1. Name of the finished pharmaceutical product

INN Name: Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 50mg / 300mg / 300mg

Trade Name: Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 50mg / 300mg / 300mg

Strength: 50/300/300 mg

Pharmaceutical form: Film coated tablet

2. Qualitative and quantitative composition

Each film coated tablet contains: 52.6 mg of Dolutegravir Sodium Equivalent to 50 mg of Dolutegravir, 300 mg of Lamivudine USP and 300 mg of Tenofovir Disoproxil fumarate (Equivalent to 245 mg of Tenofovir Disoproxil).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Dosage form: Film coated tablet

Description: Orange colored, modified capsule shaped, biconvex film coated tablets debossed with 'H 'on one side and 'D17' on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents weighing at least 30 kg.

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines. For use of antiretroviral agents for post-exposure prophylaxis the most recent official guidelines, e.g. those by WHO, should be consulted.

Limitations of Use:

- Use of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets in integrase strand transfer inhibitor (INSTI)-experienced patients should be guided by the number and type of baseline INSTI substitutions. The efficacy of dolutegravir, lamivudine and tenofovir disoproxil

fumarate tablets 50 mg twice daily is reduced in patients with an INSTI-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions, including T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R *[see Microbiology (12.4)]*.

- The dosage of this product is for HIV-1 and not for HBV.

The following points should be considered when initiating therapy with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets for the treatment of HIV-1 infection:

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should not be used in combination with ATRIPLA®, COMPLERA®, DESCOVY®, GENVOYA®, ODEFSEY®, STRIBILD®, TRUVADA®, or VEMLIDY® [See Warnings and Precautions (5.4)]

4.2 Posology and method of administration

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should be prescribed by a health care provider experienced in the management of HIV infection.

Recommended Dosage for Adult Patients:

The dose in adults and adolescents weighing at least 30 kg with HIV-1 infection not resistant to integrase inhibitors is Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets once daily taken orally without food.

Dose adjustments in adults and adolescents

Where discontinuation of therapy with one of the components of Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is indicated or where dose modification is necessary, separate preparations of dolutegravir, lamivudine and tenofovir disoproxil should be used. Please refer to the individual product information for these medicinal products.

When the patient's HIV-1 infection is known or suspected to be resistant to integrase inhibitors, additional doses of dolutegravir may be given in adults. Please refer to the product information of dolutegravir for further information or consult current WHO treatment guidelines. There is insufficient information on the use of dolutegravir in adolescents with HIV-1 infection resistant to integrase inhibitors.

Dolutegravir

May be taken without regard to food.

Adult Population	Recommended Dose
Treatment-naïve or treatment-experienced INSTI-naïve or virologically suppressed (HIV-1 RNA <50 copies per mL) adults switching to dolutegravir plus rilpivirine	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A or CYP3A inducers	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistanceb	50 mg twice daily

Patients with Renal Impairment

Lamivudine

Dosing of lamivudine is adjusted in accordance with renal function. Dosage adjustments are listed in Table

Table 1. Adjustment of Dosage of Lamivudine in Adults and Adolescents (Greater than or Equal to 25 kg) in Accordance with Creatinine Clearance

Creatinine Clearance (mL/min)	Recommended Dosage of Lamivudine
≥50	150 mg twice daily or 300 mg once daily
30-49	150 mg once daily
15-29	150 mg first dose, then 100 mg once daily

No additional dosing of lamivudine is required after routine (4-hour) hemodialysis or peritoneal dialysis.

Although there are insufficient data to recommend a specific dose adjustment of lamivudine in pediatric patients with renal impairment, a reduction in the dose and/or an increase in the dosing interval should be considered.

Tenofovir Disoproxil Fumarate

Significantly increased drug exposures occurred when tenofovir disoproxil fumarate was administered to subjects with moderate to severe renal impairment. Therefore, the dosing interval of tenofovir disoproxil fumarate tablets 300 mg should be adjusted in patients with baseline creatinine clearance below 50 mL/min using the recommendations in Table 2. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment; therefore, clinical response to treatment and renal function should be closely monitored in these patients

No dose adjustment of tenofovir disoproxil fumarate tablets 300 mg is necessary for patients with mild renal impairment (creatinine clearance 50 to 80 mL/min). Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be performed in patients with mild renal impairment

Table Dosage Adjustment for Patients with Altered Creatinine Clearance

Recommended 300 mg Dosing Interval	**Creatinine Clearance (mL/min)[a]**			**Hemodialysis Patients**
	≥50	**30 - 49**	**10 - 29**	
	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis[b]

a. Calculated using ideal (lean) body weight.

b. Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours ’ duration. Tenofovir disoproxil fumarate should be administered following completion of dialysis.

The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance below 10 mL/min; therefore, no dosing recommendation is available for these patients.

No data are available to make dose recommendations in pediatric patients with renal impairment.

Children

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should not be used in children weighing less than 30 kg since appropriate dose adjustments cannot be achieved with this product. Separate formulations containing lower amounts of dolutegravir, tenofovir disoproxil or lamivudine are required.

Elderly

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should be administered with caution to elderly patients (see section 4.4).

Renal impairment

Mild renal impairment (creatinine clearance 50-80 mL/minute):

No dose adjustment is required in patients with mild renal impairment.

Moderate or severe renal impairment (creatinine clearance >50 mL/minute):

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is not recommended for use in patients with creatinine clearance < 50 Ml/Minute (see sections 4.4 and 5.2), as appropriate dose adjustments are not possible. For these patients, separate formulations of doltegravir, lamivudine and tenofovir disoproxil should be used.

Hepatic impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). No data are available for dolutegravir in patients with severe hepatic impairment (Child-Pugh grade C); therefore, [HA688 trade name] should be used with caution in these patients.

Discontinuation of therapy

If Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is discontinued in patients co-infected with HIV and hepatitis B virus (HBV), these patients should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

Missed dose and vomiting after a dose

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance and reduce its effectiveness.

The patient should take a missed dose if it was due fewer than 12 hours ago. If more than 12 hours have passed since the dose was due, the patient should omit the missed dose and take the next scheduled dose at the usual time. The patient should not take a double dose.

If the patient vomits within 1 hour of taking Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablet, the patient should take an extra dose. If vomiting occurs more than an hour after taking the dose, the patient does not need to take an extra dose and can take the next dose as usual when it is due.

Method of administration

The recommended dose should be administered orally and the Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should be swallowed whole with water.

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablet can usually be taken with food or between meals.

DOSAGE FORMS AND STRENGTHS

Dolutegravir, Lamivudine and Tenofovir disoproxil fumarate tablets, 50 mg/300 mg /300 mg are:

Orange colored, modified capsule shaped, biconvex film coated tablets debossed with 'H' on one side and 'D17' on the other side.

4.3 Contraindications

Dolutegravir, Lamivudine and Tenofovir disoproxil fumarate tablets are contraindicated in patients:

Hypersensitivity to dolutegravir, lamivudine and tenofovir disoproxil fumarate or to any of the excipients listed in section 6.1.

- With previous hypersensitivity reaction to dolutegravir [see Warnings and Precautions (5.1)].
- Receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events [see Drug Interactions (7)].
- With a previous hypersensitivity reaction to lamivudine.

4.4 Special warnings and precautions for use

General

HBV antibody testing should be offered to all individuals before initiating lamivudine and tenofovir disoproxil-containing therapies (see below Patients with HIV and hepatitis B (HBV) or C virus (HCV) co-infections)

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 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 is contraindicated in patients who have experienced a previous hypersensitivity reaction to dolutegravir.

Effects on Serum Liver Biochemistries in Patients with Hepatitis B or C Co-infection

Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir *[see Adverse Reactions (6.1)]*. In some cases the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with dolutegravir are recommended in patients with underlying hepatic disease such as hepatitis B or C.

Fat Redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and

long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including dolutegravir. 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.

Lamivudine

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 anti retro virals. 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 lamivudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Patients with Hepatitis B Virus Co-infection

<u>Post treatment Exacerbations of Hepatitis</u>

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

monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

Important Differences among Lamivudine-Containing Products

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

Emergence of Lamivudine-Resistant HBV

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

Use with Interferon-and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine. Although no evidence of a pharmacokinetic or pharmacodynamics interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients [see Clinical Pharmacology (12.3)], hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of lamivudine should be considered as medically appropriate. Dose reduction or discontinuation of

interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6). See the full prescribing information for interferon and ribavirin.

Pancreatitis

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

Immune Reconstitution Syndrome

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

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to

onset is more variable, and can occur many months after initiation of treatment.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Tenofovir Disoproxil Fumarate

Exacerbation of Hepatitis after Discontinuation of Treatment

Discontinuation of anti-HBV therapy, including tenofovir disoproxil fumarate, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue tenofovir disoproxil fumarate should be closely monitored with both clinical and laboratory follow-up for at

least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

New Onset or Worsening Renal Impairment

Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir disoproxil fumarate. It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with tenofovir disoproxil fumarate.

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

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* Dosage and Administration (2.3)]. 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)) [See Drug Interactions (7.4)]. 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.

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, alone or in combination with other antiretrovirals. Treatment with tenofovir disoproxil fumarate should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis

or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Coadministration with Other Products

Tenofovir disoproxil fumarate should not be used in combination with other drugs containing tenofovir disoproxil fumarate or tenofovir alafenamide, including ATRIPLA, COMPLERA, DESCOVY, GENVOYA, ODEFSEY, STRIBILD, TRUVADA or VEMLIDY, Tenofovir disoproxil fumarate should not be administered in combination with HEPSERA (Adefovir dipivoxil) [See Drug Interactions (7.4)].

Patients Co infected with HIV-1 and HBV

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

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

Bone Effects

Bone Mineral Density:

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

Clinical trials evaluating tenofovir disoproxil fumarate in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the tenofovir disoproxil fumarate -treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected *[See Adverse Reactions (6.1)]*.

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

Mineralization Defects:

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of tenofovir disoproxil fumarate *[See Adverse Reactions (6.2)]*. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir disoproxil fumarate [See Warnings and Precautions (5.2)].

Osteonecrosis

Osteonecrosis has been reported particularly in patients with advanced HIV disease or following long-term combination antiretroviral therapy. Their aetiology can be multifactorial and include corticosteroid use, excessive alcohol consumption, severe immunosuppression, and being overweight. Patients should be advised to speak to their health care provider if they have joint aches and pain, joint stiffness or difficulty in movement.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including tenofovir disoproxil fumarate. During the initial phase of combination antiretroviral treatment, patients whose immune system responds 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.

Early Virologic Failure

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

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed using dolutegravir, lamivudine and tenofovir disoproxil. As this medicine contains dolutegravir, lamivudine and tenofovir disoproxil, any interactions that have been identified with these agents individually may occur with this combination tablet. Interaction studies with these agents have only been performed in adults**.**

Dolutegravir

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, Table 6) [see Contraindications (4), Drug Interactions (7.3)].

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.

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

Effect of Other Agents on the Pharmacokinetics of Dolutegravir

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

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

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir (Table 6) *[see Drug Interactions (7.3),* Clinical Pharmacology (12.3)].

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

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

Established and Other Potentially Significant Drug Interactions

Table 17 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 Dosage and Administration (2), Clinical Pharmacology (12.3).]

Table. Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interactions *[see Dosage and Administration (2)]*

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, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily (Table 2). 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]	↓Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily for treatment-naïve and

Tipranavir/ritonavir[a]		treatment- experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily (Table 2). 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		
Carbamazepine[a]	↓Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily in treatment-naïve or treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily (Table 2). 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.
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. In pediatric patients, increase the weight-based dose to twice daily (Table 2). Use alternatives to rifampin where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance. [b]

[a] See Clinical Pharmacology (12.3) Table 9 or Table 10 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 [see Microbiology (12.4)]) upon co administration with certain inducers may result in loss of therapeutic effect and development of resistance to dolutegravir or other coadministered antiretroviral agents.

Lamivudine

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) *[see Clinical Pharmacology (12.3)]*. 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 [see Warnings and Precautions (5.6), Clinical Pharmacology (12.3)].

Tenofovir disoproxil fumarate

This section describes clinically relevant drug interactions with tenofovir disoproxil fumarate. Drug interactions trials are described elsewhere in the labeling *[See Clinical Pharmacology (12.3)].*

Didanosine

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

When administered with tenofovir disoproxil fumarate, C_{max} and AUC of didanosine increased significantly [See Clinical Pharmacology (12.3)]. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions,

including pancreatitis and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving tenofovir disoproxil fumarate with didanosine 400 mg daily.

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

HIV-1 Protease Inhibitors

Tenofovir disoproxil fumarate decreases the AUC and C_{min} of atazanavir [See Clinical Pharmacology (12.3)]. When coadministered with tenofovir disoproxil fumarate, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Tenofovir disoproxil fumarate should not be coadministered with atazanavir without ritonavir.

Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations [See Clinical Pharmacology (12.3)]. Tenofovir disoproxil fumarate is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir disoproxil fumarate is coadministered with an inhibitor of these transporters, an increase in absorption may be observed. Patients receiving tenofovir disoproxil fumarate concomitantly with lopinavir/ritonavir, ritonavirboosted atazanavir, or ritonavir-boosted darunavir should be monitored for tenofovir disoproxil fumarate -associated adverse reactions. Tenofovir disoproxil fumarate should be discontinued in patients who develop tenofovir disoproxil fumarate -associated adverse reactions.

Hepatitis C Antiviral Agents

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

In patients receiving tenofovir disoproxil fumarate concomitantly with EPCLUSA, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

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

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

Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys [See Clinical Pharmacology (12.3)], 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 *[See Warnings and Precautions (5.2)].*

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

4.6 Pregnancy and lactation

Dolutegravir

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to dolutegravir during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

There are insufficient human data on the use of dolutegravir during pregnancy to inform a drug associated risk of birth defects and miscarriage. Given the limited number of pregnancies exposed to dolutegravir-based regimens reported to the APR, no definitive conclusions can be drawn on the safety of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets in pregnancy, and continued monitoring is ongoing through the APR. The background rate for major

birth defects in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) is 2.7%. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir *[see Data]*. During organogenesis in the rat and rabbit, systemic exposures (AUC) to dolutegravir were less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD). In the rat pre/postnatal developmental study, maternal systemic exposure (AUC) to dolutegravir was approximately 27 times the exposure in humans at the MRHD.

Data

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 maximum recommended human dose (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).

Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. 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]*.

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.

Data

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 post-dose.

Pediatric Use

The safety, virologic, and immunologic responses in subjects who received dolutegravir were evaluated in 46 treatment-experienced, INSTI-naïve, HIV-1–infected subjects aged 6 to less than 18 years in an open-label, multicenter, dose-finding clinical trial, IMPAACT P1093 *[see* Clinical Pharmacology (12.3), Clinical Studies (14.2)]. Frequency, type, and severity of adverse drug reactions among the 46 pediatric subjects were comparable to those observed in adults [see Adverse Reactions (6.2)]. In 17 subjects weighing at least 30 kg, pharmacokinetic parameters of dolutegravir were comparable to adults receiving 50 mg once daily [see Clinical Pharmacology (12.3)].

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

Geriatric Use

Clinical trials of dolutegravir 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 in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [see Clinical Pharmacology (12.3)].

Hepatic Impairment

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

Renal Impairment

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 *[see* Microbiology (12.4)]) 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 *[see Clinical Pharmacology (12.3)]*. Dolutegravir has not been studied in patients on dialysis.

Lamivudine

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to lamivudine during pregnancy. Physicians are encouraged to register patients by calling the Antiretroviral Pregnancy Registry at 1-800-258-4263.

Risk Summary

Available data from the Antiretroviral Pregnancy Registry 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). Lamivudine produced embryonic toxicity in rabbits at a dose that produced similar human exposures as the recommended clinical dose. The relevance of animal findings to human pregnancy registry data is not known.

Data

Human Data: Based on prospective reports from the Antiretroviral Pregnancy Registry of over 11,000 exposures to lamivudine during pregnancy resulting in live births (including over 4,300 exposed in the first trimester), there was no difference between lamivudine and overall birth defects compared with the background birth defect rate of 2.7% in the US reference population of the MACDP. The prevalence of defects in the first trimester was 3.1% (95% CI: 2.6% to 3.7%).

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 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. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg per mL (150 mg twice daily) and 2.1 to 5.2 mcg per mL (300 mg twice daily).

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.

Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of the potential for HIV-1 transmission mothers should be instructed not to breastfeed.

Pediatric Use

The safety and effectiveness of lamivudine in combination with other antiretroviral agents have been established in pediatric patients aged 3 months and older. Lamivudine scored tablet is the preferred formulation for HIV-1-infected pediatric patients who weigh at least 14 kg and for whom a solid dosage form is appropriate because pediatric subjects who received lamivudine oral solution had lower rates of virologic suppression, lower plasma lamivudine exposure, and developed viral resistance more frequently than those receiving lamivudine tablets in the ARROW trial [see Dosage and Administration (2.2), Warnings and Precautions (5.6), Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.2)].

Geriatric Use

Clinical trials of lamivudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of lamivudine in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [see Dosage and Administration (2.3), Clinical Pharmacology (12.3)].

Patients with Impaired Renal Function

Reduction of the dosage of lamivudine is recommended for patients with impaired renal function [see Dosage and Administration (2.3), Clinical Pharmacology (12.3)].

Tenofovir disoproxil fumarate

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, tenofovir disoproxil fumarate should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to tenofovir disoproxil fumarate, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

Risk Summary

Animal Data

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

Nursing Mothers

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is secreted in human milk. The impact of this exposure in breastfed infants is unknown. Because of both the potential for HIV-1 transmission and the potential for serious adverse

reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving tenofovir disoproxil fumarate.

Pediatric Use

Pediatric Patients 2 Years of Age and Older with HIV-1 infection

The safety of tenofovir disoproxil fumarate in pediatric patients aged 2 to less than 18 years is supported by data from two randomized trials in which tenofovir disoproxil fumarate was administered to HIV-1 infected treatment-experienced subjects. In addition, the pharmacokinetic profile of tenofovir in patients 2 to less than 18 years of age at the recommended doses was similar to that found to be safe and effective in adult clinical trials [See Clinical Pharmacology (12.3)].

In Study 352, 92 treatment-experienced subjects 2 to less than 12 years of age with stable, virologic suppression on stavudine-or zidovudine-containing regimen were randomized to either replace stavudine or zidovudine with tenofovir disoproxil fumarate (N=44) or continue their original regimen (N=48) for 48 weeks. Five additional subjects over the age of 12 were enrolled and randomized (tenofovir disoproxil fumarate N=4, original regimen N=1) but are not included in the efficacy analysis. After 48 weeks, all eligible subjects were allowed to continue in the study receiving open-label tenofovir disoproxil fumarate. At Week 48, 89% of subjects in the tenofovir disoproxil fumarate treatment group and 90% of subjects in the stavudine or zidovudine treatment group had HIV-1 RNA concentrations less than 400 copies/mL. During the 48 week randomized phase of the study, 1 subject in the tenofovir disoproxil fumarate group discontinued the study prematurely because of virologic failure/lack of efficacy and 3 subjects (2 subjects in the tenofovir disoproxil fumarate group and 1 subject in the stavudine or zidovudine group) discontinued for other reasons.

In Study 321, 87 treatment-experienced subjects 12 to less than 18 years of age were treated with tenofovir disoproxil fumarate (N=45) or placebo (N=42) in combination with an optimized background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm^3 and the mean baseline plasma HIV-1 RNA was 4.6 $\log_{10}$ copies/mL. At baseline, 90% of subjects harbored NRTI resistance-associated substitutions in their HIV-1 isolates. Overall, the trial failed to show a difference in virologic response between the tenofovir disoproxil fumarate and placebo treatment groups. Subgroup analyses suggest the lack of difference in virologic response may be attributable to imbalances between treatment arms in baseline viral susceptibility to tenofovir disoproxil fumarate and OBR.

Although changes in HIV-1 RNA in these highly treatment-experienced subjects were less than anticipated, the comparability of the pharmacokinetic and safety data to that observed in adults supports the use of tenofovir disoproxil fumarate in pediatric patients 12 years of age and older who weigh greater than or equal to 35 kg and whose HIV-1 isolate is expected to be sensitive to tenofovir disoproxil fumarate. [See Warnings and Precautions (5.6), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)].

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

Pediatric Patients 12 Years of Age and Older with Chronic Hepatitis B

In Study 115, 106 HBeAg negative (9%) and positive (91%) subjects aged 12 to less than 18 years with chronic HBV infection were randomized to receive blinded treatment with tenofovir disoproxil fumarate 300 mg (N=52) or placebo (N=54) for 72 weeks. At study entry, the mean HBV DNA was 8.1 $\log_{10}$ copies/mL and mean ALT was 101 U/L. Of 52 subjects treated with tenofovir disoproxil fumarate, 20 subjects were nucleos (t) ide-naïve and 32 subjects were nucleos (t) ideexperienced. Thirty-one of the 32 nucleos (t) ide-experienced subjects had prior lamivudine experience. At Week 72, 88% (46/52) of subjects in the tenofovir disoproxil fumarate group and 0% (0/54) of subjects in the placebo group had HBV DNA <400 copies/mL (69 IU/mL). Among subjects with abnormal ALT at baseline, 74% (26/35) of subjects receiving tenofovir disoproxil fumarate had normalized ALT at Week 72 compared to 31% (13/42) in the placebo group. One tenofovir disoproxil fumarate -treated subject experienced sustained HBsAg-loss and seroconversion to anti-HBs during the first 72 weeks of study participation. Safety and effectiveness of tenofovir disoproxil fumarate in pediatric patients younger than 12 years of age or less than 35 kg with chronic hepatitis B have not been established.

Geriatric Use

Clinical trials of tenofovir disoproxil fumarate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Impaired Renal Function

It is recommended that the dosing interval for tenofovir disoproxil fumarate be modified in patients with estimated creatinine clearance below 50 mL/min or in patients tenofovir disoproxil fumarate who require dialysis [See Dosage and Administration (2.3), Clinical Pharmacology (12.3)].

4.7 Undesirable Effects

Dolutegravir

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

- Hypersensitivity reactions [see Warnings and Precautions (5.1)].
- Effects on serum liver biochemistries in patients with hepatitis B or C co-infection [see Warnings and Precautions (5.2)].
- Fat Redistribution [see Warnings and Precautions (5.3)].
- Immune Reconstitution Syndrome [see Warnings and Precautions (5.4)].

Clinical Trial 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.

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 [EPZICOM®] or emtricitabine/tenofovir [TRUVADA®]). 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 (EPZICOM) once daily or fixed-dose

efavirenz/emtricitabine/tenofovir (ATRIPLA®) 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, lamivudine and tenofovir disoproxil fumarate tablets 50 mg once daily + EPZICOM and 14% in subjects receiving ATRIPLA once daily.

Treatment-emergent adverse drug reactions (ADRs) 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-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table. Treatment-Emergent Adverse Drug 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 + EPZICOM Once Daily (n = 414)**	**ATRIPLA Once Daily (n = 419)**
sychiatric				
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%
eneral Disorders				
Fatigue	<1%	<1%	2%	2%
ar 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 ATRIPLA, 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 EPZICOM or TRUVADA). 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 ADRs 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 ADR 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 ADRs in VIKING-3 were generally similar compared with observations with the 50-mg once-daily dose in adult Phase 3 trials.

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

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

Hepatobiliary Disorders: Hepatitis.

Musculoskeletal Disorders: Myositis.

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

Renal and Urinary Disorders*:* Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus.

Laboratory Abnormalities:

Treatment-Naïve Subjects: Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects 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: Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

	SPRING-2		**SINGLE**	
Laboratory Parameter **Preferred Term**	**Dolutegravir 50 mg Once Daily + 2 NRTIs** **(n = 403)**	**Raltegravir 400 mg Twice Daily + 2 NRTIs** **(n = 405)**	**Dolutegravir 50 mg + EPZICOM Once Daily** **(n = 414)**	**ATRIPLA 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) Grade 3 to 4 (<0.75 x 10^9)	 4% 2%	 3% 2%	 4% 3%	 5% 3%

ULN = Upper limit of normal.

Table: Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis[a]) and SINGLE Trials (Week 144 Analysis[a])

	SPRING-2		**SINGLE**	
Laboratory Parameter Preferred Term	**Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)**	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**Dolutegravir 50 mg + EPZICOM Once Daily (n = 414)**	**ATRIPLA 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 tablets + EPZICOM n = 30 and ATRIPLA (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 + EPZICOM n = 36 and ATRIPLA: 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.

Hepatitis B and/or Hepatitis C Virus Co-infection: In Phase 3 trials, subjects with hepatitis B and/or C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal. Overall, the safety profile in subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C virus co-infection for all treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected compared with HIV mono infected subjects receiving dolutegravir were observed in 18% vs. 3% with the 50-mg once-daily dose and 13% vs. 8% with the 50-mg twice-daily dose. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C at the start of therapy with dolutegravir, particularly in the setting where anti-hepatitis therapy was withdrawn [see Warnings and Precautions (5.2)].

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

Clinical Trials Experience in Pediatric Subjects.

IMPAACT P1093 is an ongoing multicenter, open-label, non-comparative trial of approximately 160 HIV-1-infected pediatric subjects aged 4 weeks to less than 18 years, of which 46 treatment-

experienced, INSTI-naïve subjects aged 6 to less than 18 years have been enrolled *[see Use in Specific Populations (8.4), Clinical Studies (14.2)].*

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

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

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.

Musculoskeletal

Arthralgia, myalgia.

Lamivudine

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

- Lactic acidosis and severe hepatomegaly with steatosis [see Boxed Warning, Warnings and Precautions (5.1)].
- Exacerbations of hepatitis B [see Boxed Warning, Warnings and Precautions (5.2)].
- Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C [see Warnings and Precautions (5.3)].
- Pancreatitis [see Warnings and Precautions (5.4)].
- Immune reconstitution syndrome [see Warnings and Precautions (5.5)].
- Fat redistribution [see Warnings and Precautions (5.7)].

Clinical Trials Experience

Clinical Trials Experience in Adult Subjects

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

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 RETROVIR 200 mg 3 times daily for up to 24 weeks are listed in Table 6.

Table: 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 RETROVIR (n = 251)**	**RETROVIR[a] (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		10%

Insomnia & other sleep disorders	12%	
Dizziness	11%	7%
Depressive disorders	10%	4%
Respiratory	9%	4%
Nasal signs & symptoms		
Cough	20%	11%
Skin	18%	13%
Skin rashes		
Musculoskeletal		6%
Musculoskeletal pain	9%	
Myalgia		
Arthralgia	12%	10%
	8%	6%
	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 Warnings and Precautions (5.4)]*.

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

Table: Frequencies of Selected Grade 3 to 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 RETROVIR**	**RETROVIR[b]**	**lamivudine plus**	**Placebo plus Current**

			Current Therapy[c]	**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 x ULN)	3.7%	3.6%	3.8%	1.9%
AST (>5.0 x ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (>2.5 x ULN)	0.8%	0.4%	ND	ND
Amylase (>2.0 x 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 zidovudineplus

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.

Clinical Trials Experience in Pediatric Subjects

Lamivudine oral solution has been studied in 638 pediatric subjects aged 3 months to 18 years in 3 clinical trials.

Selected clinical adverse reactions and physical findings with a greater than or equal to 5% frequency during therapy with lamivudine 4 mg per kg twice daily plus RETROVIR 160 mg per m^2

3 times daily in therapy-naive (less than or equal to 56 days of antiretroviral therapy) pediatric subjects are listed in Table.

Table: Selected Clinical Adverse Reactions and Physical Findings (Greater than or Equal to 5% Frequency) in Pediatric Subjects in Trial ACTG300

Adverse Reaction	Lamivudine plus RETROVIR (n = 236)	Didanosine (n = 235)
Body as a Whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose, and Throat		
Signs or symptoms of ears[a]	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

[a] Includes pain, discharge, erythema, or swelling of an ear.

Pancreatitis: Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric subjects receiving lamivudine alone or in combination with other antiretroviral agents. In an open-label dose-escalation trial (NUCA2002), 14 subjects (14%)

developed pancreatitis while receiving monotherapy with lamivudine. Three of these subjects died of complications of pancreatitis. In a second open-label trial (NUCA2005), 12 subjects (18%) developed pancreatitis. In Trial ACTG300, pancreatitis was not observed in 236 subjects randomized to lamivudine plus RETROVIR. Pancreatitis was observed in 1 subject in this trial who received open-label lamivudine in combination with RETROVIR and ritonavir following discontinuation of didanosine monotherapy *[see Warnings and Precautions (5.4)]*.

Paresthesias and Peripheral Neuropathies: Paresthesias and peripheral neuropathies were reported in 15 subjects (15%) in Trial NUCA2002, 6 subjects (9%) in Trial NUCA2005, and 2 subjects (less than 1%) in Trial ACTG300.

Selected laboratory abnormalities experienced by therapy-naive (less than or equal to 56 days of antiretroviral therapy) pediatric subjects are listed in Table.

Table: Frequencies of Selected Grade 3 to 4 Laboratory Abnormalities in Pediatric Subjects in Trial ACTG300

Test (Threshold Level)	**Lamivudine plus RETROVIR**	**Didanosine**
Absolute neutrophil count (<400/mm^3)	8%	3%
Hemoglobin (<7.0 g/dL)	4%	2%
Platelets (<50,000/mm^3)	1%	3%
ALT (>10 x ULN)	1%	3%
AST (>10 x ULN)	2%	4%
Lipase (>2.5 x ULN)	3%	3%
Total Amylase (>2.5 x ULN)	3%	3%

ULN = Upper limit of normal.

Pediatric Subjects Once-Daily versus Twice-Daily Dosing (COL105677): The safety of once-daily compared with twice-daily dosing of lamivudine was assessed in the ARROW trial. Primary safety assessment in the ARROW trial was based on Grade 3 and Grade 4 adverse events. The frequency of Grade 3 and 4 adverse events was similar among subjects randomized to once-daily dosing compared with subjects randomized to twice-daily dosing. One event of Grade 4 hepatitis in the once-daily cohort was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related by the investigator.

Neonates: Limited short-term safety information is available from 2 small, uncontrolled trials in South Africa in neonates receiving lamivudine with or without zidovudine for the first week of life following maternal treatment starting at Week 38 or 36 of gestation *[see Clinical Pharmacology (12.3)]*. Selected adverse reactions reported in these neonates included increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, and sepsis; 3 neonates died (1 from gastroenteritis with acidosis and convulsions, 1 from traumatic injury, and 1 from unknown causes). Two other nonfatal gastroenteritis or diarrhea cases were reported, including 1 with convulsions; 1 infant had transient renal insufficiency associated with dehydration. The absence of control groups limits assessments of causality, but it should be assumed that perinatally exposed infants may be at risk for adverse reactions comparable to those reported in pediatric and adult HIV-1-infected patients treated with lamivudine-containing combination regimens. Long-term effects of in utero and infant lamivudine exposure are not known.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of lamivudine. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine.

Body as a Whole

Redistribution/accumulation of body fat *[see Warnings and Precautions (5.7)]*.

Endocrine and Metabolic

Hyperglycemia.

General

Weakness.

Hemic and Lymphatic

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

Hepatic and Pancreatic

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

Hypersensitivity

Anaphylaxis,

urticaria.

Musculoskeletal

Muscle weakness, CPK elevation, rhabdomyolysis.

Skin

Alopecia, pruritus.

Tenofovir disoproxil fumarate

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

- Severe Acute Exacerbation of Hepatitis *[See Boxed Warning, Warnings and Precautions (5.1)]*.
- New Onset or Worsening Renal Impairment *[See Warnings and Precautions (5.2)]*.
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[See Warnings and Precautions (5.3)]*.
- Bone Effects *[See Warnings and Precautions (5.6)]*.
- Immune Reconstitution Syndrome *[See Warnings and Precautions (5.7)]*.

Adverse Reactions from 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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Adult Patients with HIV-1 Infection

More than 12,000 subjects have been treated with tenofovir disoproxil fumarate alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in clinical trials and expanded access programs. A total of 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 to 4)

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

Treatment-Naïve Patients

Study 903 −Treatment-Emergent Adverse Reactions: The most common adverse reactions seen in a double-blind comparative controlled trial in which 600 treatment-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.

Table: Selected Treatment-Emergent Adverse Reactions[a] (Grades 2 to 4) Reported in ≥5% in Any Treatment Group in Study 903 (0 to 144 Weeks)

	Tenofovir disoproxil fumarate +3TC+EFV	**d4T+3TC+EFV**
	N=299	**N=301**
Body as a Whole	14%	17%
Headache	13%	12%
Pain	8%	7%
Fever	7%	12%
Abdominal pain	9%	8%
Back pain	6%	7%
Asthenia		
Digestive System	11%	13%
Diarrhea	8%	9%
Nausea	4%	5%
Dyspepsia	5%	9%
Vomiting		
Metabolic Disorders	1%	8%
Lipodystrophy[b]		
Musculoskeletal	5%	7%
Arthralgia	3%	5%
Myalgia		

Nervous System Depression Insomnia Dizziness Peripheral neuropathy[c] Anxiety	 11% 5% 3% 1% 6%	 10% 8% 6% 5% 6%
Respiratory Pneumonia	 5%	 5%
Skin and Appendages Rash event[d]	18%	12%

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

b. Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome.

c. Peripheral neuropathy includes peripheral neuritis and neuropathy.

d. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

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 to 4 laboratory abnormalities is provided in Table.

Table: Grades 3 to 4 Laboratory Abnormalities Reported in ≥1% of Tenofovir Disoproxil Fumarate-Treated Subjects in Study 903 (0 to 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	12%	12%

U/L; F: >845 U/L)		
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 + EMTRIVA® administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse reactions observed in this trial were generally consistent with those seen in previous studies in treatment-experienced or treatment-naïve subjects (Table 12).

Changes in Bone Mineral Density

In HIV-1 infected adult subjects in Study 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving tenofovir disoproxil fumarate + lamivudine + efavirenz (−2.2% ± 3.9) compared with subjects receiving stavudine + lamivudine + efavirenz (−1.0% ± 4.6) through 144 weeks. Changes in BMD at the hip were similar between the two treatment groups (−2.8% ± 3.5 in the tenofovir disoproxil fumarate group vs. −2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24 to 48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of tenofovir disoproxil fumarate-treated subjects vs. 21% of the stavudine-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the tenofovir disoproxil fumarate group and 6 subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide) and higher serum parathyroid hormone levels and 1, 25 Vitamin D levels in the tenofovir disoproxil fumarate group relative to the stavudine group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range *[See Warnings and Precautions (5.6)]*.

Table. Selected Treatment-Emergent Adverse Reactions[a] (Grades 2 to 4) Reported in ≥5% in Any Treatment Group in Study 934 (0 to 144 Weeks)

	Tenofovir disoproxil fumarate[b] +FTC+EFV	**AZT/3TC+EFV**
	N=257	**N=254**
Gastrointestinal Disorder		
Diarrhea	9%	5%
Nausea	9%	7%
Vomiting	2%	5%
General Disorders and Administration Site Condition		
Fatigue	9%	8%
Infections and Infestations		
Sinusitis		
Upper respiratory tract infections	8%	4%
Nasopharyngitis	8%	5%
	5%	3%
Nervous System Disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	9%	7%
Insomnia	5%	7%
Skin and Subcutaneous Tissue Disorders		
Rash event[c]	7%	9%

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 TRUVADA with efavirenz in place of tenofovir disoproxil fumarate + EMTRIVA with efavirenz.

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).

Table- Significant Laboratory Abnormalities Reported in ≥1% of Subjects in Any Treatment Group in Study 934 (0 to 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 TRUVADA with efavirenz in place of tenofovir disoproxil fumarate + EMTRIVA with efavirenz.

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.

Table Selected Treatment-Emergent Adverse Reactions[a] (Grades 2 to 4) Reported in ≥3% in Any Treatment Group in Study 907 (0 to 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 W hole				
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	2%	0%	3%	2%

Pneumonia				
Nervous System Depression Insomnia Peripheral neuropathy[b] Dizziness	 4% 3% 3% 1%	 3% 2% 3% 3%	 8% 4% 5% 3%	 4% 4% 2% 1%
Skin and Appendage Rash event[c] Sweating	 5% 3%	 4% 2%	 7% 3%	 1% 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 to 4 laboratory abnormalities is provided in Table.

Table Grades 3 to 4 Laboratory Abnormalities Reported in ≥1% of tenofovir disoproxil fumarate-Treated Subjects in Study 907 (0 to 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: >990 U/L; F: >845 U/L)	7%	14%	12%	12%
Serum Amylase (>175 U/L)	6%	7%	7%	6%
Glycosuria (≥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%

Clinical Trials in Pediatric Subjects 2 Years of Age and Older with HIV-1 Infection

Assessment of adverse reactions is based on two randomized trials (Studies 352 and 321) in 184 HIV-1 infected pediatric subjects (2 to less than 18 years of age) who received treatment with tenofovir disoproxil fumarate (N=93) or placebo/active comparator (N=91) in combination with other antiretroviral agents for 48 weeks. The adverse reactions observed in subjects who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical trials in adults.

Eighty-nine pediatric subjects (2 to less than 12 years of age) received tenofovir disoproxil fumarate in Study 352 for a median exposure of 104 weeks. Of these, 4 subjects discontinued from the trial due to adverse reactions consistent with proximal renal tubulopathy. Three of these

4 subjects presented with hypophosphatemia and also had decreases in total body or spine BMD Z score *[See Warnings and Precautions (5.6)]*.

Changes in Bone Mineral Density:

Clinical trials in HIV-1 infected children and adolescents evaluated BMD changes. In Study 321 (12 to less than 18 years), the mean rate of BMD gain at Week 48 was less in the tenofovir disoproxil fumarate compared to the placebo treatment group. Six tenofovir disoproxil fumarate treated subjects and one placebo treated subject had significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline BMD Z-scores were −0.341 for lumbar spineand −0.458 for total body in the 28 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. In Study 352 (2 to less than 12 years), the mean rate of BMD gain in lumbar spine at Week 48 was similar between the tenofovir disoproxil fumarate and the d4T or AZT treatment groups. Total body BMD gain was less in the tenofovir disoproxil fumarate compared to the d4T or AZT treatment groups. One tenofovir disoproxil fumarate -treated subject and none of the d4T or AZT-treated subjects experienced significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline in BMD Z scores were −0.012 for lumbar spine and −0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. In both trials, skeletal growth (height) appeared to be unaffected *[See Warnings and Precautions (5.6)]*.

Clinical Trials in Adult Subjects with Chronic Hepatitis B and Compensated Liver Disease

Treatment-Emergent Adverse Reactions: In controlled clinical trials in 641 subjects with chronic hepatitis B (0102 and 0103), more subjects treated with tenofovir disoproxil fumarate during the 48week double-blind period experienced nausea: 9% with tenofovir Disoproxil fumarate versus 2% with HEPSERA. Other treatment-emergent adverse reactions reported in more than 5% of subjects treated with tenofovir disoproxil fumarate included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash.

During the open-label phase of treatment with tenofovir disoproxil fumarate (weeks 48 to 384) in Studies 0102 and 0103, 2% of subjects (13/585) experienced a confirmed increase in serum creatinine of 0.5 mg/dL from baseline. No significant change in the tolerability profile was observed with continued treatment for up to 384 weeks.

Laboratory Abnormalities: A summary of Grades 3 to 4 laboratory abnormalities through Week 48 is provided in Table 16. Grades 3 to 4 laboratory abnormalities were similar in subjects continuing tenofovir disoproxil fumarate treatment for up to 384 weeks in these trials.

Table Grades 3 to 4 Laboratory Abnormalities Reported in ≥1% of tenofovir disoproxil fumarate-Treated Subjects in Studies 0102 and 0103 (0 to 48 Weeks)

	Tenofovir disoproxil fumarate (N=426)	**HEPSERA (N=215)**
Any ≥ Grade 3 Laboratory Abnormality	19%	13%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	2%	3%
Serum Amylase (>175 U/L)	4%	1%
Glycosuria (≥3+)	3%	<1%
AST (M: >180 U/L; F: >170 U/L)	4%	4%
ALT (M: >215 U/L; F: >170 U/L)	10%	6%

The overall incidence of on-treatment ALT flares (defined as serum ALT greater than 2 × baseline and greater than 10 × ULN, with or without associated symptoms) was similar between tenofovir disoproxil fumarate (2.6%) and HEPSERA (2%). ALT flares generally occurred within the first 4 to 8 weeks of treatment and were accompanied by decreases in HBVDNA levels. No subject had evidence of decompensation. ALT flares typically resolved within 4 to 8 weeks without changes in study medication.

The adverse reactions observed in subjects with chronic hepatitis B and lamivudine resistance who received treatment with tenofovir disoproxil fumarate were consistent with those observed in other hepatitis B clinical trials in adults.

Clinical Trials in Adult Subjects with Chronic Hepatitis B and Decompensated Liver Disease

In a small randomized, double-blind, active-controlled trial (0108), subjects with CHB and decompensated liver disease received treatment with tenofovir disoproxil fumarate or other antiviral drugs for up to 48 weeks *[See Clinical Studies (14.2)]*. Among the 45 subjects receiving tenofovir disoproxil fumarate, the most frequently reported treatment-emergent adverse reactions of any severity were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%). Two of 45 (4%) subjects died through Week 48 of the trial due to progression of liver disease. Three of 45 (7%) subjects discontinued treatment due to an adverse event. Four of 45 (9%) subjects experienced a confirmed increase in serum creatinine of 0.5 mg/dL (1 subject also had a confirmed serum phosphorus less than 2 mg/dL through Week 48). Three of these subjects (each of whom had a Child-Pugh score greater than or equal to 10 and MELD score greater than or equal to 14 at entry) developed renal failure.

Because both tenofovir disoproxil fumarate and decompensated liver disease may have an impact on renal function, the contribution of tenofovir disoproxil fumarate to renal impairment in this population is difficult to ascertain.

One of 45 subjects experienced an on-treatment hepatic flare during the 48-week trial.

Clinical Trials in Pediatric Subjects 12 Years of Age and Older with Chronic Hepatitis B

Assessment of adverse reactions is based on one randomized study (Study GS-US-174-0115) in 106 pediatric subjects (12 to less than 18 years of age) infected with chronic hepatitis B receiving treatment with tenofovir disoproxil fumarate (N=52) or placebo (N=54) for 72 weeks. The adverse reactions observed in pediatric subjects who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical trials of tenofovir disoproxil fumarate in adults.

In this study, both the tenofovir disoproxil fumarate and placebo treatment arms experienced an overall increase in mean lumbar spine BMD over 72 weeks, as expected for an adolescent population. The BMD gains from baseline to Week 72 in lumbar spine and total body BMD in tenofovir disoproxil fumarate -treated subjects (+5% and +3%, respectively) were less than the BMD gains observed in placebo-treated subjects (+8% and +5%, respectively). Three subjects in the tenofovir disoproxil fumarate group and two subjects in the placebo group had significant (greater than 4%) lumbar spine BMD loss at Week 72. At baseline, mean BMD Z-scores in subjects randomized to tenofovir disoproxil fumarate were −0.43 for lumbar spine and −0.20 for total body, and mean BMD Z-scores in subjects randomized to placebo were −0.28 for lumbar spine and −0.26 for total body. In subjects receiving tenofovir disoproxil fumarate for 72 weeks, the mean change in BMD Z-score was −0.05 for lumbar spine and −0.15 for total body compared to +0.07 and +0.06, respectively, in subjects receiving placebo. As observed in pediatric studies of HIV-infected patients, skeletal growth (height) appeared to be unaffected [See Warnings and Precautions (5.6)].

Postmarketing Experience

The following adverse reactions have been identified during post approval use of tenofovir disoproxil fumarate. Because postmarketing 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.

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.

4.8 Overdose

Dolutegravir

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

Lamividine

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

Tenofovir disoproxil fumarate

Limited clinical experience at doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available. In Study 901, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

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

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Dolutegravir

Mechanism of action

Dolutegravir is an HIV-1 antiviral agent *[see Microbiology (12.4)]*.

Pharmacodynamics

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

Effects on Electrocardiogram

In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single-dose oral administrations of placebo, dolutegravir 250-mg suspension (exposures approximately 3–fold of the 50-mg once-daily dose at steady state), and moxifloxacin 400 mg (active control) in random sequence. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) for dolutegravir was 2.4 msec (1-sided 95% upper

CI: 4.9 msec). Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets did not prolong the QTc interval over 24 hours postdose.

Effects on Renal Function

The effect of dolutegravir on renal function was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled trial in healthy subjects (n = 37) who received dolutegravir 50 mg once daily (n = 12), dolutegravir 50 mg twice daily (n = 13), or placebo once daily (n = 12) for 14 days. A decrease in creatinine clearance, as determined by 24-hour urine collection, was observed with both doses of dolutegravir after 14 days of treatment in subjects who received 50 mg once daily (9% decrease) and 50 mg twice daily (13% decrease). Neither dose of dolutegravir had a significant effect on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol) nor effective renal plasma flow (determined by the clearance of probe drug, para-amino hippurate) compared with the placebo.

5.2 Pharmacokinetic properties

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 18) was attributed to the use of metabolic inducers in the background antiretroviral regimens of subjects receiving dolutegravir 50 mg twice daily in clinical trials. Dolutegravir was administered without regard to food in these trials.

Table: 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.

Absorption

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.

Effects of Food on Oral Absorption

Dolutegravir may be taken with or without food. Food increased the extent of absorption and slowed the rate of absorption of dolutegravir. Low-, moderate-, and high-fat meals increased dolutegravir $AUC_{(0\ to\ \infty)}$ by 33%, 41%, and 66%; increased C_{max} by 46%, 52%, and 67%; and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively.

Distribution

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.

Metabolism and Elimination

Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A. After a single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose 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).

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.

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).

Special Populations

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

HBV/HCV Co-infection: 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.

Renal Impairment*:* Renal clearance of unchanged drug is a minor pathway of elimination for 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 decreased by 40%, 23%, and 43%, respectively, compared with those in matched healthy subjects. The cause of this decrease is unknown. 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. 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 *[see Microbiology (12.4)]*) 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 requiring dialysis.

Gender: Population analyses using pooled pharmacokinetic data from adult trials indicated gender had no clinically relevant effect on the exposure of dolutegravir.

Race: Population analyses using pooled pharmacokinetic data from adult trials indicated race had no clinically relevant effect on the pharmacokinetics of dolutegravir.

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

Pediatric Patients: The pharmacokinetics of dolutegravir in HIV-1-infected children (n = 17) weighing at least 30 kg were similar to those observed in HIV-1-infected adults who received dolutegravir 50 mg once daily (Table 19) *[see Clinical Studies (14.2)]*.

Table: Dolutegravir Steady-State Pharmacokinetic Parameters in Pediatric Subjects

Weight (n)	**Dose of Dolutegravir**	**Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (%CV)**		
		C_{max} (mcg/mL)	**AUC(0-24) (mcg.h/mL)**	**C_{24} (mcg/mL)**
≥40 kg (n = 14)	ng once daily	3.89 (43)	50.1 (53)	0.99 (66)
≥30 to <40 kg (n = 3)	35 mg once daily	4.40 (54)	64.6 (64)	1.33 (93)

Population pharmacokinetic analyses demonstrate comparable exposures in children, at least 30 kg, dosed by weight-bands (35 mg or 50 mg of dolutegravir) to that observed in adults.

Drug Interactions

Drug interaction trials were performed with dolutegravir and other drugs likely to be coadministered or commonly used as probes for pharmacokinetic interactions. As dolutegravir is

not expected to affect the pharmacokinetics of other drugs dependent on hepatic metabolism (Table 20) *[see Drug Interactions (7.1)]*, the primary focus of these drug interaction trials was to evaluate the effect of coadministered drug on dolutegravir (Table).

Dosing or regimen recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir are provided in Table [see Dosage and Administration (2.1), Drug Interactions (7.3)].

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

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
			C_{max}	AUC	C_T or C24
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	_
Metformin 500 mg twice daily	50 mg twice daily	15[a]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	_
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	_	0.95 (0.79 to 1.15)	_
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)

Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)

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

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

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	C_T or C24
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine +	50 mg once	9	0.88	0.75	0.63

darunavir/ritonavir 200 mg + 600/100 mg twice daily	daily		(0.78 to 1.00)	(0.69 to 0.81)	(0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)
Fosamprenavir/ritonavir 700 mg/100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Tipranavir/ritonavir 500/200 mg twice daily	50 mg once daily	14	0.54 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Antacid (Maalox®) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (Maalox®) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Boceprevir 800 mg every 8 hours	50 mg once daily	13	1.05 (0.96 to 1.15)	1.07 (0.95 to 1.20)	1.08 (0.91 to 1.28)

Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1,200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16c	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day®) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)

Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[a] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

[a] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.

[b] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.

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

Microbiology

Mechanism of Action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. 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.

Antiviral Activity in Cell Culture

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood

mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC_{50} values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC_{50} values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Antiviral Activity in Combination with Other Antiviral Agents

The antiviral activity of dolutegravir was not antagonistic when combined with the INSTI, raltegravir; non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz or nevirapine; the nucleoside reverse transcriptase inhibitors (NRTIs), abacavir or stavudine; the protease inhibitors (PIs), amprenavir or lopinavir; the CCR5 co-receptor antagonist, maraviroc; or the fusion inhibitor, enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor, adefovir, or inhibited by the antiviral, ribavirin.

Resistance

Cell Culture: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold. Passage of mutant viruses containing the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutions included T97A, E138K, G140S, and M154I. Passage of mutant viruses containing both G140S and Q148H selected for L74M, E92Q, and N155H.

Treatment-Naïve Subjects: No subjects in the dolutegravir 50-mg once-daily treatment arms of treatment-naïve trials SPRING-2 (96 weeks) and SINGLE (144 weeks) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 12 with HIV-1 RNA greater than 400 copies per mL at failure or last visit and having resistance data). Two virologic failure subjects in SINGLE had treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1 subject with 275 copies per mL HIV-1 RNA had a treatment-emergent Q157Q/P integrase substitution detected at Week 24. None of these subjects had a corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to the background regimen was observed in the dolutegravir arm

in either the SPRING-2 or SINGLE trials. No treatment-emergent primary resistance substitutions were observed in either treatment group in the FLAMINGO trial through Week 96.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In the dolutegravir arm of the SAILING trial for treatment-experienced and INSTI-naïve subjects (n = 354), treatment-emergent integrase substitutions were observed in 6 of 28 (21%) subjects who had virologic failure and resistance data. In 5 of the 6 subjects' isolates emergent INSTI substitutions included L74L/M/I, Q95Q/L, V151V/I (n = 1 each), and R263K (n = 2). The change in dolutegravir phenotypic susceptibility for these 5 subject isolates was less than 2-fold. One subject isolate had pre-existing raltegravir resistance substitutions E138A, G140S, and Q148H at baseline and had additional emergent INSTI-resistance substitutions T97A and E138A/T with a corresponding 148-fold reduction in dolutegravir susceptibility at failure. In the comparator raltegravir arm, 21 of 49 (43%) subjects with post-baseline resistance data had evidence of emergent INSTI-resistance substitutions (L74M, E92Q, T97A, E138Q, G140S/A, Y143R/C, Q148H/R, V151I, N155H, E157Q, and G163K/R) and raltegravir phenotypic resistance.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects*:* VIKING-3 examined the efficacy of dolutegravir 50 mg twice daily plus optimized background therapy in subjects with prior or current virologic failure on an INSTI- (elvitegravir or raltegravir) containing regimen.

In VIKING-4 (ING116529), 30 subjects with current virological failure on an INSTI-containing regimen and genotypic evidence of INSTI-resistance substitutions at screening were randomized to receive either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days and then all subjects received open-label dolutegravir plus optimized background regimen from Day 8. Virologic responses at Week 48 by baseline genotypic and phenotypic INSTI resistance categories and the INSTI resistance-associated substitutions that emerged on dolutegravir treatment in VIKING-4 were consistent with those seen in VIKING-3.

Response by Baseline Genotype

Of the 183 subjects with baseline data, 30% harbored virus with a substitution at Q148, and 33% had no primary INSTI-resistance substitutions (T66A/I/K, E92Q/V, Y143R/C/H, Q148H/R/K, and N155H) at baseline, but had historical genotypic evidence of INSTI-resistance substitutions, phenotypic evidence of elvitegravir or raltegravir resistance, or genotypic evidence of INST-Iresistance substitutions at screening.

Response rates by baseline genotype were analyzed in an “as-treated” analysis at Week 48 (n = 175) (Table 22). The response rate at Week 48 to dolutegravir-containing regimens was 47% (24 of 51) when Q148 substitutions were present at baseline; Q148 was always present with additional INSTI-resistance substitutions (see Table 22). In addition, a diminished virologic response of 40% (6 of 15) was observed when the substitution E157Q or K was present at baseline with other INSTI-resistance substitutions but without a Q148H or R substitution.

Table: Response by Baseline Integrase Genotype in Subjects with Prior Experience to an Integrase Strand Transfer Inhibitor in VIKING-3

Baseline Genotype	**Week 48 (<50 copies/mL) n = 175**
Overall Response	66% (116/175)
No Q148 substitution[a]	74% (92/124)
Q148H/R + G140S/A/C without additional INSTI resistance substitution[b]	61% (17/28)
Q148H/R + ≥2 INSTI-resistance substitutions [b,c]	29% (6/21)

[a] Includes INSTI-resistance substitutions Y143R/C/H and N155H.

[b] INSTI-resistance substitutions included T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R. Two additional subjects had baseline genotypes of Q148Q/R plus L74L/I/M (virologic failure) and Q148R plus E138K (responder).

[c] The most common pathway with Q148H/R + greater than or equal to 2 INSTI-resistance substitutions had Q148+G140+E138 substitutions (n = 16).

Response by Baseline Phenotype

Response rates by baseline phenotype were analyzed in an as-treated analysis using all subjects with available baseline phenotypes through Week 48 (n = 163) (see Table 23). These baseline phenotypic groups are based on subjects enrolled in VIKING-3 and are not meant to represent definitive clinical susceptibility cut points for dolutegravir. The data are provided to guide clinicians on the likelihood of virologic success based on pretreatment susceptibility to dolutegravir in INSTI-resistant patients.

Table: Response by Baseline Dolutegravir Phenotype (Fold-Change from Reference) in Subjects with Prior Experience to an Integrase Strand Transfer Inhibitor in VIKING-3

Baseline Dolutegravir Phenotype (Fold-Change from Reference)	**Response at Week 48 (<50 copies/mL) Subset n = 163**
Overall Response	64% (104/163)
<3-fold change	72% (83/116)
3- <10-fold change	53% (18/34)
≥10-fold change	23% (3/13)

Integrase Strand Transfer Inhibitor Treatment-Emergent Resistance

There were 50 subjects with virologic failure on the dolutegravir twice-daily regimen in VIKING-3 with HIV-1 RNA greater than 400 copies per mL at the failure timepoint, Week 48 or beyond, or the last timepoint on trial. Thirty-nine subjects with virologic failure had resistance data that were used in the Week 48 analysis. In the Week 48 resistance analysis 85% (33 of 39) of the subjects with virologic failure had treatment-emergent INSTI-resistance substitutions in their isolates. The most common treatment-emergent INSTI-resistance substitution was T97A. Other frequently emergent INSTI-resistance substitutions included L74M, I or V, E138K or A, G140S, Q148H, R or K, M154I, or N155H. Substitutions E92Q, Y143R or C/H, S147G, V151A, and E157E/Q each emerged in 1 to 3 subjects' isolates. At failure, the median dolutegravir foldchange from reference was 61-fold (range: 0.75 to 209) for isolates with emergent INSTI- resistance substitutions (n = 33).

Resistance to one or more background drugs in the dolutegravir twice-daily regimen also emerged in 49% (19 of 39) subjects in the Week 48 resistance analysis.

Cross-Resistance

Site-Directed Integrase Strand Transfer Inhibitor-Resistant Mutant HIV-1 and HIV-2 Strains: The susceptibility of dolutegravir was tested against 60 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) and 6 INSTI- resistant site-directed mutant HIV-2 viruses. The single INSTI-resistance substitutions T66K, I151L, and

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

Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent antiviral activity against 2 NNRTI-resistant, 3 NRTI-resistant, and 2 PI resistant HIV-1 mutant clones compared with the wild-type strain.

Lamivudine

Mechanism of Action

Lamivudine is an antiretroviral agent [see Microbiology (12.4)].

Pharmacokinetics

Pharmacokinetics in Adults

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 to10 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 AUC24,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 to 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.

Absorption and Bioavailability: 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.

Effects of Food on Oral Absorption: Lamivudine tablets and oral solution may be administered with or without food. An investigational 25-mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-1-infected subjects on 2 occasions, once in the fasted state and once with food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state (T_{max}: 3.2 ± 1.3 hours) compared with the fasted state (T_{max}: 0.9 ± 0.3 hours); C_{max} in the fed state was 40% ± 23% (mean ± SD) lower than in the fasted state. There was no significant difference in systemic exposure (AUC∞) in the fed and fasted states.

Distribution: 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.

Metabolism: 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.

Elimination: 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.

Specific Populations

Patients with Renal Impairment: The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-1-infected adults with impaired renal function (Table 24).

Table: 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

Tmax 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 [see Dosage and Administration (2.3)].

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.

Patients with Hepatic Impairment: 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.

Patients with Hepatic Impairment: 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.

Pediatric Patients*:* The pharmacokinetics of lamivudine have been studied after either single or repeat doses of lamivudine in 210 pediatric subjects. Pediatric subjects receiving lamivudine oral solution (dosed at approximately 8 mg per kg per day) achieved approximately 25% lower plasma concentrations of lamivudine compared with HIV-1-infected adults. Pediatric subjects receiving lamivudine oral tablets achieved plasma concentrations comparable to or slightly higher than those observed in adults. The absolute bioavailability of both lamivudine tablets and oral solution are lower in children than adults. The relative bioavailability of lamivudine oral solution is approximately 40% lower than tablets containing lamivudine in pediatric subjects despite no difference in adults. Lower lamivudine exposures in pediatric patients receiving lamivudine oral solution is likely due to the interaction between lamivudine and concomitant solutions containing sorbitol (such as ZIAGEN). Modeling of pharmacokinetic data suggests increasing the dosage of lamivudine oral solution to 5 mg per kg taken orally twice daily or 10 mg per kg taken orally once daily (up to a maximum of 300 mg daily) is needed to achieve sufficient concentrations of lamivudine [see Dosage and Administration (2.2)]. There are no clinical data in HIV-1 infected pediatric patients coadministered with sorbitol-containing medicines at this dose.

The pharmacokinetics of lamivudine dosed once daily in HIV-1-infected pediatric subjects aged 3 months through 12 years was evaluated in 3 trials (PENTA-15 [n = 17], PENTA 13 [n = 19], and ARROW PK [n = 35]). All 3 trials were 2-period, crossover, open-label pharmacokinetic trials of twice-versus once-daily dosing of abacavir and lamivudine. These 3 trials demonstrated that once-daily dosing provides similar $AUC_{0 \text{ to } 24}$ to twice-daily dosing of lamivudine at the same total daily dose when comparing the dosing regimens within the same formulation (i.e., either the oral

solution or the tablet formulation). The mean C_{max} was approximately 80% to 90% higher with lamivudine once-daily dosing compared with twice-daily dosing.

Table. Pharmacokinetic Parameters (Geometric Mean [95% CI]) after Repeat Dosing of Lamivudine in 3 Pediatric Trials

	Trial (Number of Subjects)					
	ARROW PK (n = 35)		**PENTA-13 (n = 19)**		**PENTA-15 (n = 17)[a]**	
Age Range	**3-12 years**		**2-12 years**		**3- 36 months**	
Formulation	**Tablet**		**Solution[b] and Tablet[c]**		**Solution[b]**	
Parameter	**Once Daily**	**Twice Daily**	**Once Daily**	**Twice Daily**	**Once Daily**	**Twice Daily**
C_{max} (mcg/mL)	3.17 (2.76, 3.64)	1.80 (1.59, 2.04)	2.09 (1.80, 2.42)	1.11 (0.96, 1.29)	1.87 (1.65, 2.13)	1.05 (0.88, 1.26)
$AUC_{(0-24)}$ (mcg•h/mL)	13.0 (11.4, 14.9)	12.0 (10.7, 13.4)	9.80 (8.64, 11.1)	8.88 (7.67, 10.3)	8.66 (7.46, 10.1)	9.48 (7.89, 11.4)

[a] n = 16 for PENTA-15 Cmax.

[b] Solution was dosed at 8 mg per kg per day.

[c] Five subjects in PENTA-13 received lamivudine tablets.

Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric subjects after multiple oral dosing with lamivudine. CSF samples were collected between 2 and 4 hours postdose. At the dose of 8 mg per kg per day, CSF lamivudine concentrations in 8 subjects ranged from 5.6% to 30.9% (mean ± SD of 14.2% ± 7.9%) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 mcg per mL.

Limited, uncontrolled pharmacokinetic and safety data are available from administration of lamivudine (and zidovudine) to 36 infants aged up to 1 week in 2 trials in South Africa. In these trials, lamivudine clearance was substantially reduced in 1-week-old neonates relative to pediatric subjects (aged over 3 months) studied previously. There is insufficient information to establish the

time course of changes in clearance between the immediate neonatal period and the age-ranges over 3 months old *[see Adverse Reactions (6.1)]*.

Geriatric Patients: The pharmacokinetics of lamivudine after administration of lamivudine to subjects over 65 years have not been studied [see Use in Specific Populations (8.5)].

Male and Female Patients: There are no significant or clinically relevant gender differences in lamivudine pharmacokinetics.

Racial Groups: There are no significant or clinically relevant racial differences in lamivudine pharmacokinetics.

Drug Interaction Studies

Effect of Lamivudine on the Pharmacokinetics of Other Agents: Based on *in vitro* study results, lamivudine at therapeutic drug exposures is not expected to affect the pharmacokinetics of drugs that are substrates of the following transporters: organic anion transporter polypeptide 1B1/3 (OATP1B1/3), breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K, organic cation transporter 1 (OCT1), OCT2, or OCT3.

Effect of Other Agents on the Pharmacokinetics of Lamivudine: Lamivudine is a substrate of MATE1, MATE2-K, and OCT2 in vitro. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations. This interaction is not considered clinically significant as no dose adjustment of lamivudine is needed.

Lamivudine is a substrate of P-gp and BCRP; however, considering its absolute bioavailability (87%), it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore, coadministration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Interferon Alfa: There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a trial of 19 healthy male subjects [see Warnings and Precautions (5.3)].

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine

(n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects *[see Warnings and Precautions (5.3)]*.

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

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

Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult subjects given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 hours).

Microbiology

Mechanism of Action

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.

Antiviral Activity

The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and fresh human peripheral blood lymphocytes (PBMCs) using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC_{50} values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-

G and group O viruses (n = 3 except n = 2 for clade B) respectively. The EC50 values against HIV-2 isolates (n = 4) ranged from 0.003 to 0.120 microM in PBMCs. Lamivudine was not antagonistic to all tested anti-HIV agents.

Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

Resistance

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

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

Genotypic and Phenotypic Analysis of On-Therapy HIV-1 Isolates from Subjects with Virologic Failure

Trial EPV20001: Fifty-three of 554 (10%) subjects enrolled in EPV20001 were identified as virological failures (plasma HIV-1 RNA level greater than or equal to 400 copies per mL) by Week 48. Twenty-eight subjects were randomized to the lamivudine once-daily treatment group and 25 to the lamivudine twice-daily treatment group. The median baseline plasma HIV-1 RNA levels of subjects in the lamivudine once-daily group and lamivudine twice-daily group were 4.9 $\log_{10}$ copies per mL and 4.6 $\log_{10}$ copies per mL, respectively.

Genotypic analysis of on-therapy isolates from 22 subjects identified as virologic failures in the lamivudine once-daily group showed that isolates from 8 of 22 subjects contained a treatment-emergent lamivudine resistance-associated substitution (M184V or M184I), isolates from 0 of 22 subjects contained treatment-emergent amino acid substitutions associated with zidovudine resistance (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E), and isolates from 10 of 22 subjects contained treatment-emergent amino acid substitutions associated with efavirenz resistance (L100I, K101E, K103N, V108I, or Y181C).

Genotypic analysis of on-therapy isolates from subjects (n = 22) in the lamivudine twice-daily treatment group showed that isolates from 5 of 22 subjects contained treatment-emergent lamivudine resistance substitutions, isolates from 1 of 22 subjects contained treatment-emergent zidovudine resistance substitutions, and isolates from 7 of 22 subjects contained treatment-emergent efavirenz resistance substitutions.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from subjects (n = 13) receiving lamivudine once daily showed that isolates from 7 of 13 subjects showed an 85-to 299-fold decrease in susceptibility to lamivudine, isolates from 12 of 13 subjects were susceptible to zidovudine, and isolates from 8 of 13 subjects exhibited a 25-to 295-fold decrease in susceptibility to efavirenz.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from subjects (n = 13) receiving lamivudine twice daily showed that isolates from 4 of 13 subjects exhibited a 29-to 159-fold decrease in susceptibility to lamivudine, isolates from all 13 subjects were susceptible to zidovudine, and isolates from 3 of 13 subjects exhibited a 21-to 342-fold decrease in susceptibility to efavirenz.

Trial EPV40001: Fifty subjects received lamivudine 300 mg once daily plus zidovudine 300 mg twice daily plus abacavir 300 mg twice daily and 50 subjects received lamivudine 150 mg plus zidovudine 300 mg plus abacavir 300 mg all twice-daily. The median baseline plasma HIV-1 RNA levels for subjects in the 2 groups were 4.79 $\log_{10}$ copies per mL and 4.83 $\log_{10}$ copies per mL, respectively. Fourteen of 50 subjects in the lamivudine once-daily treatment group and 9 of 50 subjects in the lamivudine twice-daily group were identified as virologic failures.

Genotypic analysis of on-therapy HIV-1 isolates from subjects (n = 9) in the lamivudine once-daily treatment group showed that isolates from 6 subjects had an abacavir and/or lamivudine resistance-associated substitution M184V alone. On-therapy isolates from subjects (n = 6) receiving lamivudine twice daily showed that isolates from 2 subjects had M184V alone, and isolates from 2 subjects harbored the M184V substitution in combination with zidovudine resistance-associated amino acid substitutions.

Phenotypic analysis of on-therapy isolates from subjects (n = 6) receiving lamivudine once daily showed that HIV-1 isolates from 4 subjects exhibited a 32-to 53-fold decrease in susceptibility to lamivudine. HIV-1 isolates from these 6 subjects were susceptible to zidovudine.

Phenotypic analysis of on-therapy isolates from subjects (n = 4) receiving lamivudine twice daily showed that HIV-1 isolates from 1 subject exhibited a 45-fold decrease in susceptibility to lamivudine and a 4.5-fold decrease in susceptibility to zidovudine.

Pediatrics: Pediatric subjects receiving lamivudine oral solution concomitantly with other antiretroviral oral solutions (abacavir, nevirapine/efavirenz, or zidovudine) in ARROW developed viral resistance more frequently than those receiving tablets. At randomization to once-daily or

twice-daily dosing of lamivudine plus abacavir, 13% of subjects who started on tablets and 32% of subjects who started on solution had resistance substitutions. The resistance profile observed in pediatrics is similar to that observed in adults in terms of the genotypic substitutions detected and relative frequency, with the most commonly detected substitutions at M184 (V or I) [see Clinical Studies (14.2)].

Cross-Resistance

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

Tenofovir disoproxil fumarate

Mechanism of Action

Tenofovir disoproxil fumarate is an antiviral drug [See Microbiology (12.4)].

Pharmacokinetics

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

Absorption

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 mcg/mL and 2.29 ± 0.69 mcghr/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.

Distribution

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 mcg/mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.

Metabolism and Elimination

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

Following IV administration of tenofovir, approximately 70 to 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.

Effects of Food on Oral Absorption

Administration of tenofovir disoproxil fumarate 300 mg tablets following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir AUC0-∞ of approximately 40% and an increase in C_{max} of approximately 14%. However, administration of tenofovir disoproxil fumarate with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the drug. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 0.33 ± 0.12 mcg/mL and 3.32 ± 1.37 mcg•hr/mL following multiple doses of tenofovir disoproxil fumarate 300 mg once daily in the fed state, when meal content was not controlled.

Special Populations

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

Gender: Tenofovir pharmacokinetics are similar in male and female subjects.

Pediatric Patients 2 Years of Age and Older: Steady-state pharmacokinetics of tenofovir were evaluated in 31 HIV-1 infected pediatric subjects 2 to less than 18 years (Table 26). Tenofovir

exposure achieved in these pediatric subjects receiving oral once daily doses of tenofovir disoproxil fumarate 300 mg (tablet) or 8 mg/kg of body weight (powder) up to a maximum dose of 300 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil fumarate 300 mg.

Table Mean (± SD) Tenofovir Pharmacokinetic Parameters by Age Groups for HIV-1-infected Pediatric Patients

Dose and Formulation	**300 mg Tablet**	**8 mg/kg Oral Powder**
	12 to <18 Years (N=8)	**2 to <12 Years (N=23)**
C_{max} (mcg/mL)	0.38 ± 0.13	0.24 ± 0.13
AUC_{tau} (mcg•hr/mL)	3.39 ± 1.22	2.59 ± 1.06

Tenofovir exposures in 52 HBV-infected pediatric subjects (12 to less than 18 years of age) receiving oral once-daily doses of tenofovir disoproxil fumarate 300 mg tablet were comparable to exposures achieved in HIV-1 infected adults and adolescents receiving once-daily doses of 300 mg.

Geriatric Patients*:* Pharmacokinetic trials have not been performed in the elderly (65 years and older).

Patients with Impaired Renal Function: The pharmacokinetics of tenofovir are altered in subjects with renal impairment *[See Warnings and Precautions (5.2)]*. In subjects with creatinine clearance below 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and $AUC_{0 \text{ to } \infty}$ of tenofovir were increased (Table 27). It is recommended that the dosing interval for tenofovir disoproxil fumarate be modified in patients with estimated creatinine clearance below 50 mL/min or in patients with ESRD who require dialysis *[See* Dosage and Administration (2.3)].

Table Pharmacokinetic Parameters (Mean ± SD) of Tenofovir[a] 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} (mcg/mL)	0.34 ± 0.03	0.33 ± 0.06	0.37 ± 0.16	0.60 ± 0.19
$AUC_{0-\infty}$	2.18 ± 0.26	3.06 ± 0.93	6.01 ± 2.50	15.98 ± 7.22

(mcg•hr/mL)				
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.

Patients with Hepatic Impairment: 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.

Assessment of Drug Interactions

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

Tenofovir disoproxil fumarate has been evaluated in healthy volunteers in combination with other antiretroviral and potential concomitant drugs. Tables 28 and 29 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of tenofovir disoproxil fumarate on the pharmacokinetics of coadministered drug. Coadministration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Concomitant dosing of tenofovir disoproxil fumarate with didanosine significantly increases the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions (Table 14). The mechanism of this interaction is unknown.

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

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

Coadministered Drug	**Dose of Coadministered Drug (mg)**	**N**	**% Change of Tenofovir Pharmacokinetic Parameters[b] (90% CI)**		
			C_{max}	**AUC**	**C_{min}**
Atazanavir[c]	400 once daily × 14 days	33	↑14 (↑8 to↑20)	↑ 24 (↑21 to ↑28)	↑2 (↑15 to ↑30)
Atazanavir/ Ritonavir[c]	300/100 once daily	12	↑34 (↑20 to↑51)	↑37 (↑30 to ↑45)	↑29 (↑21 to ↑36)
Darunavir/Ritonavir[d]	300/100 twice daily	12	↑24 (↑8 to↑ 42)	↑ 22 (↑ 10 to ↑ 35)	↑37 (↑ 19 to ↑57)
Indinavir	800 three times daily × 7 days	13	↑14 (↓3 to ↑33)	⇔	⇔
Ledipasvir/ Sofosbuvir[e,f]	90/400 once daily × 10 days	24	↑47 (↑ 37to ↑58)	↑35 (↑ 29 to ↑ 42)	↑ 47 (↑ 38 to ↑57)
Ledipasvir/ Sofosbuvir[e,g]		23	↑ 64 (↑ 54 to ↑74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/ Sofosbuvir[h]	90/400 once daily × 14 days	15	↑79 (↑ 56 to↑104)	↑ 98 (↑ 77 to ↑123)	↑ 163 (↑ 132 to↑197)
Ledipasvir/ Sofosbuvir[i]	90/400 once daily × 10 days	14	↑ 32 (↑ 25 to ↑39)	↑ 40 (↑ 31 to ↑ 50)	↑ 91 (↑ 74 to ↑110)
Ledipasvir/ Sofosbuvir[j]	90/400 once	29	↑ 61	↑ 65	↑ 115

	daily × 10 days		(↑ 51 to ↑72)	(↑ 59 to ↑ 71)	(↑105 to ↑126)
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑66)
Saquinavir/ Ritonavir	1000/100 twice daily ×14 days	35	⇔	⇔	↑ 23 (↑16 to↑ 30)
Sofosbuvir[k]	400 single dose	16	↑ 25 (↑ 8 to ↑45)	⇔	⇔
Sofosbuvir/ Velpatasvir[l]	400/100 once daily	24	↑ 55 (↑ 43 to ↑68)	↑ 30 (↑24 to ↑ 36)	↑ 39 (↑ 31 to ↑ 48)
Sofosbuvir/ Velpatasvir[m]	400/100 once daily	29	↑ 55 (↑45 to ↑ 66)	↑ 39 (↑ 33 to ↑44)	↑ 52 (↑ 45 to ↑ 59)
Sofosbuvir/ Velpatasvir[n]	400/100 once daily	15	↑ 77 ↑53 to ↑104)	↑ 81 (↑ 68 to ↑94)	↑ 121 (↑ 100 to ↑ 143)
Sofosbuvir/ Velpatasvir[o]	400/100 once daily	24	↑ 36 ↑ 25 to ↑ 47)	↑ 35 (↑ 29 to ↑42)	↑ 45 (↑ 39 to ↑ 51)
Sofosbuvir/ Velpatasvir[p]	400/100 once daily	24	↑ 44 ↑ 33 to ↑ 55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑ 76 to ↑ 92)
Sofosbuvir/ Velpatasvir[q]	400/100 once daily	30	↑ 46 ↑ 39 to ↑ 54)	↑ 40 (↑ 34 to ↑ 45)	↓ 70 (↑ 61 to ↑ 79)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↑ 13 (↑ 1 to ↑ 27)	⇔	⇔
Tipranavir/ Ritonavir[r]	500/100 twice daily	22	↓ 23 (↓32 to ↓ 13)	↓ 2 (↓9 to ↑ 5)	↑ 7 (↓ 2 to ↑17)

	750/200 twice daily(23 doses)	20	↓ 38 (↓ 46 to ↓ 29)	↑ 2 (↓ 6 to ↑ 10)	↑14 (↑ 1 to ↑27)

a. Subjects received tenofovir disoproxil fumarate 300 mg once daily.

b. Increase = ↑; Decrease = ↓; No Effect = ⇔

c. Reyataz Prescribing Information.

d. Prezista Prescribing Information.

e. Data generated from simultaneous dosing with HARVONI (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provide similar results.

f. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate.

g. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate.

h. Study conducted with ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate) coadministered with HARVONI.

i. Study conducted with COMPLERA (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) coadministered with HARVONI.

j. Study conducted with TRUVADA (emtricitabine/tenofovir disoproxil fumarate) + dolutegravir coadministered with HARVONI.

k. Study conducted with ATRIPLA coadministered with SOVALDI ® (sofosbuvir).

l. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate.

m. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate.

n. Study conducted with ATRIPLA coadministered with EPCLUSA (sofosbuvir/velpatasvir).

o. Study conducted with STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) coadministered with EPCLUSA.

p. Study conducted with COMPLERA coadministered with EPCLUSA.

q. Administered as raltegravir + emtricitabine/tenofovir disoproxil fumarate.

r. Aptivus Prescribing Information.

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

Table Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of tenofovir disoproxil fumarate

Coadministered Drug	**Dose of Coadministered Drug (mg)**	**N**	**% Change of Tenofovir Pharmacokinetic Parameters[b] (90% CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	⇔	NA
Atazanavir[b]	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to↓32)
Atazanavir[b]	Atazanavir/ Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓25[c] (↓ 42 to ↓ 3)	↓ 23[c] (↓ 46 to ↑ 10)
Darunavir[d]	Darunavir/Ritonavir 300/100 once daily	12	↑ 16 (↓ 6 to ↑ 42)	↑ 21 (↓ 5 to ↑ 54)	↑ 24 (↓ 10 to ↑ 69)
Didanosine[e]	250 once, simultaneously with tenofovir disoproxil fumarate and a light meal[f]	33	↓ 20[g] (↓ 32 to ↓ 7)	g ⇔	NA
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Entecavir	1 mg once daily × 10 days	28	⇔	↑13 (↑ 11 to ↑ 15)	⇔

Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	⇔ ⇔	⇔ ⇔	⇔ ⇔
Saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑ 41) ⇔	↑ 29[h] (↑ 12 to ↑ 48) ⇔	↑ 47[h] (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	⇔	⇔	⇔
Tipranavir[i]	Tipranavir/Ritonavir 500/100 twice daily	22	↓ 17 (↓ 26 to ↓ 6)	↓ 18 (↓ 25 to ↓ 9)	↓ 21 (↓ 30 to ↓ 10)
	Tipranavir/Ritonavir 750/200 twice daily (23 doses)	20	↓ 11 (↓ 16 to ↓ 4)	↓ 9 (↓15 to ↓ 3)	↓ 12 (↓ 22 to 0)

a. Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable

b. Reyataz Prescribing Information.

c. In HIV-infected subjects, addition of tenofovir disoproxil fumarate to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3-and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone. d. Prezista Prescribing Information.

e. Videx EC Prescribing Information. Subjects received didanosine enteric-coated capsules.

f. 373 kcal, 8.2 g fat

g. Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions.

h. Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir disoproxil fumarate and ritonavir-boosted saquinavir are co administered.

i. Aptivus Prescribing Information.

Microbiology

Mechanism of Action

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

Activity against HIV

Antiviral Activity

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

Resistance

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

In Study 903 of treatment-naïve subjects (tenofovir disoproxil fumarate + lamivudine + efavirenz versus stavudine + lamivudine + efavirenz) *[See Clinical Studies (14.1)]*, genotypic analyses of isolates from subjects with virologic failure through Week 144 showed development of efavirenz and lamivudine resistance-associated substitutions to occur most frequently and with no difference between the treatment arms. The K65R substitution occurred in 8/47 (17%) of analyzed patient isolates in the tenofovir disoproxil fumarate arm and in 2/49 (4%) of analyzed patient isolates in the stavudine arm. Of the 8 subjects whose virus developed K65R in the tenofovir disoproxil fumarate arm through 144 weeks, 7 occurred in the first 48 weeks of treatment and one at Week 96. One patient in the tenofovir disoproxil fumarate arm developed the K70E substitution in the virus. Other substitutions resulting in resistance to tenofovir disoproxil fumarate were not identified in this trial.

In Study 934 of treatment-naïve subjects (tenofovir disoproxil fumarate + EMTRIVA + efavirenz versus zidovudine (AZT)/lamivudine (3TC) + efavirenz) *[See Clinical Studies (14.1)]*, genotypic analysis performed on HIV-1 isolates from all confirmed virologic failure subjects with greater than 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation showed development of efavirenz resistance-associated substitutions occurred most frequently and was similar between the two treatment arms. The M184V substitution, associated with resistance to EMTRIVA and lamivudine, was observed in 2/19 of analyzed subject isolates in the tenofovir disoproxil fumarate + EMTRIVA group and in 10/29 of analyzed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no subjects have developed a detectable K65R substitution in their HIV-1 as analyzed through standard genotypic analysis.

Cross Resistance

Cross resistance among certain reverse transcriptase inhibitors has been recognized. The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1 infected subjects treated with abacavir or didanosine. HIV-1 isolates with this substitution also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross resistance among these drugs may occur in patients whose virus harbors the K65R or K70E substitution. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of three zidovudine-associated reverse

transcriptase substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), showed a 3.1-fold decrease in the susceptibility to tenofovir.

In Studies 902 and 907 conducted in treatment-experienced subjects (tenofovir disoproxil fumarate + Standard Background Therapy (SBT) compared to placebo + SBT) *[See Clinical Studies (14.1)]*, 14/304 (5%) of the tenofovir disoproxil fumarate -treated subjects with virologic failure through Week 96 had greater than 1.4-fold (median 2.7-fold) reduced susceptibility to tenofovir. Genotypic analysis of the baseline and failure isolates showed the development of the K65R substitution in the HIV-1 reverse transcriptase gene.

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

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

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

Studies 902 and 907 Phenotypic Analyses

Phenotypic analysis of baseline HIV-1 from treatment-experienced subjects (N=100) demonstrated a correlation between baseline susceptibility to tenofovir disoproxil fumarate and response to tenofovir disoproxil fumarate therapy. Table 30 summarizes the HIV-1 RNA response by baseline tenofovir disoproxil fumarate susceptibility.

Table HIV-1 RNA Response at Week 24 by Baseline tenofovir disoproxil fumarate Susceptibility (IntentTo-Treat)[a]

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

a. Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram assay (Virco).

b. Fold change in susceptibility from wild-type.

c. Average HIV-1 RNA change from baseline through Week 24 ($DAVG_{24}$) in log_{10} copies/mL.

Activity against HBV

Antiviral Activity

The antiviral activity of tenofovir against HBV was assessed in the HepG2 2.2.15 cell line. The EC_{50} values for tenofovir ranged from 0.14 to 1.5 μM, with CC_{50} (50% cytotoxicity concentration) values greater than 100 μM. In cell culture combination antiviral activity studies of tenofovir with the nucleoside HBV reverse transcriptase inhibitors entecavir, lamivudine, and telbivudine, and with the nucleoside HIV-1 reverse transcriptase inhibitor emtricitabine, no antagonistic activity was observed.

Resistance

Cumulative tenofovir disoproxil fumarate genotypic resistance has been evaluated annually for up to 384 weeks in Studies 0102, 0103, 0106, 0108, and 0121 with the paired HBV reverse

transcriptase amino acid sequences of the pretreatment and on-treatment isolates from subjects who received at least 24 weeks of tenofovir disoproxil fumarate monotherapy and remained viremic with HBV DNA greater than or equal to 400 copies/mL (69 IU/mL) at the end of each study year (or at discontinuation of tenofovir disoproxil fumarate monotherapy) using an as-treated analysis. In the nucleotide-naïve population from Studies 0102 and 0103, HBeAg-positive subjects had a higher baseline viral load than HBeAg-negative subjects and asignificantly higher proportion of the subjects remained viremic at their last time point on tenofovir disoproxil fumarate monotherapy (15% versus 5%, respectively).

HBV isolates from these subjects who remained viremic showed treatment-emergent substitutions (Table 31); however, no specific substitutions occurred at a sufficient frequency to be associated with resistance to tenofovir disoproxil fumarate (genotypic and phenotypic analyses).

Table Amino Acid Substitutions in Viremic Subjects across HBV Trials of tenofovir disoproxil fumarate

	Compensated Liver Disease			**Decompensated Liver Disease (N=39)[d]**
	Nucleotide-Naïve (N=417)[a]	**HEPSERA-Experienced (N=247)[b]**	**Lamivudine-Resistant (N=136)[c]**	
Viremic at Last Time Point on tenofovir disoproxil fumarate	38/417 (9%)	37/247 (15%)	9/136 (7%)	7/39 (18%)
Treatment-Emergent Amino Acid Substitutions[e]	18[f]/32 (56%)	11[g]/31 (35%)	6[h]/8 (75%)	3/5 (60%)

a. Nucleotide-naïve subjects from Studies 0102 (N=246) and 0103 (N=171) receiving up to 384 weeks of treatment with tenofovir disoproxil fumarate.

b. HEPSERA-experienced subjects from Studies 0102/0103 (N=195) and 0106 (N=52) receiving up to 336 weeks of treatment with tenofovir disoproxil fumarate after switching to tenofovir disoproxil fumarate from HEPSERA. Study 0106, a randomized, double-blind, 168-week Phase 2 trial, has been completed.

c. Lamivudine-resistant subjects from Study 0121 (N=136) receiving up to 96 weeks of treatment with tenofovir disoproxil fumarate after switching to tenofovir disoproxil fumarate from lamivudine.

d. Subjects with decompensated liver disease from Study 0108 (N=39) receiving up to 48 weeks of treatment with tenofovir disoproxil fumarate.

e. Denominator includes those subjects who were viremic at last time point on tenofovir disoproxil fumarate monotherapy and had evaluable paired genotypic data.

f. Of the 18 subjects with treatment-emergent amino acid substitutions during Studies 0102 and 0103, 5 subjects had substitutions at conserved sites and 13 subjects had substitutions only at polymorphic sites, and 8 subjects had only transient substitutions that were not detected at the last time point on tenofovir disoproxil fumarate.

g. Of the 11 HEPSERA-experienced subjects with treatment-emergent amino acid substitutions, 2 subjects had substitutions at conserved sites and 9 had substitutions only at polymorphic sites.

h. Of the 6 lamivudine-resistant subjects with treatment-emergent substitutions during Study 0121, 3 subjects had substitutions at conserved sites and 3 had substitutions only at polymorphic sites.

Cross Resistance

Cross resistance has been observed between HBV nucleoside/nucleotide analogue reverse transcriptase inhibitors.

In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204I/V substitutions associated with resistance to lamivudine and telbivudine showed a susceptibility to tenofovir ranging from 0.7- to 3.4-fold that of wild type virus. The rtL180M and rtM204I/V double substitutions conferred 3.4-fold reduced susceptibility to tenofovir. HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V, and rtM250V substitutions associated with resistance to entecavir showed a susceptibility to tenofovir ranging from 0.6- to 6.9-fold that of wild type virus.

HBV strains expressing the adefovir resistance-associated substitutions rtA181V and/or rtN236T showed reductions in susceptibility to tenofovir ranging from 2.9-to 10-fold that of wild type virus. Strains containing the rtA181T substitution showed changes in susceptibility to tenofovir ranging from 0.9-to 1.5-fold that of wild type virus.

One hundred fifty-two subjects initiating tenofovir disoproxil fumarate therapy in Studies 0102, 0103, 0106, 0108, and 0121 harbored HBV with known resistance substitutions to HBV nucleos(t)ide analogue reverse transcriptase inhibitors: 14 with adefovir resistance-associated substitutions (rtA181S/T/V and/or rtN236T), 135 with lamivudine resistance-associated substitutions (rtM204I/V), and 3 with both adefovir and lamivudine resistance-associated substitutions. Following up to 384 weeks of tenofovir disoproxil fumarate treatment, 10 of the 14 subjects with adefovir-resistant HBV, 124 of the 135 subjects with lamivudine-resistant HBV, and 2 of the 3 subjects with both adefovir-and lamivudine-resistant HBV achieved and maintained virologic suppression (HBV DNA less than 400 copies/mL [69 IU/mL]). Three of the 5 subjects whose virus harbored both the rtA181T/V and rtN236T substitutions remained viremic.

5.3 Preclinical safety data

Dolutegravir

Carcinogenesis, Mutagenesis, Impairment of Fertility

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-fold higher than those in humans at the recommended dose of 50 mg twice daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 10-fold and 15-fold higher in males and females, respectively, than those in humans at the recommended dose of 50 mg twice daily.

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, Mutagenesis, Impairment of Fertility

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 vivo* 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, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

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

Animal Toxicology and/or Pharmacology

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

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

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose, (Ceolus KG 802) , Hydroxy propyl cellulose, (Klucel EXF), Croscarmellose Sodium, (Ac-Di-sol SD-711), Isopropyl Alcohol, Magnesium Stearate, (LIGAMED-MF-2-V), Microcrystalline cellulose, (Ceolus KG 1000), Sodium starch glycollate, Type A (Primojel), Mannitol (25 C), Microcrystalline cellulose, (Avicel-PH101), Povidone, (Kollidon -30), Sodium Stearyl Fumarate (PG-100), Opadry II orange 85F530128(iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.), Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

<2 Years**>**

6.4 Special precautions for storage

Store below 30°C (86°F)

6.5 Nature and contents of container

Container Pack: 30's HDPE Container, 90's HDPE Container, 180's HDPE Container.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

7.1 Name and Address of Manufacturer

Name : M/s Annora Pharma Private Limited
Address : Sy. No. 261, Annaram Village Gummadidal Mandal,
Sangareddy District, Telangana, India.
Country : India
Telephone : + 91-8458-284200

7.2 Name and Address of Principal

Name : Hetero Labs Limited
Business Address : 7-2-A2, Hetero Corporate,
Industrial Estates, Sanath Nagar,
Hyderabad-500 018
Telangana.
Country : INDIA
Telephone : 0091-040-23704923/24

8. Registration Number

Not Applicable

9. Category for Distribution

Prescription only medicine-List I

10. Date of Publication of This Package Insert