

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed

O USE TENOFOVIR DISOPROXIL FUMARATE TABLETS

· Lactic acidosis/severe hepatomegaly with steatosis:

Discontinue treatment in patients who develop symptoms

r laboratory findings suggestive of lactic acidosis or

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.

onouncedhepatotoxicity. (5.3) leutrophils (<750/mm³) safely and effectively. See full prescribing information for administration with Other Products: Do not use with other DOSAGE FORMS AND STRENGTHS tenofovir disoproxil fumarate included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain and skin rash. Fasting Triglycerides (>750 mg/dL) tenofovir-containing products (e.g., ATRIPLA, COMPLERA, lenofovir disoproxil fumarate is available as tablets During the open-label phase of treatment with tenofovir disoproxil furnarate (weeks 48-384) in Studies 0102 and 0103, 2% of subjects TENOFOVIR DISOPROXIL FUMARATE tablets, for oral use DESCOVY, GENVOYA, ODEFSEY, STRIBILD, TRUVAD or Study 934 - Treatment Emergent Adverse Reactions: In Study 934, 511 antiretroviral-naïve subjects received either tenofovir Read this Patient Information before you start taking tenofovir disoproxil fumarate tablets Tenofovir disoproxil furnarate tablets 300 mg contain 300 mg of tenofovir disoproxil furnarate which is equivalent to 245 mg of tenofovir Initial U.S. Approval Date: 2001 /EMLIDY). Do not administer in combination with HEPSERA. disoproxil furnarate + EMTRIVA® administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered was observed with continued treatment for up to 384 weeks. and each time you get a refill. There may be new information. This information does not in combination with efavirenz (N=254). Adverse reactions observed in this trial were generally consistent with those seen in Laboratory Abnormalities: A summary of Grade 3-4 laboratory abnormalities through Week 48 is provided in Table 10. Grade 3-4 laboratory WARNINGS: POST TREATMENT EXACERBATION OF HEPATITIS take the place of talking with your healthcare provider about your medical condition or See full prescribing information for complete HBV- infected patients before initiating therapy with tenofovir Table 10 Grades 3-4 Laboratory Abnormalities Reported in ≥1% of Tenofovir Disoproxil Fumarate-Treated Subjects in Studies 0102 disoproxil fumarate. Tenofovir disoproxil fumarate should only In HIV-1 infected adult subjects in Study 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar and 0103 (0-48 Weeks) Severe acute exacerbations of hepatitis have been be used as part of an appropriate antiretroviral combination reported in HBV-infected patients who have discontinued vudine + efavirenz (-1.0% \pm 4.6) through 144 weeks. Changes in BMD at the hip were similar between the two treatment group regimen in HIV-infected patients with or without HBV 5.1 Exacerbation of Hepatitis after Discontinuation of Treatmen What is the most important information I should know about tenofovir disoproxil TENOFOVIR DISOPROXIL FUMARATE (N=426) HEPSERA (N=215) Discontinuation of anti-HBV therapy, including tenofovir disoproxil fumarate, may be associated with severe acute exacerbations of hepatitis. anti-hepatitis B therapy, including tenofovir disoproxil coinfection. (5.5) (-2.8% ± 3.5 in the tenofovir disoproxil furnarate group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction fumarate tablets? Patients infected with HBV who discontinue tenofovir disoproxil fumarate should be closely monitored with both clinical and laboratory fumarate. Hepatic function should be monitored closely • Decreases in bone mineral density (BMD): Consider in BMD occurred in the first 24-48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of tenofovir soproxil 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. Any ≥ Grade 3 Laboratory Abnormality follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. assessment of BMD in patients with a history of pathologic in these patients. If appropriate, resumption of Tenofovir disoproxil fumarate tablets can cause serious side effects, including: fracture or other risk factors for osteoporosis or bone loss. nically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the tenofovir disoproxil fumarate group and 5.2 New Onset or Worsening Renal Impairment 3% subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specificant) in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific vir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular 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 Worsening of your Hepatitis B infection. Your hepatitis B Virus (HBV) infection may injury with severe hypophosphatemia), has been reported with the use of tenofovir disoproxil fumarate [see Adverse Reactions (6.2)]. Serum Amvlase (>175 U/L Tenofovir disoproxil fumarate is a nucleotide analog HIV-1 reverse patients. May necessitate further evaluation and treatment. become worse (flare-up) if you take tenofovir disoproxil fumarate tablets and then stop it. It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically phosphatase, these changes resulted in values that remained within the normal range [See Warnings and Precautions (5.6)]. 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 (0–144 Weeks) transcriptase inhibitor and an HBV reverse transcriptase inhibitor. (5.7) Tenofovir disoproxil fumarate is indicated in combination with • Triple nucleoside-only regimens: Early virologic failure has A "flare-up" is when your HBV infection suddenly returns in a worse way than before. Table 6 Selected Treatment-Emergent Adverse Reactions^a (Grades 2-4) Reported in ≥5% in Any Treatment Group in Study 934 AST (M: >180 U/L; F: >170 U/L other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 2 years of age and older. (1) phosphorus, urine glucose, and urine protein be assessed prior to initiation of tenofovir disoproxil fumarate, and periodically Do not let your tenofovir disoproxil furnarate tablet run out. Refill your prescription or Tenofovir disoproxil fumarate^b + FTC + EFV AZT/3TC + EFV The overall incidence of on-treatment ALT flares (defined as serum ALT greater than 2 imes baseline and greater than 10 imes ULN. talk to your healthcare provider before your tenofovir disoproxil fumarate tablets are all -----ADVERSE REACTIONS--chronic hepatitis B in adults and pediatric patients 12 years of line HIV-infected adult subjects: Most common adverse reactions (incidence greater the period of the peri Dosing interval adjustment of tenofovir disoproxil fumarate and close monitoring of renal function are recommended in all patients Tenofovir disoproxil fumarate is indicated for the treatment of with or without associated symptoms) was similar between tenofovir disoproxil fumarate (2.6%) and HEPSERA (2%). ALT flares with creatinine clearance below 50 ml/min [See Dosage and Administration (2.3)]. No safety or efficacy data are available in generally occurred within the first 4-8 weeks of treatment and were accompanied by decreases in HBV DNA levels. No subject rointestinal Disorder (incidence greater than or equal to 10%, Grades 2 - 4) are rash, patients with renal impairment who received tenofovir disoproxil fumarate using these dosing guidelines, so the potential benefit age and older. (1) diarrhea, headache, pain, depression, asthenia, and nausea Do not stop taking tenofovir disoproxil fumarate tablet without first talking to your of tenofovir disoproxil fumarate therapy should be assessed against the potential risk of renal toxicity. -----DOSAGE AND ADMINISTRATION-----The adverse reactions observed in subjects with chronic hepatitis B and lamivudine resistance who received treatment with Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple healthcare provider. Recommended dose for the treatment of HIV-1 or chronic
 In HBV-infected subjects with compensated liver disease: most tenofovir disoproxil furnarate were consistent with those observed in other hepatitis B clinical trials in adults. non-steroidal anti-inflammatory drugs (NSAIDs)) [See Drug Interactions (7.4)]. Cases of acute renal failure after initiation of nepatitis B in adults and pediatric patients 12 years of age common adverse reaction (all grades) was nausea (9%). (6.1) Clinical Trials in Adult Subjects with Chronic Hepatitis B and Decompensated Liver Diseas high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared If you stop taking tenofovir disoproxil fumarate, your healthcare provider will need to and older (35 kg or more): 300 mg once daily taken orally In pediatric subjects: Adverse reactions in pediatric subjects were In a small randomized, double-blind, active-controlled trial (0108), subjects with CHB and decompensated liver disease received treatment stable on tenofovir DF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if General Disorders and Administration Site Condition without regard to food. (2.1) consistent with those observed in adults. (6.1) with tenofovir disoproxil fumarate or other antiviral drugs for up to 48 weeks [See Clinical Studies (14.2)]. Among the 45 subjects receivin check your health often and do blood tests regularly to check your HBV infection. needed, in patients at risk for renal dysfunction. Recommended dose for the treatment of HIV-1 in In HBV-infected subjects with decompensated liver disease: Tell your healthcare provider about any new or unusual symptoms you may have after pediatric patients (2 to less than 12 years of age): most common adverse reactions (incidence greater than or equal Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%). Two of 45 (4%) subjects died proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients. nfections and Infestations Tablets: for pediatric patients weighing greater than or equal to to 10%, all grades) were abdominal pain, nausea, insomnia, 17 kg who can swallow an intact tablet, one Tenofovir pruritus, vomiting, dizziness, and pyrexia. (6.1) 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 you stop taking tenofovir disoproxil fumarate tablet. 5.3 Lactic Acidosis/Severe Hepatomegaly with Steatosis disoproxil fumarate tablet (300 mg based on body weight) To report SUSPECTED ADVERSE REACTIONS, contact Strides Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including phosphorus less than 2mg/dL through Week 48). Three of these subjects (each of whom had a Child-Pugh score greater than or equal to 10 and Talk to your doctor about taking an HIV test before starting treatment with Upper respiratory tract infections tenofovir tenofovir DF, 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 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 once daily taken orally without regard to food. (2.2)

• Dose recommended in renal impairment in adults:

www.fda.gov/medwatch tenofovir disoproxil fumarate tablet for chronic hepatitis B. You should also get a Creatinine clearance 30-49 mL/min: 300 mg every 48 hours and steatosis even in the absence of marked transaminase elevations). difficult to ascertain. Nervous System Disorders test for HBV if you are taking tenofovir disoproxil fumarate tablet for treatment of ----DRUG INTERACTIONS----5.4 Coadministration with Other Products (Coadminine clearance 10-29 mL/min: 300 mg every 72 to Didanosine: Coadministration increases didanosine concentrations. Use with caution and monitor for evidence Tenofovir disoproxil fumarate should not be used in combination with other drugs containing tenofovir disoproxil fumurate or tenofovir Clinical Trials in Pediatric Subjects 12 Years of Age and Older with Chronic Hepatitis B alafenamide, including ATRIPLA, COMPLERA, DESCOVY, GENVOYA, ODEFSEY, STRIBILD, TRUVAD or VEMLIDY. Assessment of adverse reactions is based on one randomized study (Study GS-US-174-0115) in 106 pediatric subjects (12 to less than What is tenofovir disoproxil fumarate tablet? Hemodialysis: 300 mg every 7 days or after approximately

UI ulualiosine toxiotiy (e.g., patients)

Consider dose reductions or discontinuations of didanosine Tenofovir disoproxil fumarate should not be administered in combination with HEPSERA (adefovir dipivoxil) [See Drug Interactions (7.4)]. 8 years of age) infected with chronic hepatitis B receiving treatment with tenofovir disoproxil fumarate (N=52) or placebo (N=54) for 12 hours of dialysis. (2.3) 72 weeks. The adverse reactions observed in pediatric subjects who received treatment with tenofovir disoproxil fumarate were consistent Tenofovir disoproxil fumarate tablet is a prescription medicine used: if warranted. (7.1) Depression with those observed in clinical trials of tenofovir disoproxil furnarate in adults. Due to the risk of development of HIV-1 resistance, tenofovir disporavil furnarate should only be used in HIV-1 and HRV coinfected nations as 1. with other antiviral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) in Tablets: 300 mg (3) atazanavir concentrations and increases tenofovir In this study, both the tenofovir disoproxil fumarate and placebo treatment arms experienced an overall increase in mean part of an appropriate antiretroviral combination regimen concentrations. When coadministered with tenofovir Skin and Subcutaneous Tissue Disorders lumbar spine BMD over 72 weeks, as expected for an adolescent population. The BMD gains from baseline to Week 72 in lumbar people 2 years of age and older. HIV is the virus that causes AIDS (Acquired Immune HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with tenofovir disoproxil fumarate. ----CONTRAINDICATIONSspine and total body BMD in tenofovir disoproxil furnarate-treated subjects (+5% and +3%, respectively) were less than the It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment Deficiency Syndrome). gains observed in placebo-treated subjects (+8% and +5%, respectively). Three subjects in the tenofovir disoproxil Coadministration of tenofovir disoproxil fumarate with -----WARNINGS AND PRECAUTIONS----fumarate group and two subjects in the placebo group had significant (greater than 4%) lumbar spine BMD loss at Week 72. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug. • When used with other HIV medicines, tenofovir disoproxil fumarate may reduce At baseline, mean BMD Z-scores in subjects randomized to tenofovir disoproxil furnarate 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. • New onset or worsening renal impairment: Can include ritonavir increases tenofovir concentrations. Monitor for From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of tenofovir disoproxil fumarate + EMTRIVA the amount of HIV in your blood (called "viral load"). Tenofovir disoproxil fumarate acute renal failure and Fanconi syndrome. Assess estimated In clinical trials in HIV-1 infected adults, tenofovir disoproxil fumarate was associated with slightly greater decreases in bone In subjects receiving tenofovir disoproxil furnarate for 72 weeks, the mean change in BMD Z-score was -0.05 for lumbar spin creatinine clearance before initiating treatment with Tenofovir -----USE IN SPECIFIC POPULATIONS-may also help to increase the number of CD4 (T) cells in your blood which help disoproxil fumarate. In patients at risk for renal dysfunction,

• Nursing mothers: Women infected with HIV should be : Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculopapular, rash pruritic, and rash vesicula d = 0.15 for total body compared to ± 0.07 and ± 0.06 , respectively, in subjects receiving placebo. As observed in pediatric studies of HIV Laboratory Abnormalities: Laboratory abnormalities observed in this trial were generally consistent with those seen in previous trials infected patients, skeletal growth (height) appeared to be unaffected [See Warnings and Precautions (5.6)]. to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving tenofovir disoproxil fight off other infections. Reducing the amount of HIV and increasing the CD4 (T) cell assess estimated creatinine clearance, serum phosphorus, instructed not to breast feed. (8.3) fumarate ISee Adverse Reactions (6.1)]. urine glucose and urine protein before initiating treatment 6.2 Postmarketing Experience with tenofovir disoproxil fumarate and periodically during Table 7 Significant Laboratory Abnormalities Reported in ≥1% of Subjects in Any Treatment Group in Study 934 (0–144 Weeks) count may improve your immune system. This may reduce your risk of death e following adverse reactions have been identified during postapproval use of tenofovir disoproxil fumarate. Because postmarketing reaction 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 are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal or infections that can happen when your immune system is weak (opportunistic 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 relationship to drug exposure with concurrent or recent use of nephrotoxic drugs. (5.2) N = 257N = 254hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be allergic reaction, including angiodem • Tenofovir disoproxil fumarate does not cure HIV infection or AIDS. People taking unaffected [See Adverse Reactions (6.1)]. FULL PRESCRIBING INFORMATION: CONTENTS* 8 USE IN SPECIFIC POPULATIONS Metabolism and Nutrition Disorders tenofovir disoproxil fumarate may still develop infections or other conditions Fasting Cholesterol (>240 mg/dL) WARNING: POST TREATMENT EXACERBATION OF HEPATITIS 22% lactic acidosis, hypokalemia, hypophosphatem 8.1 Pregnancy and future fracture risk are unknown. Assessment of BMD should be considered for adults and pediatric patients who have a history of associated with HIV infection. 8.3 Nursing Mothers Respiratory, Thoracic, and Mediastinal Disorders 1 INDICATIONS AND USAGE pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and (M: >990 U/L; F: >845 U/L) 8.4 Pediatric Use vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate You must stay on continuous HIV therapy to control infection and decrease 1.1 HIV-1 Infection 8.5 Geriatric Use 1.2 Chronic Hepatitis B consultation should be obtained. 8.6 Patients with Impaired Renal Function HIV-related illnesses. Mineralization Defects: pancreatitis, increased amylase, abdominal pain DOSAGE AND ADMINISTRATION Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which 10 OVERDOSAGE Hepatobiliary Disorders It is very important that you stay under the care of your healthcare provider. 2.1 Recommended Dose in Adults and Pediatric Patients AST (M: >180 U/L, F: >170 U/L may contribute to fractures, have been reported in association with the use of tenofovir disoproxil fumarate [See Adverse hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT) 12 Years of Age and Older (35 kg or more) 11 DESCRIPTION actions (6.2)]. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. • It is not known if tenofovir disoproxil fumarate is safe and effective for the treatment AIT (M: >215 U/L: F: >170 U/L) Skin and Subcutaneous Tissue Disorders 2.2 Recommended Dose in Pediatric Patients 2 Years to Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of 12 CLINICAL PHARMACOLOG of HIV-1 infection in children under the age of 2 years. Hemoglobin (<8.0 mg/dL) Less than 12 Years of Age renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing 12.1 Mechanism of Action tenofovir DF [See Warnings and Precautions (5.2)]. 2.3 Dose Adjustment for Renal Impairment in Adult lyperglycemia (>250 ma/dL) 2. to treat chronic (long-lasting) hepatitis B virus (HBV) in people 12 years of age and older. rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy 5.7 Immune Reconstitution Syndrome 3 DOSAGE FORMS AND STRENGTHS 12.4 Microbiology reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy. Renal and Urinary Disorders Tenofovir disoproxil fumarate will not cure HBV. 13 NONCLINICAL TOXICOLOGY 4 CONTRAINDICATIONS including tenofovir disoproxil fumarate. During the initial phase of combination antiretroviral treatment, patients whose Glycosuria (≥3+) acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute .1 Carcinogenesis, Mutagenesis, Impairment of Fertility Tenofovir disoproxil fumarate may lower the amount of HBV in your body. immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria WARNINGS AND PRECAUTIONS 13.2 Animal Toxicology and/or Pharmacology bacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia (PCP), or tuberculosis], which may 5.1 Exacerbation of Hepatitis after Discontinuation of General Disorders and Administration Site Conditions Tenofovir disoproxil fumarate may improve the condition of your liver. Fasting Triglycerides (>750 mg/dL necessitate further evaluation and treatment. 14 CLINICAL STUDIES 1 Clinical Efficacy in Adults with HIV-1 Infection • The long-term effects of taking tenofovir disoproxil fumarate for treatment of chronic Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting

a. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of tenofovir disoproxil fumarate + EMTRIVA with 5.2 New Onset or Worsening Renal Impairment The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: 5.3 Lactic Acidosis/Severe Henatomenaly with Steatosis 14.2 Clinical Efficacy in Adults with Chronic Henatitis B hepatitis B infection are not known. 5.4 Coadministration with Other Products 16 HOW SUPPLIED/STORAGE AND HANDLING Clinical trials in HIV-infected subjects have demonstrated that certain regimens that only contain three nucleoside reverse Treatment-Emergent Adverse Reactions: The adverse reactions seen in treatment experienced subjects were generally consistent with 7 DRUG INTERACTIONS It is not known if tenofovir disoproxil fumarate is safe and effective for treatment of transcriptase inhibitors (NRTI) are generally less effective than triple drug energemens 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 17 PATIENT COUNSELING INFORMATION 5.6 Bone Effects chronic hepatitis B in children under the age of 12 years. 5.7 Immune Reconstitution Syndrome * Sections or subsections omitted from the full prescribing of resistance substitutions have been reported. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing A summary of moderate to severe, treatment-emergent adverse reactions that occurred during the first 48 weeks of Study 907 is provided in 7.1 Didanosine What should I tell my healthcare provider before taking tenofovir disoproxil fumarate 5.8 Early Virologic Failure information are not listed ADVERSE REACTIONS this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued Table 8 Selected Treatment-Emergent Adverse Reactions^a (Grades 2–4) Reported in ≥3% in Any Treatment Group in Study 907 (0–48 Weeks) ADVERSE REACTIONS 6.1 Adverse Reactions from Clinical Trials Experience in patients who develop didanosine-associated adverse reactions. The following adverse reactions are discussed in other sections of the labeling: Before you take tenofovir disoproxil fumarate tablet, tell your healthcare provider if you: When administered with tenofovir disoproxil furnarate, 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 6.2 Postmarketing Experience Severe Acute Exacerbation of Hepatitis [See Boxed Warning, Warnings and Precautions (5.1)]. Tenofovir disoproxil DRUG INTERACTIONS have liver problems, including hepatitis B (HBV) infection. New Onset or Worsening Renal Impairment [See Warnings and Precautions (5.2)]. Tenofovir disoproxil (N=182)fumarate (N=368) fumarate (N=368) fumarate (N=170) • Lactic Acidosis/Severe Hepatomegaly with Steatosis [See Boxed Warning, Warnings and Precautions (5.3)]. (Week 0-24) (Week 0-24) (Week 0-48) observed in patients receiving tenofovir disoproxil fumarate with didanosine 400 mg daily. have kidney problems. 7.2 HIV-1 Protease Inhibitor Bone Effects [See Warnings and Precautions (5.6)] n patients weighing greater than 60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered 7.3 Hepatitis C Antiviral Agents • Immune Reconstitution Syndrome [See Warnings and Precautions (5.7)] have bone problems. with tenofovir disoproxil fumarate. In patients weighing less than 60 kg, the didanosine dose should be reduced to 200 mg once 7.4 Drugs Affecting Renal Function daily when it is coadministered with tenofovir disoproxil furnarate. When coadministered, tenofovir disoproxil furnarate and didanosine EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat). For additional have any other medical conditions, including HIV infection. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be information on coadministration of tenofovir disproxil fumarate and didanosine, please refer to the full prescribing information FULL PRESCRIBING INFORMATION firectly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. are pregnant or plan to become pregnant. It is not known if tenofovir disoproxil Clinical Trials in Adult Patients with HIV-1 Infection Abdominal pain fumarate tablet will harm your unborn baby. WARNING: POST TREATMENT EXACERBATION OF HEPATITIS 7.2 HIV-1 Protease Inhibitors More than 12,000 subjects have been treated with tenofovir disoproxil fumarate alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in clinical trials and expanded access programs. A total of 1,544 subjects have received tenofovir disoproxil fumarate 300 mg once daily in clinical trials; over 11,000 subjects have received tenofovir Tenofovir disoproxil fumarate decreases the AUC and C... of atazanavir (See Clinical Pharmacology (12.3)]. When coadministered with Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis Chest pain **Pregnancy Registry.** There is a pregnancy registry for women who take antiviral tenofovir disoproxil furnarate, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Tenofovir disoproxil furnarate should not be coadministered with atazanavir without ritonavir. B therapy, including tenofovir disoproxil fumarate. Hepatic function should be monitored closely with both clinical medicines during pregnancy. Its purpose is to collect information about the health of and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including disoproxil fumarate in expanded access programs. tenofovir disoproxil fumarate. If appropriate, resumption of anti-hepatitis B therapy may be warranted [See Warnings Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase The most common adverse reactions (incidence greater than or equal to 10%, Grades 2-4) identified from any of the 3 large you and your baby. Talk to your healthcare provider about how you can take part in tenofovir concentrations [See Clinical Pharmacology (12.3)]. Tenofovir disoproxil furnarate is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir disoproxil furnarate is co-administered with an inhibitor of these controlled clinical trials include rash, diarrhea, headache, pain, depression, asthenia, and nausea. INDICATIONS AND USAGE Treatment-Naïve Patients transporters, an increase in absorption may be observed. Patients receiving tenofovir disoproxil furnarate concomitantly with lopinavir/ritonavi Study 903 - Treatment-Emergent Adverse-Reactions: The most common adverse reactions seen in a double-blind comparative controlled are breastfeeding or plan to breastfeed. Do not breastfeed if you are taking 1.1 HIV-1 Infection ionavir-boosted atazanavir, or ritonavir-boosted darunavir should be monitored for tenofovir disoproxil fumarate -associated adverse Tenofovir disoproxil fumarate is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in trial in which 600 treatment-naïve subjects received tenofovir disoproxil fumarate (N=299) or stavudine (N=301 in combination with reactions. Tenofovir disoproxil furnarate should be discontinued in patients who develop tenofovir disoproxil furnarate-associated adverse tenofovir disoproxil fumarate tablets. Tenofovir passes into your breast milk. You amivudine and efavirenz for 144 weeks (Study 903) were mild to moderate gastrointestinal events and dizziness adults and pediatric patients 2 years of age and older. Mild adverse reactions (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea, and nausea. Selected should not breastfeed because of the risk of passing HIV to your baby. Talk to your The following points should be considered when initiating therapy with tenofovir disoproxil fumarate for the treatment of HIV-1 7.3 Hepatitis C Antiviral Agents treatment-emergent moderate to severe adverse reactions are summarized in Table 4. Coadministration of tenofovir disoproxil furnarate and EPCLUSA® (sofosbuvir/velpatasvir) or HARVONI (ledipasvir/sofosbuvir) has been shown healthcare provider about the best way to feed your baby. Table 4 Selected Treatment-Emergent Adverse Reactions^a (Grades 2-4) Reported in ≥5% in Any Treatment Group in Study 903 to increase tenofovir exposure [See Clinical Pharmacology (12.3)]. Tenofovir disoproxil fumarate should not be used in combination with ATRIPLA®, COMPLERA®, DESCOVY®, GENVOYA® Pneumonia ODEFSEY®, STRIBILD®, TRUVAD® or VEMLIDY® [See Warnings and Precautions (5.4)]. In patients receiving Tenofovir disoproxil fumarate concomitantly with EPCLUSA, monitor for adverse reactions associated with tenofovir DF. Tell your healthcare provider about all the medicines you take, including prescription and 1.2 Chronic Hepatitis B Tenofovir disoproxil fumarate + 3TC + EFV d4T + 3TC + EFV Depression In patients receiving tenofovir disoproxil furnarate concomitantly with HARVONI without an HIV-1 protease inhibitor/ritonavir or an non-prescription medicines, vitamins and herbal supplements. ovir disoproxil fumarate is indicated for the treatment of chronic hepatitis B in adults and pediatric patients 12 years of age and HIV-1 protease inhibitor/cobicistat combination, monitor for adverse reactions associated with tenofovir disoproxil fumarate. Tenofovir disoproxil fumarate tablet may affect the way other medicines work, and other Peripheral neuropathy In patients receiving tenofovir disoproxil fumarate concomitantly with HARVONI and an HIV-1 protease inhibitor/ritonavir or an The following points should be considered when initiating therapy with tenofovir disoproxil fumarate for the treatment of HBV infection: Body as a Whole HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofov medicines may affect how tenofovir disoproxil fumarate tablet works. • The indication in adults is based on safety and efficacy data from treatment of subjects who were nucleoside-treatment-naïve 17% concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with and subjects who were treatment-experienced with documented resistance to lamivudine. Subjects were adults with tenofovir disoproxil fumarate. Do not take tenofovir disoproxil fumarate tablet if you also take: Rash event^c HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease [See Clinical Studies (14.2)]. 7.4 Drugs Affecting Renal Function Sweating • other medicines that contain tenofovir (ATRIPLA®, COMPLERA®, DESCOVY®. • Tenofovir disoproxil fumarate was evaluated in a limited number of subjects with chronic hepatitis B and decompensated 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 Abdominal pain 12% liver disease, [See Adverse Reactions (6.1), Clinical Studies (14.2)]. GENVOYA®, ODEFSEY®, STRIBILD®, TRUVADA®, VEMLIDY®) Myalgia • The numbers of subjects in clinical trials who had adefovir resistance-associated substitutions at baseline were too small to Back pain 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)]. adefovir (HEPSERA®) reach conclusions of efficacy [See Microbiology (12.4), Clinical Studies (14.2)]. Asthenia Weight loss In the treatment of chronic hepatitis B, tenofovir disoproxil fumarate should not be administered in combination with HEPSERA (adefovir 2 DOSAGE AND ADMINISTRATION igestive System Especially tell your healthcare provider if you take the following medications. a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug. 2.1 Recommended Dose in Adults and Pediatric Patients 12 Years of Age and Older (35 kg or more) Diarrhea 11% Peripheral neuropathy includes peripheral neuritis and neuropathy. didanosine (Videx, Videx EC) 8 USE IN SPECIFIC POPULATIONS For the treatment of HIV-1 or chronic hepatitis B: The dose is one 300 mg tenofovir disoproxil fumarate tablet once daily taken orally, c. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash atazanavir (Reyataz) Dyspepsia Laboratory Abnormalities: Laboratory abnormalities observed in this trial occurred with similar frequency in the tenofovir disoproxil fumarate and In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. Safety and efficacy in pediatric patients with There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of darunavir (Prezista) Vomiting placebo-treated groups. A summary of Grade 3-4 laboratory abnormalities is provided in Table 9. chronic hepatitis B weighing less than 35 kg have not been established Table 9 Grade 3-4 Laboratory Abnormalities Reported in ≥1% of Tenofovir Disoproxil Fumarate-Treated Subjects in Study 907 (0-48 Weeks) human response, tenofovir disoproxil fumarate should be used during pregnancy only if clearly needed. 2.2 Recommended Dose in Pediatric Patients 2 Years to Less than 12 Years of Age Metabolic Disorders lopinavir with ritonavir (Kaletra) 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 1-800-258-426 ledipasvir with sofosbuvir (HARVONI®) For the treatment of HIV-1 in pediatric patients 2 years of age and older the recommended oral dose of tenofovir disoproxil Placebo (N=182) Tenofovir disoproxil fumarate (N=368) Tenofovir disoproxil fumarate tablet is 8 mg of tenofovir disoproxil fumarate per kilogram of body weight (up to a maximum of 300 mg) once Risk Summary fumarate (N=368) sofosbuvir with velpatasvir (EPCLUSA) daily administered as oral tablets. fumarate (N=170) (Week 0-24) (Week 0-24) (Week 0-48) 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 (Week 24-48) Tenofovir disoproxil fumarate is available as tablets in 300 mg strengths for pediatric patients who weigh greater than or equal to Know the medicines you take. Keep a list of them to show your healthcare provider or Myalgia comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. 17 kg and who are able to reliably swallow intact tablets. The dose is one tablet once daily taken orally, without regard to food. Any ≥ Grade 3 Laboratory 38% 34% 25% 35% Jervous System 8.3 Nursing Mothers pharmacist when you get a new medicine. Tables 2 contain dosing recommendations for tenofovir disoproxil fumarate tablets based on body weight. Weight should be Depression 11% Triglycerides (>750 mg/dL) How should I take tenofovir disoproxil fumarate tablet? to avoid risking postnatal transmission of HIV-1. Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum Insomnia 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 Table 2 Dosing Recommendations for Pediatric Patients ≥2 Years of Age and Weighing ≥17 kg Using Tenofovir disoproxil 14% 12% 12% See "What is the most important information I should know about tenofovir disoproxil (M: >990 U/L; F: >845 U/L) breast-feed if they are receiving tenofovir disoproxil furnarate. Peripheral neuropathy Serum Amylase (>175 U/I Body Weight Kilogram (kg) Tablets Once Daily Anxiety Take tenofovir disoproxil fumarate tablet exactly as your healthcare provider tells you to Pediatric Patients 2 Years of Age and Older with HIV-1 infection The safety of tenofovir disoproxil furnarate in pediatric patients aged 2 to less than 18 years is supported by data from two AST (M: >180 U/L: F: >170 U/L) 3% 4% randomized trials in which tenofovir disoproxil furmarate 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 Pneumonia Safety and efficacy of tenofovir disoproxil fumarate in patients younger than 12 years of age have not been established. Take tenofovir disoproxil fumarate tablet at the same time every day. ALT (M: >215 U/L; F: >170 U/L) 2% 4% in and Appendage: 2.3 Dose Adjustment for Renal Impairment in Adults similar to that found to be safe and effective in adult clinical trials [See Clinical Pharmacology (12.3)]. Adults and children 12 years of age and older, the usual dose of tenofovir disoproxil Significantly increased drug exposures occurred when tenofovir disoproxil furnarate was administered to subjects with moderate to severe renal impairment [see Clinical Pharmacology (12.3)]. Therefore, the dosing interval of tenofovir disoproxil furnarate Serum Glucose (>250 U/L) 4% In Study 352, 92 treatment-experienced subjects 2 to less than 12 years of age with stable, virologic suppression on fumarate is one 300 mg tablet each day. Neutrophils (<750/mm³) 2% stavudine-or zidovudine-containing regimen were randomized to either replace stavudine or zidovudine with tenofovi tablets 300 mg should be adjusted in patients with baseline creatinine clearance below 50 mL/min using the recommendations Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug. disoproxil furmarate (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 furmarate N=4, original regimen N=1) but are not included in the efficacy in Table 3. 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. • If you are an adult with kidney problems, your healthcare provider may tell you to take b Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome. 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 Peripheral neuropathy includes peripheral neuritis and neuropathy analysis. After 48 weeks, all eligible subjects were allowed to continue in the study receiving open-label tenofovir disoproxi tenofovir disoproxil fumarate tablets less often. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients furnarate. At Week 48, 89% of subjects in the tenofovir disoproxil furnarate 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 ^d Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash. 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 • For children 2 to 12 years of age, your healthcare provider will prescribe the right dose of Laboratory Abnormalities: With the exception of fasting cholesterol and fasting triglyceride elevations that were more common these patients [See Warnings and Precautions (5.2)]. There are no data to recommend use of Tenofovir disoproxil furnarate tablets randomized phase of the study, 1 subject in the tenofovir disoproxil furnarate group discontinued the study prematurely because of virologic failure/lack of efficacy and 3 subjects (2 subjects in the tenofovir disoproxil furnarate group and 1 subject 300 mg in patients with renal impairment in the stayudine group (40% and 9%) compared with tenofovir disoproxil fumarate (19% and 1%) respectively, laboratory who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical trials in adults. tenofovir disoproxil fumarate tablets based on your child's body weight. abnormalities observed in this trial occurred with similar frequency in the tenofovir disoproxil fumarate and stavudine treatment Eighty-nine pediatric subjects (2 to less than 12 years of age) received tenofovir disoproxil furnarate in Study 352 for a median exposure No dose adjustment of tenofovir disoproxil fumarate tablets 300 mg is necessary for patients with mild renal impairment in the stavudine or zidovudine group) discontinued for other reasons. 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] • Tell your healthcare provider if your child has problems with swallowing tablets. arms. A summary of Grade 3-4 laboratory abnormalities is provided in Table 5. (creatinine clearance 50-80 mL/min). Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, In Study 321, 87 treatment-experienced subjects 12 to less than 18 years of age were treated with tenofovir disoproxil furnarate (N=45) or and urine protein should be performed in patients with mild renal impairment [See Warnings and Precautions (5.2)]. Table 5 Grades 3-4 Laboratory Abnormalities Reported in \geq 1% of Tenofovir Disoproxil Fumarate-Treated Subjects in Study 903 placebo (N=42) in combination with an optimized background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/ mm³ and the mean baseline plasma HIV-1 RNA was 4.6 log10 copies/mL. At baseline, 90% of subjects harbored NRTI resistance-associated Take tenofovir disoproxil fumarate tablets by mouth, with or without food. and Precautions (5.6)]. Table 3 Dosage Adjustment for Patients with Altered Creatinine Clearance Do not miss a dose of tenofovir disoproxil fumarate tablet. If you miss a dose of 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 furnarate compared to the placebo treatment group. Six tenofovir disoproxil furnarate 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 spine and -0.458 for total body in the 28 subjects who were treated with tenofovir disoproxil furnarate 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 furnarate in the mean rate of BMD gain in lumbar spine at Week 48 was similar between the tenofovir disoproxil furnarate in the mean rate of BMD gain in lumbar spine at Week 48 was similar between the tenofovir disoproxil furnarate in the place of the place o substitutions in their HIV-1 isolates. Overall, the trial failed to show a difference in virologic response between the tenofovir disoproxil furnarate Tenofovir disoproxil fumarate + 3TC + EFV d4T + 3TC + EFVtenofovir disoproxil fumarate tablet, take the missed dose as soon as you remember. (mL/min)^a Hemodialysis Patients 10–29 ≥50 30–49 If it is almost time for your next dose of tenofovir disoproxil fumarate tablet, do not take Any ≥ Grade 3 Laboratory Abnormality Every Every the missed dose. Take the next dose of tenofovir disoproxil fumarate tablet at your Recommended 300 mg Every 7 days or after a total of 24 hours 48 hours 72 to 96 hours the mean rate of BMID gain in lumbar spine at week 48 was similar between the tenorovir disoproxil furnarate and the 041 or AZT treatment groups. Total body BMID gain was less in the tenofovir disoproxil furnarate compared to the d4T or AZT treatment groups. One tenofovir disoproxil furnarate -treated subject and none of the d4T or AZT-treated subjects experienced significant (greater than 4%) lumbar spine BMID loss at Week 48. Changes from baseline in BMID Z scores were -0.012 for lumbar spine and -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil furnarate in pediatric patients younger than 2 years of age with HIV-1 infection have not been established. reatine Kinase (M: >990 U/L; F: >845 U/L) • If you take too much tenofovir disoproxil fumarate tablet, call your local poison control Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. Tenofovir disoproxil center or go right away to the nearest hospital emergency room.

Hematuria (>100 RBC/HPF)

670 mm x 500 mm Front side printing Page 1 of 2



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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 48-week double-blind period experienced nausea: 9% with tenofovir disoprox

PATIENT INFORMATION

Tenofovir Disoproxil Fumarate Tablets

(ten of' oh vir)

- See "What is the most important information I should know about tenofovir disoproxil
- New or worse kidney problems, including kidney failure, can happen in some people who take tenofovir disoproxil fumarate tablet. Your healthcare provider should do blood tests to check your kidneys before you start treatment with tenofovir disoproxil fumarate tablets, If you have had kidney problems in the past or need to take another medicine that can cause kidney problems, your healthcare provider may need to do blood tests to check
- your kidneys during your treatment with tenofovir disoproxil fumarate tablet. **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. Tell your healthcare provider right away if you get these symptoms: weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal
- **Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. Tell your healthcare provider right away if you get these symptoms: skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.
- Bone problems can happen in some people who take tenofovir disoproxil fumarate tablet Bone problems include bone pain, softening or thinning (which may lead to fractures).
- Your healthcare provider may need to do additional tests to check your bones. Changes in your immune system (Immune Reconstitution Syndrome) can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider if you start having new symptoms after starting your HIV medicine.

The most common side effects in all people who take tenofovir disoproxil fumarate are:

- nausea pain
- rash diarrhea weakness
- headache
- In some people with advanced HBV-infection, other common side effects may include:
- sleeping problems
- itching vomiting
- dizziness
- Tell your healthcare provider if you have any side effect that bothers you or that does not go

These are not all the possible side effects of tenofovir disoproxil fumarate tablet. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to

How should I store tenofovir disoproxil fumarate tablet?

Strides Pharma Inc at 1877-244-9825 or FDA at 1-800-FDA-1088.

- Store tenofovir disoproxil fumarate tablets at room temperature between 68 °F to 77 °F (20 °C to 25 °C).
- Keep tenofovir disoproxil fumarate tablets in the original container. Do not use tenofovir disoproxil fumarate tablets if the seal over the bottle opening is
- broken or missing. Keep the bottle tightly closed.

Keep tenofovir disoproxil fumarate tablet and all medicines out of the reach of children. General information about tenofovir disoproxil fumarate tablet:

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use tenofovir disoproxil fumarate tablet for a condition for which it was not prescribed. Do not give tenofovir disoproxil fumarate tablet to other people, even if they have the same condition you have. It may harm them.

- Avoid doing things that can spread HIV-1 or HBV infection to others. Do not share or re-use needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- Do not have any kind of sex without protection. Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen,

A vaccine is available to protect people at risk for becoming infected with HBV. You can ask your healthcare provider for information about this vaccine.

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

You may report side effects to Strides Pharma Inc. at 1-877-244-9825 or go to www. stridesshasun.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

What are the ingredients in tenofovir disoproxil fumarate tablet? **Active Ingredient:** tenofovir disoproxil fumarate

Inactive Ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The tablets are coated with **Opadry White Y-1-7000**, which contains Hypromellose, Titanium dioxide USP & Polyethylene

glycol 400 (Macrogol) USP. This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by: Strides Shasun Limited Bengaluru, India Distributed by:

Strides Pharma Inc. East Brunswick, NJ 08816 Revised: 12/2017

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Pediatric Patients 12 Years of Age and Older with Chronic Henatitis R 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 log10 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)ideexper Thirty-one of the 32 nucleos(t)ide-experienced subjects had prior lamivadine 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 furnarate had normalized ALT at Week 72 compared to 31% (13/42) in the placebo group. One tenofovir disoproxil fumarate-treated subject

Safety and effectiveness of tenofovir disoproxil fumarate in pediatric patients younger than 12 years of age or less than 35 kg with chronic 8.5 Geriatric Use Clinical trials of tenofovir disoproxil fumarate did not include sufficient numbers of subjects aged 65 and over to determine whether they

experienced sustained HBsAq-loss and seroconversion to anti-HBs during the first 72 weeks of study participation.

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. 8.6 Patients with Impaired Renal Function 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), Clinical Pharmacology (12.3)]. Limited clinical experience at doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available. In Study 901.

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.

Tenofovir disoproxil fumarate (a prodrug of tenofovir) is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. In vivo tenofovir disoproxil furnarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine Tenofovir exhibits activity against HIV-1 reverse transcriptase. The chemical name of tenofovir disoproxil fumarate is 9-[(R)-2- [[bis[[(isopropoxycarbor

propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$ and a molecular weight of 635.52. It has the following

Tenofovir disoproxil fumarate is available as tablets. Tenofovir disoproxil furnarate tablets are for oral administration in strength of 300 mg of tenofovir disoproxil furnarate, which is equivalent to 245 mg of tenofovir disoproxil. Each tablet contains the following inactive ingredients: crosscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The tablets are coated with **Opadry White Y-1-7000**, which

In this insert, all dosages are expressed in terms of tenofovir disoproxil fumarate except where otherwise noted 12 CLINICAL PHARMACOLOGY

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

contains Hypromellose, Titanium dioxide USP & Polyethylene glycol 400 (Macrogol) USP.

pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. enofovir 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 (C_{max}) are achieved in 1.0 \pm 0.4 hrs. C_{max} and AUC values are 0.30 \pm 0.09 μ g/mL and 2.29 \pm 0.69 μ g·hr/mL, respectively. The pharmacokinetics of tenofovir are dose proportional over a tenofovir disoproxil fumarate dose range of 75 to 600 mg and are not In a single-dose bioequivalence study conducted under non-fasted conditions (dose administered with 4 oz. applesauce) in healthy adult

volunteers, the mean Cmax of tenofovir was 26% lower for the oral powder relative to the tablet formulation. Mean AUC of tenofovir was 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 μ g/mL. The volume of distribution at steady-state is 1.3 \pm 0.6 L/kg and 1.2 \pm 0.4 L/kg, following intravenous

administration of tenofovir 1.0 mg/kg and 3.0 mg/kg. In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes. Following IV administration of tenofovir approximately 70-80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of tenofovir disoproxil fumarate, the terminal elimination half-life of tenofov

is approximately 17 hours. After multiple oral doses of tenofovir disoproxil furnarate 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 furnarate 300 mg tablets following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) Administration of tendroin disportant limited so of my acidets biolowing a high-rat filed (\sim) of the control tenofovir when compared to fasted administration of the drug. Food delays the time to tenofovir ρ_{mx} by approximately 1 hour. C_{mx} and AUC of tenofovir are 0.33 \pm 0.12 μ g/mL and 3.32 \pm 1.37 μ g/hr/mL following multiple doses of tenofovir disoproxil fumarate 300 mg once daily in the fed state, when meal content was not controlled.

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

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 11). Tenofovir exposure achieved in these pediatric subjects receiving oral once daily doses of tenofovir disoproxil furnarate 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 fumarate300 mg. Table 11 Mean (\pm SD) Tenofovir Pharmacokinetic Parameters by Age Groups for HIV-1-infected Pediatric Patients

12 to <18 Years (N=8)
0.38 ± 0.13
3.39 ± 1.22
2 to less than 18 years of age) receiving oral once-daily doses of to exposures achieved in HIV-I-infected adults and adolescents

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 nd Precautions (5.2)]. In subjects with creatinine clearance below 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, and AUC_{0-x} of tenofovir were increased (Table 12). It is recommended that the dosing interval for tenofovir disoproxil furnarate be modified in patients with estimated creatinine clearance below 50 mL/min or in patients with ESRD who require dialysis [See Dosage and

le 12 Pharmacokinetic Parameters (Mean \pm SD) of Tenofovir $^{ m e}$ in Subjects with Varying Degrees of Renal Function						
Baseline Creatinine Clearance (mL/min)	>80 (N=3)	50-80 (N=10)	30-49 (N=8)	12-29 (N=11)		
C _{max} (µg/mL)	0.34 ± 0.03	0.33 ± 0.06	0.37 ± 0.16	0.60 ± 0.19		
AUC _{0-∞} (μg•hr/mL)	2.18 ± 0.26	3.06 ± 0.93	6.01 ± 2.50	15.98 ± 7.22		
CL/F (mL/min)	1043.7 ± 115.4	807.7 ± 279.2	444.4 ± 209.8	177.0 ± 97.1		
Cl (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 furnarate 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.

At concentrations substantially higher (~300-fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism

experiments and the known elimination pathway of tenofovir, the potential for CYP mediated interactions involving tenofovir with Tenofovir disoproxil furnarate has been evaluated in healthy volunteers in combination with other antiretroviral and potential concomitant drugs. Tables 13 and 14 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 furnarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Concomitant dosing of tenofovir disoproxil furnarate with didanosine significantly increases the C_{\max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil furnarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions

No clinically significant drug interactions have been observed between tenofovir disoproxil fumarate and efavirenz, methadone, nelfinavir, Table 13 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovira in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministere d Drug (mg)	N	% Change of Tenofo (90% CI)	arameters ^b	
			C _{max}	AUC	C _{min}
Atazanavir ^c	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Atazanavir/ Ritonavir ^c	300/100 once daily	12	↑ 34 (↑ 20 to ↑ 51)	↑ 37 (↑ 30 to ↑ 45)	↑ 29 (↑ 21 to ↑ 36)
Darunavir/Ritonavir ^d	300/100 twice daily	12	↑ 24 (↑ 8 to ↑ 42)	↑ 22 (↑ 10 to ↑ 35)	↑ 37 (↑ 19 to ↑ 57)
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Ledipasvir/ Sofosbuvir ^{e,f}	90/400 once daily x 10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑ 42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/ Sofosbuvir ^{e,g}		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/ Sofosbuvirh	90/400 once daily x 14 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to↑197)
Ledipasvir/ Sofosbuvir ⁱ	90/400 once daily x 10 days	14	↑ 32 (↑ 25 to ↑ 39)	↑ 40 (↑ 31 to ↑ 50)	↑ 91 (↑ 74 to ↑ 110)
Ledipasvir/ Sofosbuvirl	90/400 once daily x 10 days	29	↑ 61 (↑ 51 to ↑ 72)	↑ 65 (↑ 59 to ↑ 71)	↑ 115 (↑ 105 to ↑ 126)
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)

Saquinavir/ Ritonavir	1000/100 twice daily × 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)
Sofosbuvir ¹	400 single dose	16	↑ 25 (↑ 8 to ↑ 45)	⇔	\$
Sofosbuvir/ Velpatasvir ^m	400/100 once daily	24	↑ 55 (↑ 43 to ↑ 68)	↑ 30 (↑ 24 to ↑ 36)	↑ 39 (↑ 31 to ↑ 48)
Sofosbuvir/ Velpatasvir ⁿ	400/100 once daily	29	↑ 55 (↑ 45 to ↑ 66)	↑ 39 (↑ 33 to ↑ 44)	↑ 52 (↑ 45 to ↑ 59)
Sofosbuvir/ Velpatasvirº	400/100 once daily	15	↑ 77 (↑ 53 to ↑ 104)	↑ 81 (↑ 68 to ↑ 94)	↑ 121 (↑ 100 to ↑ 143)
Sofosbuvir/ Velpatasvir ^p	400/100 once daily	24	↑ 36 (↑ 25 to ↑ 47)	↑ 35 (↑ 29 to ↑ 42)	↑ 45 (↑ 39 to ↑ 51)
Sofosbuvir/ Velpatasvir ^q	400/100 once daily	24	↑ 44 (↑ 33 to ↑ 55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑ 76 to ↑ 92)
Sofosbuvir/ Velpatasvir ^r	400/100 once daily	30	↑ 46 (↑ 39 to ↑ 54)	↑ 40 (↑ 34 to ↑ 45)	↑ 70 (↑ 61 to ↑ 79)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑ 13 (↑ 1 to ↑ 27)	⇔	\$
Tipranavir/ Ritonavir*	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 furnarate 300 mg once daily. b. Increase $= \uparrow$; Decrease $= \downarrow$; No Effect =; NC = Not Calculated c. Revataz Prescribing Information

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

Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF h. Study conducted with ATRIPLA (efavirenz/emtricitabine/tenofovir DF) coadministered with HARVONI.

i. Study conducted with COMPLERA (emtricitabine/rilpivirine/tenofovir DF) coadministered with HARVONI. i. Study conducted with ATRIPLA coadministered with SOVALDI (sofosbuyir).

I. Study conducted with TRUVADA (emtricitabine/tenofovir DF) + dolutegravir coadministered with HARVON m.Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF. n. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF. o. Study conducted with ATRIPLA coadministered with EPCLUSA (sofosbuvir/velpatasvir). Study conducted with STRIBILD (elvitegravir/cobicistat/em q. Study conduted with COMPLERA coadministered with EPCLUSA

r. Administered as raltegravin +emtricitabine/tenofovir DF Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in distilled water at 25 °C.

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 14 Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Tenofovir Discoroxi

Coadministered	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters ^a (90% CI)			
Drug			C _{max}	AUC	C _{min}	
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	⇔	NA	
Atazanavir⁵	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° (↓ 42 to ↓ 3)	↓ 23° (↓ 46 to ↑ 10)	
Darunavir ^d	Darunavir/Ritonavir 300/100 mg 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 x 10 days	28	⇔	↑ 13 (↑ 11 to ↑ 15)	⇔	
Indinavir	800 three times daily \times 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔	
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔	
Lopinavir	Lopinavir/Ritonavir 400/100 twice		⇔	⇔	⇔	
Ritonavir	daily ×14 days	24	⇔	⇔	⇔	
Saquinavir	Saquinavir/Ritonavir 1000/100 twice	32	↑ 22 (↑ 6 to ↑ 41)	↑ 29 ^h (↑ 12 to ↑ 48)	↑ 47 ^h (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)	
Ritonavir	daily ×14 days		⇔	⇔	,	
Tacrolimus	0.05 mg/kg twice dailyx 7 days	21	⇔	⇔	⇔	
Tipropouir	Tipranavir/Ritonavir 500/100 twice daily	22	↓ 17(↓ 26 to ↓ 6)	↓ 18(↓ 25 to ↓ 9)	↓ 21(↓ 30 to ↓ 10)	
Tipranavir ⁱ	Tipranavir/Ritonavir 750/200 twice daily (23 doses)	20	↓ 11(↓ 16 to ↓ 4)	↓ 9(↓ 15 to ↓ 3)	↓ 12(↓ 22 to 0)	

a. Increase $= \uparrow$; Decrease $= \downarrow$; No Effect $= \Leftrightarrow$; NA = Not Applicable b. Revataz Prescribing Information c. In HIV-infected subjects, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone

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

12.4 Microbiology

Antiviral Activity

Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions h. Increases in AUC and C and C are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and Aptivus Prescribing Information

Mechanism of Actior 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 HB\ 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 .

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 EC₅₀ (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 agains HIV-1 clades A, B, C, D, E, F, G, and O (EC₅₀ values ranged from 0.5 μ M to 2.2 μ M) and strain specific activity against HIV-2 (EC₅₀ values ranged from 1.6 μ M to 5.5 μ M).

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 a. Subjects achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48 and 144 showed development of efavirenz and lamivadine 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 furnarate 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 furnarate 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.

HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in

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 furnarate have developed a detectable K65R substitution in their HIV-1 as analyzed through standard genotypic analysis. 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 mediated by any of the following human CYP isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of *in vitro* compared to Placebo + SBT) [See Clinical Studies (14.1)], 14/304 (5%) of the tenofovir disoproxil furnarate-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 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 o 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 M41. 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 response: to tenofovir disoproxil furmarate therapy. Subjects whose virus expressed an LT4V substitution without zidovudine resistance associated substitutions (N=8) had reduced response to tenofovir disoproxil furmarate. 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

Phenotypic analysis of baseline HIV-1 from treatment-experienced subjects (N=100) demonstrated a correlation between baseline susceptibility to tenofovir disoproxil furnarate and response to tenofov response by baseline tenofovir disoproxil fumarate susceptibility Table 15 HIV-1 RNA Response at Week 24 by Baseline Tenofovir Disoproxil Fumarate Susceptibility (Intent-To-Treat)^a Baseline Tenofovir Disoproxil Fumarate Susceptibility^b

<1	-0.74 (35			
>1 and ≤3	-0.56 (49			
>3 and ≤4	-0.3 (7)			
>4	-0.12 (9)			
ptibility 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 (DAV $\mathbf{G}_{\mathbf{24}}$) in \log_{10} copies/mL.

The antiviral activity of tenofovir against HBV was assessed in the HepG2 2.2.15 cell line. The EC_{so} values for tenofovir ranged from 0.14 to 1.5 μ M, with CC_{cc} (50% cytotoxicity concentration) values greater than 100 μ M. In cell culture combination antiviral activity studies of transcriptase inhibitor emtricitabine, no antagonistic activity was observed.

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 pre-treatment and on-treatment isolates from subjects who received at least 24 weeks of tenofovir disoproxil furnarate 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 furnarati 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 a significantly 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 16); however, no specific substitutions occurred at a sufficient frequency to be associated with resistance to tenofovir disoproxil fumarate (genotypic and phenotypic

Table 16 Amino Acid Substitutions in Viremic Subjects across HBV Trials of Tenofovir Disoproxil Fumarate

		Danamananta		
	Nucleotide-Naïve (N=417)³	HEPSERA-experienced (N=247) ^b	Lamivudine- Resistant (N=136)c	Decompensate Liver Disease (N=39) ^d
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	18/32 (56%)	119/31 (35%)	6 ^h /8 (75%)	3/5 (60%)
a. Nucleotide-naïve subjects from Studie	es 0102 (N=246) ar	nd 0103 (N=171) receivin	g up to 384 weeks of t	reatment with tend

- h HFPSFRA-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 furnarate after switching to tenofovir disoproxil furnarate from lamiyuding
- 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
- 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 The primary efficacy endpoint in both trials was complete response to treatment defined as HBV DNA <400 copies/mL (69 IU/mL)and
- 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 Table 20 Histological, Virological, Biochemical, and Serological Response at Week 48 conserved sites and 3 had substitutions only at polymorphic sites.

Cross-resistance has been observed between HBV nucleoside/nucleotide analogue reverse transcriptase inhibitors. In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204l/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/l, 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)) de 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 furnarate 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.

13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 5 times that observed in humans at the therapeutic dose.

Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil furnarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats. 13.2 Animal Toxicology and/or Pharmacology

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) 2-20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia,

14 CLINICAL STUDIES 14.1 Clinical Efficacy in Adults with HIV-1 Infection

Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicenter trial comparing tenofovir disoproxil fumarate (300 mg once daily) administered in combination with lamivudine and efavirenz versus stavudine (d4T), lamivudine, and efavirenz in 600 antiretroviral-naïve subjects. Subjects had a mean age of 36 years (range 18-64), 74% were male, 64% were Caucasian and 20% were Black. The mean baseline CD4+ cell count was 279 cells/mm³ (range 3-956) and median baseline plasma HIV-1 RNA was

DNA ≥1,000 IU/mL), and genotypic evidence of lamivudine resistance (rtM204I/V +/-rtL180M). One hundred forty-one

48 and 144 weeks are presented in Table 17 Table 17 Outcomes of Randomized Treatment at Week 48 and 144 (Study 903)

Outcomes	Tenofovir disoproxil fumarate + 3TC + EFV (N=299)	d4T + 3TC +EFV (N=301)	Tenofovir disoproxil fumarate +3TC + EFV (N=299)	d4T + 3TC + EFV (N=301)
Respondera	79%	82%	68%	62%
Virologic failure ^b	6%	4%	10%	8%
Rebound	5%	3%	8%	7%
Never suppressed	0%	1%	0%	0%
Added an antiretroviral agent	1%	1%	2%	1%
Death	<1%	1%	<1%	2%
Discontinued due to adverse event	6%	6%	8%	13%
Discontinued for other reasons ^c	8%	7%	14%	15%

b. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144

c. Includes lost to follow-up, subject's withdrawal, noncompliance, protocol violation and other reasons. Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (> or \leq 100,000 copies/mL) and CD4+ cell count (< or \geq 200 cells/mm³). Through 144 weeks of therapy, 62% and 58% of subjects in the tenofovir disoproxil fumarate and stavudine arms, respectively achieved and maintained confirmed HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4+ cell count was 263 cells/mm³ for the tenofovir disoproxil furnarate arm and 283 cells/mm³ for the stavudine arm. Through 144 weeks, 11 subjects in the tenofovir disoproxil furnarate group and 9 subjects in the stavudine group experienced

Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter trial comparing emtricitabline + tenofovir disoproxil fumarate administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naïve subjects. From Weeks 96 to 144 of the trial, subjects received a fixed-dose combination of emtricitabine and tenofovir with efavirenz in place of emtricitabine + tenofovir disoproxil fumarate with efavirenz. Subjects had a mean age of 38 years (range 18-80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline CD4+ cell count was 245 cells/mm³ (range 2-1191) and median baseline plasma HIV-1 RNA was 5.01 \log_{10} copies/mL (range 3.56-6.54). Subjects were stratified by baseline CD4+ cell count (< or \geq 200 cells/mm³);

41% had CD4+ cell counts <200 cells/mm3 and 51% of subjects had baseline viral loads >100.000 copies/mL. Treatment

outcomes through 48 and 144 weeks for those subjects who did not have efavirenz resistance at baseline are presented in Table 18.

Table 18 Outcomes of Randomized Treatment at Week 48 and 144 (Study 934)

Treatment-Experienced Adult Patients

	At Week	48	At Week 144		
Outcomes	FTC +Tenofovir disoproxil fumarate + EFV (N=244)	AZT/3TC+EFV (N=243)	FTC +Tenofovir disoproxil fumarate + EFV (N=227)°	AZT/3TC+EFV (N=229) ^a	
Responder ^b	84%	73%	71%	58%	
Virologic failure ^c	2%	4%	3%	6%	
Rebound	1%	3%	2%	5%	
Never suppressed	0%	0%	0%	0%	
Change in antiretroviral regimen	1%	1%	1%	1%	
Death	<1%	1%	1%	1%	
Discontinued due to adverse event	4%	9%	5%	12%	
Discontinued for other reasons ^d	10%	14%	20%	22%	

a. Subjects who were responders at Week 48 or Week 96 (HIV-1 RNA <400 copies/mL) but did not consent to continue the trial after the abacavir/emtricitabine/lamivudine resistance-associated M184V substitution. HIV-1 RNA responses among these subjects were durable Week 48 or Week 96 were excluded from analysis b. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144. c. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Weeks 48 and 144.

Through Week 48, 84% and 73% of subjects in the emtricitabine + tenofovir disoproxil fumarate group and the zidovudine/lamivudine the proportion of subjects who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the zidovudine/lamivudine group in this open-label trial. In addition, 80% and 70% of subjects in the emtricitabine + tenofovir disoproxil furnarate group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <50 copies/mL through Week 48 (64% and 56% through Week 144). The mean increase from baseline in CD4* cell count was 190 cells/mm³ in the EMTRIVA + tenofovir disoproxil fumarate group and 158 cells/mm³ in the zidovudine/lamivudine group at Week 48 (312 and 271 cells/mm³ at Week 144). Through 48 weeks, 7 subjects in the emtricitabine + tenofovir disoproxil furnarate group and 5 subjects in the zidovudine/lamivudine group experienced a new CDC Class C event (10 and 6 subjects through 144 weeks).

Study 907 was a 24-week, double-blind placebo-controlled multicenter trial of tenofovir disoproxil fumarate added to a stable background regimen of antiretroviral agents in 550 treatment-experienced subjects. After 24 weeks of blinded trial treatment, all subjects continuing on trial were offered open-label tenofovir disoproxil furmarate for an additional 24 weeks. Subjects had a mean baseline CD4+ cell count of 427 cells/mm3 (range 23-1385), median baseline plasma HIV-1 RNA of 2340 (range 50-75,000) copies/mL, and mean duration of prior HIV-1 treatment was 5.4 years. Mean age of the subjects was 42 years, 85% were male

The percent of subjects with HIV-1 RNA <400 copies/mL and outcomes of subjects through 48 weeks are summarized in Table 19.

Table 19 Outcomes of Randomized Treatment (Study 907)							
	0-24 we	eks	0-48 weeks	24-48 weeks Placebo Crossover to tenofovir disoproxil fumarate(N=170)			
Outcomes	Tenofovir disoproxil fumarate (N=368)	Placebo(N=182)	Tenofovir disoproxil fumarate (N=368)				
HIV-1 RNA <400 copies/mLa	40%	11%	28%	30%			
Virologic failure ^b	53%	84%	61%	64%			
Discontinued due to adverse event	3%	3%	5%	5%			
Discontinued for other reasons ^c	3%	3%	5%	1%			

a. Subjects with HIV-1 RNA < 400 copies/mL and no prior study drug discontinuation at Week 24 and 48 respectively. b. Subjects with HIV-1 RNA ≥400 copies/mL efficacy failure or missing HIV-1 RNA at Week 24 and 48 respectively.

c. Includes lost to follow-up, subject withdrawal, noncompliance, protocol violation and other reasons. At 24 weeks of therapy, there was a higher proportion of subjects in the tenofovir disoproxil fumarate arm compared to the placebo arm with HIV-1 RNA <50 copies/mL (19% and 1%, respectively). Mean change in absolute CD4+ cell counts by Week 24 was +11 cells/mm³ for the tenofovir disoproxil fumarate group and -5 cells/mm³ for the placebo group. Mean change in absolute CD4+ cell counts by Week 48 was +4 cells/mm3 for the tenofovir disoproxil furnarate group Through Week 24, one subject in the tenofovir disoproxil furmarate group and no subjects in the placebo arm experienced a new

14.2 Clinical Efficacy in Adults with Chronic Hepatitis B

HBeAg-Negative Chronic Hepatitis B Study 0102 was a Phase 3, randomized, double-blind, active-controlled trial of tenofovir disoproxil fumarate 300 mg compared to HEPSERA 10 mg in 375 HBeAg- (anti-HBe+) subjects with compensated liver function, the majority of whom were nucleoside-naïve. The mean age of subjects was 44 years, 77% were male, 25% were Asian, 65% were Caucasian, 17% had previously received alpha-interferon therapy and 18% were nucleoside-experienced (16% had prior lamivudine experience). At baseline, subjects had a

Study 0103 was a Phase 3 randomized double-blind active-controlled trial of tenofovir disoproxil fumarate 300 mg compared

to HEPSERA 10 mg in 266 HBe4g+ nucleoside-naïve subjects with compensated liver function. The mean age of subjects was 34 years, 69% were male, 36% were Asian, 52% were Caucasian, 16% had previously received alpha-interferon therapy, and <5% were nucleoside experienced. At baseline, subjects had a mean Knodell necroinflammatory score of 8.4; mean plasma HBV DNA was 8.7 log₁₀ copies /mL; and mean serum ALT was 147 U/L. The primary data analysis was conducted after all subjects reached 48 weeks of treatment and results are summarized below.

	0102 (HBeAg-)		0103 (HBeAg+)	
	Tenofovir disoproxil fumarate (N=250)	HEPSERA (N=125)	Tenofovir disoproxil fumarate (N=176)	HEPSERA (N=90)
mplete Response	71%	49%	67%	12%
stology Histological sponse ^a	72%	69%	74%	68%
BV DNA 400 copies/mL(<69 IU/mL)	93%	63%	76%	13%
T rmalized ALT ^b	76%	77%	68%	54%
rology BeAg Loss/Seroconversion	NA°	NA°	20%/19%	16%/16%
BsAg Loss/Seroconversion	0/0	0/0	3%/1%	0/0

a. Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis b. The population used for analysis of ALT normalization included only subjects with ALT above ULN at baseline.

c. NA = Not Applicable

Treatment Beyond 48 Weeks In Studies 0102 (HBeAg-negative) and 0103 (HBeAg-positive), subjects who completed double-blind treatment (389 and 196 subjects who were originally randomized to tenofovir disoproxil furnarate and HEPSERA, respectively) were eligible to roll over to open-label In Study 0102, 266 of 347 subjects who entered the open-label period (77%) continued in the study through Week 384. Among subjects randomized to tenofovir disoproxil fumarate followed by open-label treatment with tenofovir disoproxil fumarate. 73% had HBV DNA <400 copies/ml (69 IU/ml), and 63% had ALT normalization at Week 384. Among subjects randomized to HEPSERA followed by open-label treatment with tenofovir disoproxil furnarate, 80% had HBV DNA <400 copies/mL (69 IU/ml), and 63% had ALT normalization at Week 384. Among subjects randomized to HEPSERA followed by open-label treatment with tenofovir disoproxil furnarate, 80% had HBV DNA <400 copies/mL (69 IU/ml). mL) and 70% had ALT normalization through Week 384. At Week 384, both HBsAg loss and seroconversion were approximatel

In Study 0103, 146 of 238 subjects who entered the open-label period (61%) continued in the study through Week 384. Among subjects randomized to tenofovir disoproxil fumarate, 49% had HBV DNA <400 copies/mL (69 IU/mL), 42% had ALT normalizatio and 20% had HBeAg loss (13% seroconversion to anti-HBe antibody) through Week 384. Among subjects randomized to HEPSERA followed by open-label treatment with tenofovir disoproxil fumarate, 56% had HBV DNA <400 copies/mL (69 IU/mL), 50% had ALT normalization, and 28% had HBeAg loss (19% seroconversion to anti-HBe antibody) through Week 384. At Week 384, HBsAg loss Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs)

and seroconversion were 11% and 8% respectively, in subjects initially randomized to tenofovir disoproxil fumarate and 12% and 10%,

respectively, in subjects initially randomized to HEPSERA. Of the originally randomized and treated 641 subjects in the two studies, liver biopsy data from 328 subjects who received continuing open-label treatment with tenofovir disoproxil fumarate monotherapy were available for analysis at baseline, Week 48 and Week 240. There were no apparent differences between the subset of subjects who had liver biopsy data at Week 240 and those subjects remaining on open-label tenofovir disoproxil furnarate without biopsy data that would be expected to affect histological outcomes at Week 240. Among the 328 subjects evaluated, the observed histological response rates were 80% and 88% at Week 48 and Week 240, respectively. In the subjects without cirrhosis at baseline (Ishak fibrosis score 0.4), 92% (216/235) and 95% (223/235) had either improvement or no change in Ishak fibrosis score at Week 48 and Week 240, respectively. In subjects with cirrhosis at baseline (Ishak fibrosis score 5-6), 97% (90/93) and 99% (92/93) had either improvement or no change in Ishak fibrosis score at Week 48 and Week 240, respectively. Twenty-nine percent (27/93) and 72% (67/93) of subjects with cirrhosis at baseline experienced regression of cirrhosis by Week 48 and Week 240, respectively with a reduction in Ishak fibrosis score of at least 2 points. No definitive conclusions can be established about the remaining study population who were not part of this subset analysis.

Patients with Lamivudine-Resistant Chronic Hepatitis B Study 121 was a randomized, double-blind, active-controlled trial evaluating the safety and efficacy of tenofovir disporoxil 20% were Black. The mean baseline UD4* cell count was 279 cells/mill (large 6-950) and median baseline planta inter-count was 279 cells/mill (large 6-950) and median baseline planta inter-count was 279 cells/mill (large 417-5,130,000). Subjects were stratified by baseline HIV-1 RNA and CD4* cell count. Forty-three percent of subjects had baseline viral loads >100,000 copies/mL and 39% had CD4* cell counts <200 cells/mm³. Treatment outcomes through subjects were HBeAg-negative, 46% were HBeAg-positive, and 56% had abnormal ALT, Subjects had a mean HBV DNA of 6.4 log., copies/ mL and mean serum ALT of 71 U/L at baseline After 96 weeks of treatment, 126 of 141 subjects (89%) randomized to tenofovir disoproxil fumarate had HBV DNA <400

copies/mL (69 IU/mL), and 49 of 79 subjects (62%) with abnormal ALT at baseline had ALT normalization. Among the HBeAg-positive subjects randomized to tenofovir disoproxil furnarate, 10 of 65 subjects (15%) experienced HBeAg loss, and 7 of 65 subjects (11%) experienced anti-HBe seroconversion through Week 96. The proportion of subjects with HBV DNA concentrations below 400 copies/mL (69 IU/mL) at Week 96 was similar between the tenofovir disoproxil fumarate monotherapy and the comparator arms. Across the combined chronic hepatitis B treatment trials, the number of subjects with adefovir-resistance associated substitutions

at baseline was too small to establish efficacy in this subgroup. Patients with Chronic Hepatitis B and Decompensated Liver Disease Tenofovir disoproxil furnarate was studied in a small randomized, double-blind, active-controlled trial evaluating the safety of tenofovir disoproxil furnarate compared to other antiviral drugs in subjects with chronic hepatitis B and decompensated liver disease through 48 weeks (Study 0108). Forty-five adult subjects (37 males and 8 females) were randomized to the tenofovir disoproxil furnarate treatment arm. At baseline, 69% subjects were HBeAg-negative, and 31% were HBeAg-positive. Subjects had a mean Child-Pugh score of 7, a mean MELD score of 12, mean HBV DNA of 5.8 \log_{10} copies/mL and mean serum ALT of 61 U/L at baseline. Trial endpoints were discontinuation due to an adverse event and confirmed increase in serum creatinine \geq 0.5 mg/dL or confirmed serum phosphorus of

< 2 mg/dL. [See Adverse Reactions (6.1)]. At 48 weeks, 31/44 (70%) and 12/26 (46%) tenofovir disoproxil furnarate-treated subjects achieved an HBV DNA <400 copies/mL (69 IU/mL), and normalized ALT, respectively. The trial was not designed to evaluate treatment impact on clinical endpoints such as progression of liver disease, need for liver transplantation, or death. 16 HOW SUPPLIED/STORAGE AND HANDLIN

Tenofovir Disoproxil Furnarate Tablets 300 mg are white circular film-coated convex tablets containing 300 mg of tenofovir

disoproxil furnarate, which is equivalent to 245 mg of tenofovir disoproxil, engraved TDF on one side and plain on other side and are available in a 40 cc/50 cc HDPE container containing a desiccant (silica gel sachet) and closed with child-resistant screw cap.: Bottle of 30 tablets (NDC 64380-714-04) Store tenofovir disoproxil furnarate tablets at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room

17 PATIENT COUNSELING INFORMATION Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use). Tenofovir disoproxil fumarate is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with

Keep the bottle tightly closed. Dispense only in original container. Do not use if seal over bottle opening is broken or missing

HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using tenofovir disoproxil Advice patients to avoid doing things that can spread HIV or HBV to others. Do not share needles or other injection equipment • Do not share personal items that can have blood or body fluids on them, liketoothbrushes and razor blades. • Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the

• Do not breastfeed. Tenofovir is excreted in breast milk and it is not known whether it can harm the baby. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk The long term effects of tenofovir disoproxil fumarate are unknown. Tenofovir disoproxil fumarate tablets are for oral ingestion only.

chance of sexual contact with semen, vaginal secretions, or blood.

. If you have HIV-1 infection, with or without HBV coinfection, it is important to take tenofovir disoproxil furnarate tablets with combination • It is important to take tenofovir disoproxil fumarate tablets on a regular dosing schedule and to avoid missing doses

 Severe acute exacerbations of hepatitis have been reported in patients who are infected with HBV or coinfected with HBV and HIV-1 and have discontinued tenofovir disoproxil furnarate [See Warnings and Precautions (5.1)]. Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent (e.g. high-dose or multiple NSAIDs) [See Warnings and Precautions Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with tenofovir disoproxil umarate should be suspended in any patient who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicit [See Warnings and Precautions (5.3)].

Tenofovir disoproxil fumarate should not be coadministered with ATRIPLA, COMPLERA, DESCOVY, GENVOYA, ODEFSEY, STRIBILD, TRUVADA, or VEMLIDY [See Warnings and Precautions (5.4)]. Tenofovir disoproxil furnarate should not be administered in combination with HEPSERA /See Warnings and Precautions (5.4)1. Decreases in bone mineral density have been observed with the use of tenofovir disoproxil fumarate. Bone mineral density monitorin should be considered in patients who have a history of pathologic bone fracture or at risk for osteopenia (See Warnings and Precautions group, respectively, achieved and maintained HIV-1 RNA <400 copies/mL (71% and 58% through Week 144). The difference in inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection [See Warnings and Precautions

> In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. The relationship between response and long-term prevention of outcomes such as hepatocellular carcinoma is not known

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