe adverse reactions are summarized in Table 8.

Table 8: Selected Treatment-Emergent Adverse Reactionsa (Grades 2-4) Reported in ≥5% in Any Treatment Group in Study 903 (0-144 Weeks)

	Tenofovir disoproxil fumarate +3TC+EFV	**d4T+3TC+EFV**
	N=299	**N=301**
Rash event	18%	12%
Headache	14%	17%
Pain	13%	12%
Diarrhea	11%	13%
Depression	11%	10%
Back pain	9%	8%
Nausea	8%	9%
Fever	8%	7%
Abdominal pain	7%	12%
Asthenia	6%	7%
Anxiety	6%	6%

Vomiting	5%	9%
Insomnia	5%	8%
Arthralgia	5%	7%
Pneumonia	5%	5%
Dyspepsia	4%	5%
Dizziness	3%	6%
Myalgia	3%	5%
Lipodystrophy[c]	1%	8%
Peripheral neuropathy[d]	1%	5%

[a.] Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

[b]. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

[c.]Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome.

[d].Peripheral neuropathy includes peripheral neuritis and neuropathy.

Laboratory Abnormalities:

With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the stavudine group (40% and 9%) compared with tenofovir disoproxil fumarate (19% and 1%), respectively, laboratory abnormalities observed in this trial occurred with similar frequency in the tenofovir disoproxil fumarate and stavudine treatment arms. A summary of Grades 3 - 4 laboratory abnormalities is provided in Table 9.

Table 9. Grades 3-4 Laboratory Abnormalities Reported in ≥1% of Tenofovir disoproxil fumarate - Treated Subjects in Study 903 (0-144 Weeks)

	Tenofovir disoproxil fumarate + 3TC + EFV	**d4T + 3TC + EFV**
	N=299	**N=301**
Any ≥Grade 3 Laboratory Abnormality	36%	42%
Fasting Cholesterol (>240 mg/dL)	19%	40%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	12%	12%
Serum Amylase (>175 U/L)	9%	8%
AST (M: >180 U/L; F: >170 U/L)	5%	7%
ALT (M: >215 U/L; F: >170 U/L)	4%	5%
Hematuria (>100 RBC/HPF)	7%	7%
Neutrophils (<750/mm^3)	3%	1%
Fasting Triglycerides (>750 mg/dL)	1%	9%

Study 934 - Treatment Emergent Adverse Reactions: In Study 934,511 antiretroviral-naïve subjects received either tenofovir disoproxil fumarate + emtricitabine administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254).

The most common adverse reactions (incidence greater than or equal to 10%, all grades) included diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. Table 10 provides the treatment-emergent adverse reactions (Grades 2−4) occurring in greater than or equal to 5% of subjects treated in any treatment group

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 24-48 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 Special Warnings and Precautions for Use].**

Table 10: Selected Treatment-Emergent Adverse Reactionsa (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 934 (0-144 Weeks)

	Tenofovir disoproxil fumarate[b] +FTC+EFV	**AZT/3TC+EFV**
	N=257	**N=254**
Fatigue	9%	8%
Depression	9%	7%
Nausea	9%	7%
Diarrhea	9%	5%
Dizziness	8%	7%
Upper respiratory tract infections	8%	5%
Sinusitis	8%	4%
Rash event[c]	7%	9%
Headache	6%	5%
Insomnia	5%	7%
Nasopharyngitis	5%	3%
Vomiting	2%	5%

[a.]Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

[b].From Weeks 96 to 144 of the trial, subjects received emtricitabine/tenofovir disoproxil fumarate

with EFV in place of tenofovir disoproxil fumarate + FTC with EFV.

[c].Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculopapular, rash pruritic, and rash vesicular.

Laboratory Abnormalities: Laboratory abnormalities observed in this trial were generally consistent with those seen in previous trials (Table 11).

Table 11. Significant Laboratory Abnormalities Reported in ≥1% of Subjects in Any Treatment Group in Trial 934 (0−144 Weeks)

	Tenofovir disoproxil fumarate[a] + FTC + EFV	**AZT/3TC + EFV**
	N=257	**N=254**
Any ≥Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240 mg/dL)	22%	24%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L; F: >170 U/L)	3%	3%
ALT (M: >215 U/L; F: >170 U/L)	2%	3%
Hemoglobin (<8.0 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria (≥3+)	<1%	1%
Neutrophils (<750/mm^3)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

[a] From Weeks 96 to 144 of the trial, subjects received emtricitabine/tenofovir disoproxil fumarate with EFV in place of tenofovir disoproxil fumarate + emtricitabine (FTC) with efavirenz (EFV).

Treatment-Experienced Patients

Treatment-Emergent Adverse Reactions: The adverse reactions seen in treatment-experienced subjects were generally consistent with those seen in treatment-naïve subjects including mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting, and flatulence. Less than 1% of subjects discontinued participation in the clinical trials due to gastrointestinal adverse reactions (Study 907).

A summary of moderate to severe treatment-emergent adverse reactions that occurred during the first 48 weeks of Study 907 is provided in Table 12.

Table 12. Selected Treatment-Emergent Adverse Reactionsa (Grades 2-4) Reported in ≥3% in Any Treatment Group in Study 907 (0-48 Weeks)

	Tenofovir disoproxil fumarate (N=368) (Week 0-24)	Placebo (N=182) (Week 0-24)	Tenofovir disoproxil fumarate (N=368) (Week 0-48)	Placebo crossover to Tenofovir disoproxil fumarate (N=170) (Week 24-48)
Body as a Whole				
Asthenia	7%	6%	11%	1%
Pain	7%	7%	12%	4%
Headache	5%	5%	8%	2%
Abdominal pain	4%	3%	7%	6%
Back pain	3%	3%	4%	2%
Chest pain	3%	1%	3%	2%
Fever	2%	2%	4%	2%
Digestive System				
Diarrhea	11%	10%	16%	11%
Nausea	8%	5%	11%	7%
Vomiting	4%	1%	7%	5%
Anorexia	3%	2%	4%	1%
Dyspepsia	3%	2%	4%	2%
Flatulence	3%	1%	4%	1%
Respiratory				
Pneumonia	2%	0%	3%	2%
Nervous System				
Depression	4%	3%	8%	4%
Insomnia	3%	2%	4%	4%
Peripheral neuropathy[b]	3%	3%	5%	2%
Dizziness	1%	3%	3%	1%
Skin and Appendage				
Rash event[c]	5%	4%	7%	1%
Sweating	3%	2%	3%	1%
Musculoskeletal				
Myalgia	3%	3%	4%	1%
Metabolic				
Weight loss	2%	1%	4%	2%

[a.] Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

[b.] Peripheral neuropathy includes peripheral neuritis and neuropathy.

[c.] Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory Abnormalities: Laboratory abnormalities observed in this trial occurred with similar frequency in the tenofovir disoproxil fumarate and placebo-treated groups. A summary of Grades 3-4 laboratory abnormalities is provided in Table 13.

Table 13. Grades 3-4 Laboratory Abnormalities Reported in ≥1% of Tenofovir disoproxil fumarate - Treated Subjects in Study 907 (0–48 Weeks)

	Tenofovir disoproxil fumarate (N=368) (Week 0-24)	**Placebo (N=182) (Week 0–24)**	**Tenofovir disoproxil fumarate (N=368) (Week 0-48)**	**Placebo Crossover to Tenofovir disoproxil fumarate (N=170) (Week 24-48)**
Any ≥ Grade 3 Laboratory Abnormality	25%	38%	35%	34%
Triglycerides (>750 mg/dL)	8%	13%	11%	9%
Creatine Kinase (M: >990U/L; F: >845 U/L)	7%	14%	12%	12%
Serum Amylase (>175 U/L)	6%	7%	7%	6%
Glucosuria (≥3+)	3%	3%	3%	2%
AST (M: >180 U/L; F: >170 U/L)	3%	3%	4%	5%
ALT (M: >215 U/L; F: >170 U/L)	2%	2%	4%	5%
Serum Glucose (>250 U/L)	2%	4%	3%	3%
Neutrophils (<750 mm^3)	1%	1%	2%	1%

Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use. Because these reactions are reported voluntarily from a population of uncertain 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.

Investigations

Weight increased

Musculoskeletal

Arthralgia, myalgia.

Psychiatric

Anxiety.

Lamivudine

Body as a Whole

Redistribution/accumulation of body fat

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 Special Warnings and Precautions for Use],** posttreatment exacerbations of hepatitis B **[See Special Warnings and Precautions for Use].**

Hypersensitivity

Anaphylaxis, urticaria.

Musculoskeletal

Muscle weakness, CPK elevation, rhabdomyolysis.

Skin

Alopecia, pruritus.

Post-marketing reports of lamivudine received by pharmacovigilance program of India (PvPI) include hearing loss.

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.

If you experience any side effects, talk to your doctor or pharmacist or write to **drugsafety@cipla.com.** You can also report side effects directly via the National Pharmacovigilance Program of India by calling on **1800 180 3024** or you can report to Cipla ltd. On 18002677779. By reporting side effects, you can help provide more information on the safety of this product.

Overdose

There is no known specific treatment for overdose with dolutegravir or lamivudine. 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

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

Pharmacological Properties

Mechanism of Action

Dolutegravir, lamivudine and tenofovir disoproxil fumarate are HIV-1 antiviral agents.

Dolutegravir

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

Lamivudine

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

Tenofovir disoproxil fumarate

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

Pharmacodynamic Properties

Effects on Electrocardiogram

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

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.

Pharmacokinetics Properties

Dolutegravir

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. The non-linear exposure of dolutegravir following 50 mg twice daily compared with 50 mg once daily in HIV-1-infected subjects (Table 14) was attributed to the use of metabolic inducers in the background antiretroviral regimens of subjects receiving dolutegravir 50 mg twice daily in clinical trials.

Table 14. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV–1– Infected Adults

Parameter	**50 mg Once Daily Geometric Mean[a] (%CV)**	**50 mg Twice Daily Geometric Mean[b] (%CV)**
$AUC_{(0-24)}$ (mcg.h/mL)	53.6 (27)	75.1 (35)
C_{max} (mcg/mL)	3.67 (20)	4.15 (29)
C_{min} (mcg/mL)	1.11 (46)	2.12 (47)

[a] Based on population pharmacokinetic analyses using data from SPRING-1 and SPRING-2.

[b] Based on population pharmacokinetic analyses using data from VIKING (ING112961) and VIKING-3.

Lamivudine

The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-1-infected adult subjects after administration of single intravenous (IV) doses ranging from 0.25 to 8 mg per kg, as well as single and multiple (twice-daily regimen) oral doses ranging from 0.25 to 10 mg per kg.

The pharmacokinetic properties of lamivudine have also been studied as single and multiple oral doses ranging from 5 mg to 600 mg per day administered to HBV-infected subjects.

The steady-state pharmacokinetic properties of the lamivudine 300-mg tablet once daily for 7 days compared with the lamivudine 150-mg tablet twice daily for 7 days were assessed in a crossover trial in 60 healthy subjects. Lamivudine 300 mg once daily resulted in lamivudine exposures that were similar to lamivudine 150 mg twice daily with respect to plasma $AUC_{24,ss}$; however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared with the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough values were lower compared with the 150-mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations.

The pharmacokinetics of lamivudine was evaluated in 12 adult HIV-1-infected subjects dosed with lamivudine 150 mg twice daily in combination with other antiretroviral agents. The geometric mean (95% CI) for $AUC_{(0-12)}$ was 5.53 (4.58, 6.67) mcg.h per mL and for C_{max} was 1.40 (1.17, 1.69) mcg per mL.

Tenofovir disoproxil fumarate

The pharmacokinetics of tenofovir disoproxil fumarate has been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption

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 $C_{24\,h}$ ranging from 1.2 to 1.5.

Dolutegravir plasma concentrations increased in a less than dose-proportional manner above 50 mg. Dolutegravir is a P-gp substrate *in vitro*. The absolute bioavailability of dolutegravir has not been established.

Lamivudine

Absolute bioavailability in 12 adult subjects was 86% ± 16% (mean ± SD) for the 150-mg tablet and 87% ± 13% for the oral solution. After oral administration of 2 mg per kg twice a day to 9 adults with HIV-1, the peak serum lamivudine concentration (C_{max}) was 1.5 ± 0.5 mcg per mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0.25 to 10 mg per kg.

The accumulation ratio of lamivudine in HIV-1-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg per kg twice daily.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted subjects is approximately 25%. Following oral administration of a single dose of tenofovir disoproxil fumarate 300 mg to HIV-1 infected subjects in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1.0 ± 0.4 hrs. C_{max} and AUC values are 0.30 ± 0.09 µg/mL and 2.29 ± 0.69 µg·hr/mL, respectively.

The pharmacokinetics of tenofovir are dose proportional over a tenofovir disoproxil fumarate dose range of 75 to 600 mg and are not affected by repeated dosing.

In a single-dose bioequivalence study conducted under non-fasted conditions (dose administered with 4 oz. applesauce) in healthy adult volunteers, the mean C_{max} of tenofovir was 26% lower for the oral powder relative to the tablet formulation. Mean AUC of tenofovir was similar between the oral powder and tablet formulations.

Effect of Food

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets may be taken with or without food.

Distribution

Dolutegravi*r*

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.

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.

Lamivudine

The apparent volume of distribution after IV administration of lamivudine to 20 subjects was 1.3 ± 0.4 L per kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of lamivudine to human plasma proteins is less than 36%. *In vitro* studies showed that over the concentration range of 0.1 to 100 mcg per mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

Tenofovir disoproxil fumarate

In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/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.

Metabolism and Elimination

Dolutegravir

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.

Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A.

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).

After a single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose was excreted unchanged in feces. Thirty-one percent of the total oral dose was excreted in 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 low (less than 1% of the dose).

Lamivudine

Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite of lamivudine is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours). Serum concentrations of this metabolite have not been determined. Lamivudine is not significantly metabolized by cytochrome P450 enzymes.

The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 mL per min (mean ± SD). In 20 HIV-1-infected subjects given a single IV dose, renal clearance was 280.4 ± 75.2 mL per min (mean ± SD), representing 71% ± 16% (mean ± SD) of total clearance of lamivudine.

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 ($t_{1/2}$) ranged from 5 to 7 hours. In HIV-1-infected subjects, total clearance was 398.5 ± 69.1 mL per min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range of 0.25 to 10 mg per kg.

Tenofovir disoproxil fumarate

In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes.

Following IV administration of tenofovir, approximately 70-80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of tenofovir disoproxil fumarate, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of tenofovir disoproxil fumarate 300 mg once daily (under fed conditions), 32 ± 10% of the administered dose is recovered in urine over 24 hours.

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Special Populations

Geriatric Patients

Dolutegravir: Population pharmacokinetic analysis indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir.

Lamivudine and tenofovir disoproxil fumarate: The pharmacokinetics of lamivudine after administration of lamivudine to subjects over 65 years have not been studied **[see Use in Special Populations].**

Patients with Hepatic Impairment

The safety and efficacy of dolutegravir, lamivudine and tenofovir disoproxil fumarate in patients with hepatic impairment has not yet been established.

Dolutegravir: 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. The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied.

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.

Patients with Renal Impairment

The safety and efficacy of dolutegravir, lamivudine and tenofovir disoproxil fumarate in patients with renal impairment has not yet been established.

Dolutegravir: In a trial comparing 8 subjects with severe renal impairment (CrCl less than 30 mL per min) with 8 matched healthy controls, AUC, C_{max}, and C_{24} of dolutegravir were lower by 40%, 23%, and 43%, respectively, compared with those in matched healthy subjects. Population pharmacokinetic analysis using data from SAILING and VIKING-3 trials indicated that mild and moderate renal impairment had no clinically relevant effect on the exposure of dolutegravir. Dolutegravir has not been studied in patients requiring dialysis.

Lamivudine: The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-1-infected adults with impaired renal function (Table 15).

Table 15. Pharmacokinetic Parameters (Mean ± SD) after a Single 300-mg Oral Dose of Lamivudine in 3 Groups of Adults with Varying Degrees of Renal Function

Parameter	**Creatinine Clearance Criterion (Number of Subjects)**		
	>60 mL/min (n = 6)	**10-30 mL/min (n = 4)**	**<10 mL/min (n = 6)**
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C_{max} (mcg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC∞ (mcg•h/mL)	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

T_{max} was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of lamivudine be modified in patients with renal impairment.

Based on a trial in otherwise healthy subjects with impaired renal function, hemodialysis increased lamivudine clearance from a mean of 64 to 88 mL per min; however, the length of time of hemodialysis (4 hours) was insufficient to significantly alter mean lamivudine exposure after a single-dose administration. Continuous ambulatory peritoneal dialysis and automated peritoneal dialysis have negligible effects on lamivudine clearance. Therefore, it is recommended, following correction of dose for creatinine clearance, that no additional dose modification be made after routine hemodialysis or peritoneal dialysis.

The effects of renal impairment on lamivudine pharmacokinetics in pediatric patients are not known.

Tenofovir disoproxil fumarate: The pharmacokinetics of tenofovir are altered in subjects with renal impairment **[See Special Warnings and Precautions for Use]**. In subjects with creatinine clearance below 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and $AUC_{0-\infty}$ of tenofovir were increased (Table 16).

Table 16. Pharmacokinetic Parameters (Mean ± SD) of Tenofovira in Subjects with Varying Degrees

of Renal Function

Baseline Creatinine Clearance (mL/min)	**>80 (N=3)**	**50–80 (N=10)**	**30–49 (N=8)**	**12–29 (N=11)**
C_{max} (µg/mL)	0.34 ± 0.03	0.33 ± 0.06	0.37 ± 0.16	0.60 ± 0.19
$AUC_{0-\infty}$ (µg·hr/mL)	2.18 ± 0.26	3.06 ± 0.93	6.01 ± 2.50	15.98 ± 7.22
CL/F (mL/min)	1043.7 ± 115.4	807.7 ± 279.2	444.4 ± 209.8	177.0 ± 97.1
CL_{renal} (mL/min)	243.5 ± 33.3	168.6 ± 27.5	100.6 ± 27.5	43.0 ± 31.2

[a.] 300 mg, single dose of tenofovir disoproxil fumarate

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

HBV or HCV Co-infected Patients

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.

Gender

There are no significant or clinically relevant gender differences in dolutegravir, lamivudine or tenofovir disoproxil fumarate pharmacokinetics.

Race

There are no significant or clinically relevant racial differences in dolutegravir or lamivudine pharmacokinetics.

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

Pregnancy

Lamivudine: Lamivudine pharmacokinetics were studied in 36 pregnant women during 2 clinical trials conducted in South Africa. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples.

Non-Clinical Properties

Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Dolutegravir

Carcinogenesis

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 times 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 times and 15 times higher in males and females, respectively, than those in humans at the recommended dose of 50 mg twice daily.

Mutagenesis

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

Impairment of Fertility

In a study conducted in rats, there were no effects on mating or fertility with dolutegravir up to 1,000 mg per kg per day. This dose is associated with an exposure that is approximately 24 times higher than the exposure in humans at the recommended dose of 50 mg twice daily.

Lamivudine

Carcinogenesis

Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) the human exposures at the recommended dose of 300 mg

Mutagenesis

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. Lamivudine showed no evidence of *in-viv*o genotoxic activity in the rat at oral doses of up to 2,000 mg per kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection.

Impairment of Fertility

In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg per kg per day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

Tenofovir disoproxil fumarate

Carcinogenesis

Long-term oral carcinogenicity studies of TDF 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

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, TDF was negative when administered to male mice.

Impairment of Fertility

There were no effects on fertility, mating performance or early embryonic development when TDF 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.

Description

CIPANEC is a fixed-dose combination tablet containing an Integrase Strand Transfer inhibitor (dolutegravir) and 2 nucleoside analogues [lamivudine and tenofovir disoproxil fumarate (tenofovir DF)] with inhibitory activity against HIV.

Dolutegravir is an Integrase Strand Transfer inhibitor. The chemical name of dolutegravir sodium is sodium (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl6,8-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 441.36 g per mol.

Lamivudine is a synthetic nucleotide analogue. The chemical name of lamivudine is (2R,cis)-4-ami-o-1(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2’,3’-dideoxy, 3’-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3 g per mol.

Tenofovir disoproxil fumarate is nucleotide analogue. 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 $C_{19}H_30N_5O_{10}P \bullet C_4H_4O_4$ and a molecular weight of 635.52.

Pharmaceutical Particulars

Incompatibilities

Not applicable

Shelf-life

As on the pack

Packaging Information

CIPANEC is available in the pack of 30 tablets

Storage and Handling Instructions

Do not store above 30˚C.

Keep out of reach of children.

Patient Counselling Information

What is CIPANEC?

CIPANEC is a prescription HIV-1 (Human Immunodeficiency Virus type 1) medicine used to treat HIV-1 infection in adults weighing more than 40 kg.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

CIPANEC contains 3 prescription medicines, dolutegravir, lamivudine and tenofovir disoproxil fumarate. Other ingredients which are present in **CIPANEC** are Titanium Dioxide IP, Lake Brilliant Blue FCF, Indigo carmine

CIPANEC is not for use by itself in people who have or have had resistance to dolutegravir, lamivudine or tenofovir disoproxil fumarate.

How should I take CIPANEC?

Take **CIPANEC** exactly as your healthcare provider tells you to take it.

Take **CIPANEC** tablets by mouth, with or without food.

Do not change your dose or stop taking **CIPANEC** without first talking with your healthcare provider. Stay under a healthcare provider's care when taking **CIPANEC**.

Do not miss a dose of **CIPANEC**. Missing a dose lowers the amount of medicine in your blood. Refill your **CIPANEC** prescription before you run out of medicine.

If you take too much **CIPANEC**, call your healthcare provider or go to the nearest hospital emergency room right away

Who should not take CIPANEC?

Do not take CIPANEC if you:

- are allergic to any of the ingredients in **CIPANEC**
- take dofetilide

What should I tell my healthcare provider before taking CIPANEC?

Before you take **CIPANEC**, tell your healthcare provider about all of your medical conditions, including if you:

- have ever had an allergic reaction to any ingredients of **CIPANEC**.
- have or have had liver problems, including hepatitis B or C infection.

- have kidney problems.
- have bone problems
- have HIV infection
- are pregnant or plan to become pregnant. **CIPANEC** may harm your unborn baby.
    - You should not take **CIPANEC** at the time of becoming pregnant or during the first 12 weeks of pregnancy. Your healthcare provider may change your medicine during this time in your

pregnancy.
    - If you can become pregnant, your healthcare provider will perform a pregnancy test before you start treatment with **CIPANEC**.
    - If you can become pregnant, you should consistently use effective birth control (contraception) during treatment with **CIPANEC.**
    - Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with **CIPANEC**.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take CIPANEC**
    - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
    - It is not known if **CIPANEC** can pass to your baby in your breast milk.
    - Talk with your healthcare provider about the best way to feed your baby.

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

Some medicines interact with **CIPANEC**. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take **CIPANEC** with other medicines.

What are the possible side effects of CIPANEC?

CIPANEC can cause serious side effects including:

Allergic reactions. Call your healthcare provider right away if you develop a rash with **CIPANEC**. Stop taking **CIPANEC** and get medical help right away if you develop a rash with any of the following signs or symptoms:

- fever
- generally ill feeling o 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

Serious liver problems can happen in people who take **CIPANEC.** 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 **CIPANEC**. Liver problems, including liver failure have also happened in people without a history of liver disease or other risk factors. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis). In some cases, these serious liver problems can lead to death.

Tell your healthcare provider right away if you get these symptoms: skin or the white part of your eyes turns yellow, dark “tea-colored” urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.

Build-up of an acid in your blood (lactic acidosis). Lactic acidosis can happen in some people who take **CIPANEC**. 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
- feel cold, especially in your arms and legs
- unusual (not normal) muscle pain
- feel dizzy or light-headed
- trouble breathing
- have a fast or irregular heartbeat
- stomach pain with nausea and vomiting

Your healthcare provider may do blood tests to check your liver. **Call your healthcare provider right away if you develop 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)
- nausea or vomiting
- loss of appetite
- 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 or very overweight (obese).

New or worse kidney problems, including kidney failure. Your healthcare provider should do blood and urine tests to check your kidneys before you start and during treatment with **CIPANEC**. Your healthcare provider may tell you to stop taking **CIPANEC** if you get new or worse kidney problems

Bone Problems can happen in some children or adults who take **CIPANEC**. Bone problems include bone pain, or softening or thinning of bones, which may lead to fractures. Your healthcare provider may need to do tests to check your bones or your child’s bones.

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 **CIPANEC.**

The most common side effects which may occur due to CIPANEC include:

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

These are not all the possible side effects of **CIPANEC**. Call your doctor for medical advice about side effects**.**

How to report an adverse event?

If you experience any side effects, talk to your doctor or pharmacist or write to **drugsafety@cipla.com.** You can also report side effects directly via the national pharmacovigilance program of India by calling on **1800 180 3024** or you can report to Cipla ltd. On **18002677779**. By reporting side effects you can help provide more information on the safety of this product.

How to store CIPANEC?

Do not store above 30˚C.

Keep out of reach of children

Details of Manufacturer

Mfg By Cipla Ltd

Registered Office: Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg Lower Parel, Mumbai – 400 013, India

Details of Permission or Licence Number with Date

MF-43/2019. 20 May 2019

Date of Revision

10/04/2020

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

This product is not authorized for supply into the private market.

Any other use is not authorized