HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TEMIXYS safely and effectively. See full prescribing information for TEMIXYS.

TEMIXYS (lamivudine and tenofovir disoproxil fumarate) tablets, for oral use
Initial U.S. Approval: 2018

WARNING: POSTTREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine or tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.1)

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.1, 5.2, 5.4, 5.6)	10/2019
Dosage and Administration (2.1)	10/2019
Early Virologic Failure	Removed 10/2019

----------INDICATIONS AND USAGE----------

TEMIXYS, a combination of two nucleoside reverse transcriptase inhibitors (lamivudine and tenofovir disoproxil fumarate), is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg. (1)

----------DOSAGE AND ADMINISTRATION----------

- Testing: Prior to initiation and during treatment with TEMIXYS, patients should be tested for hepatitis B virus infection and HIV-1 infection. Prior to initiation and during use of TEMIXYS, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. (2.1)
- Recommended dose in adults and pediatric patients weighing at least 35 kg: One tablet once daily with or without food. (2.2)
- Renal impairment: Not recommended in patients with estimated creatinine clearance less than 50 mL/min or patients with end-stage renal disease requiring hemodialysis. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablet: 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate (3)

----------CONTRAINDICATIONS----------

- TEMIXYS is contraindicated in patients with previous hypersensitivity to any of the components of this product. (4)

----------WARNINGS AND PRECAUTIONS----------

- Co-infected HIV-1/HBV Patients: Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported. (5.1)
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Avoid administering TEMIXYS with concurrent or recent use of nephrotoxic drugs. (5.2)
- Immune reconstitution syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment (5.3)
- Decreases in bone mineral density (BMD): Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.4)
- Lactic acidosis and severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.5)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving interferon and ribavirin-based regimens. Monitor for treatment-associated toxicities. Discontinue TEMIXYS as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.7)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.8)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence greater than 10%, with lamivudine and tenofovir disoproxil fumarate) were headache, pain, depression, diarrhea, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Celltrion, Inc. at 1-844-837-6511 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Tenofovir disoproxil fumarate increases didanosine concentrations. Dose reduction and close monitoring for didanosine toxicity are warranted. (7.2)
- Coadministration decreases atazanavir concentration. When coadministered with TEMIXYS, use atazanavir given with ritonavir. (7.2)
- Coadministration of TEMIXYS with certain HIV-1 protease inhibitors or certain drugs to treat HCV increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.2)
- Sorbitol: Avoid chronic administration of sorbitol with TEMIXYS. (7.4)
- Consult Full Prescribing Information prior to and during treatment for important drug interactions. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Breastfeeding not recommended due to potential for HIV transmission. (8.2)

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

Revised: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: POSTTREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine or tenofovir disoproxil fumarate. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue TEMIXYS and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti- hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

TEMIXYS is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients weighing at least 35 kg.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation and During Treatment with TEMIXYS

Prior to initiation treatment with TEMIXYS, test patients for hepatitis B virus infection *[see Warnings and Precautions (5.1)]*.

Prior to initiation and during use of TEMIXYS, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus *[see Warnings and Precautions (5.2)]*.

2.2 Recommended Dose for Adult and Pediatric Patients Weighing at Least 35 kg

TEMIXYS is a two-drug fixed-dose combination product containing 300 mg of lamivudine (3TC) and 300 mg of tenofovir disoproxil fumarate (TDF). The recommended dosage of TEMIXYS in HIV-1 infected adult and pediatric patients weighing at least 35 kg is one tablet taken orally once daily with or without food.

2.3 Not Recommended in Renal Impairment

Because TEMIXYS is a fixed-dose combination formulation and cannot be dose adjusted, it is not recommended for patients with impaired renal function (creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis *[see Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

TEMIXYS contains 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate.

The tablets are white, oblong shape, film-coated tablets debossed with “C 0” on one side and plain on the other side.

4 CONTRAINDICATIONS

TEMIXYS is contraindicated in patients with a previous hypersensitivity reaction to any of the components contained in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV

All patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy.

Posttreatment Exacerbations of Hepatitis: Discontinuation of anti-HBV therapy, including 3TC and TDF may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue TEMIXYS should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since posttreatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

If treatment with EPIVIR-HBV, TDF or a tenofovir alafenamide (TAF)-containing product is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid emergence of HIV-1 resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV-1 treatment.

5.2 New Onset or Worsening Renal Impairment

TDF, a component of TEMIXYS, is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of TDF *[see Adverse Reactions (6.2)]*.

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

Avoid TEMIXYS with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs [NSAIDs]) *[see Drug Interactions (7.1)]*. Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir disoproxil fumarate. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in patients at risk of renal dysfunction.

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including 3TC and TDF. During the initial phase of combination antiretroviral treatment, HIV-1 infected patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

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

5.4 Bone Loss and Mineralization Defects

Bone Mineral Density (BMD):

In clinical trials in HIV-1 infected adults, TDF was associated with greater decreases in BMD and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving TDF *[see Adverse Reactions (6.1)]*.

Clinical trials evaluating TDF-containing regimens in pediatric subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected pediatric subjects less than 18 years of age, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the TDF-treated HIV-1 infected pediatric subjects as compared to the control groups. In all pediatric trials, normal skeletal growth (height) was not affected for the duration of the clinical trials.

The effects of TDF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. The long-term effect of lower spine and total body BMD on skeletal growth in pediatric patients, and in particular, the effects of long-duration exposure in younger children is unknown.

Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial. Assessment of BMD should be considered for adults and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. If bone abnormalities are suspected, appropriate consultation should be obtained.

Mineralization Defects:

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

5.5 Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals. Treatment with TEMIXYS should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.6 Risk of Adverse Reactions Due to Drug Interactions

The concomitant use of TEMIXYS and other drugs may result in known or potentially significant drug interactions, some of which may lead to possible clinically significant adverse reactions from greater exposures of concomitant drugs *[see Drug Interactions (7.2)]*.

See Table 3 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with TEMIXYS; review concomitant medications during therapy with TEMIXYS; and monitor for adverse reactions associated with the concomitant drugs.

5.7 Risk of Hepatic Decompensation When Used with Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as 3TC, a component of TEMIXYS. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with 3TC in HIV-1/HCV co-infected patients *[see Clinical Pharmacology (12.3)]*, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and

interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and 3TC should be closely monitored for treatment-associated toxicities, especially hepatic decompensation.

Discontinuation of 3TC should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6). See the full prescribing information for interferon and ribavirin.

5.8 Pancreatitis

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, 3TC, a component of TEMIXYS, should be used with caution. Treatment with TEMIXYS should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

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

- Exacerbations of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.1)]*
- New onset or worsening renal impairment *[see Warnings and Precautions (5.2)]*
- Immune reconstitution syndrome *[see Warnings and Precautions (5.3)]*
- Bone Loss and Mineralization Defects *[see Warnings and Precautions (5.4)]*
- Lactic acidosis and severe hepatomegaly with steatosis *[see Warnings and Precautions (5.5)]*
- Hepatic decompensation in patient co-infected with HIV-1 and hepatitis C *[see Warnings and Precautions (5.7)]*
- Pancreatitis *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

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

Lamivudine and Tenofovir Disoproxil Fumarate

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

In Trial 903, 600 antiretroviral-naïve subjects received TDF (N=299) or stavudine (d4T) (N=301) administered in combination with lamivudine (3TC) and efavirenz (EFV) for 144 weeks. The most common adverse reactions were mild to moderate gastrointestinal events and dizziness. Mild adverse reactions (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea, and nausea. Table 1 provides the treatment-emergent adverse reactions (Grade 2-4) occurring in greater than or equal to 5% of subjects treated in any treatment group.

Table 1: Selected Adverse Reactions[a] (Grades 2-4) Reported in ≥5% in Any Treatment Group in Trial 903 (0-144 Weeks)

	TDF + 3TC + EFV	d4T + 3TC + EFV
	N=299	N=301
Rash event[b]	18%	12%
Headache	14%	17%
Pain	13%	12%
Diarrhea	11%	13%
Depression	11%	10%
Back pain	9%	8%
Nausea	8%	9%
Fever	8%	7%
Abdominal pain	7%	12%
Asthenia	6%	7%
Anxiety	6%	6%
Vomiting	5%	9%
Insomnia	5%	8%
Arthralgia	5%	7%
Pneumonia	5%	5%
Dyspepsia	4%	5%
Dizziness	3%	6%
Myalgia	3%	5%
Lipodystrophy[c]	1%	8%
Peripheral neuropathy[d]	1%	5%

[a] Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
[b] Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.
[c] Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome.
[d] Peripheral neuropathy includes peripheral neuritis and neuropathy.

Laboratory Abnormalities: Table 2 provides a list of laboratory abnormalities (Grades 3-4) observed in Trial 903. With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the d4T group (40% and 9%) compared with tenofovir disoproxil fumarate group (19% and 1%), respectively, laboratory abnormalities observed in this trial occurred with similar frequency in the tenofovir disoproxil fumarate and d4T treatment arms.

Table 2: Grades 3-4 Laboratory Abnormalities Reported in ≥1% of tenofovir disoproxil fumarate-treated subjects in Trial 903 (0-144 Weeks)

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

Pancreatitis:

Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experiences pediatric subjects receiving 3TC alone or in combination with other antiretroviral agents *[see Warnings and Precautions (5.8)]*.

Changes in Bone Mineral Density:

In HIV-1 infected adult subjects in Trial 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving TDF + 3TC + EFV (−2.2% ± 3.9) compared with subjects receiving d4T + 3TC + EFV (−1.0% ± 4.6) through 144 weeks. Changes in BMD at the hip were similar between the two treatment groups (−2.8% ± 3.5 in the TDF group vs. −2.4% ± 4.5 in the d4T group). In both groups, the majority of the reduction in BMD occurred in the first 24-48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of TDF-treated subjects vs. 21% of the d4T-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the TDF group and 6 subjects in the d4T group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone- specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide) and higher serum parathyroid hormone levels and 1,25 Vitamin D levels in the TDF group relative to the d4T group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range *[see Warnings and Precautions (5.4)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use for each of the individual components of TEMIXYS. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to 3TC and TDF.

Lamivudine

Body as a Whole: Redistribution/accumulation of body fat.

Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

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

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis *[see Warnings and Precautions (5.5)]*, posttreatment exacerbations of hepatitis B *[see Warnings and Precautions (5.1)]*.

Hypersensitivity: Anaphylaxis, urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Skin: Alopecia, pruritus.

Tenofovir disoproxil fumarate

Immune System Disorders: allergic reaction, including angioedema.

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

Respiratory, Thoracic, and Mediastinal Disorders: dyspnea.

Gastrointestinal Disorders: pancreatitis, increased amylase, abdominal pain.

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

Skin and Subcutaneous Tissue Disorders: rash.

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

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

General Disorders and Administration Site Conditions: asthenia.

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

7 DRUG INTERACTIONS

7.1 Drugs Affecting Renal Function

Tenofovir, a component of TEMIXYS, is primarily eliminated by the kidneys *[see Clinical Pharmacology (12.3)]*. Coadministration of TEMIXYS with drugs that are eliminated by active tubular secretion may increase serum concentrations of tenofovir and/or coadministered drug. Some examples include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[see Warnings and Precautions (5.2)]*. Drugs that decrease renal function may increase concentrations of tenofovir.

Do not administer TEMIXYS with HEPSERA (adefovir dipivoxil).

7.2 Established and Significant Interactions

Table 3 provides a listing of established or clinically significant drug interactions. The drug interactions described are based on studies conducted with TDF *[see Clinical Pharmacology (12.3)]*.

Table 3: Established and Significant[a] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Trials

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
NRTI: didanosine	↑ didanosine	Patients receiving TDF, a component of TEMIXYS, and didanosine should be monitored closely for didanosine-associated adverse reactions. Discontinue didanosine in patients who develop didanosine-associated adverse reactions. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving TDF with didanosine 400 mg daily. In patients weighing greater than 60 kg, reduce the didanosine dose to 250 mg when it is coadministered with TDF. In patients weighing less than 60 kg, reduce the didanosine dose to 200 mg when it is coadministered with TDF. When coadministered, tenofovir disoproxil fumarate and Videx® - EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).
HIV-1 Protease Inhibitors: Atazanavir	↓ atazanavir	When coadministered with TEMIXYS, atazanavir 300 mg should be given with ritonavir 100 mg.
lopinavir/ritonavir atazanavir/ritonavir darunavir/ritonavir	↑ tenofovir	Monitor patients receiving TEMIXYS concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir for TDF-associated adverse reactions. Discontinue TEMIXYS in patients who develop TDF-associated adverse reactions.
Hepatitis C Antiviral Agents: sofosbuvir/velpatasvir sofosbuvir/velpatasvir/ voxilaprevir	↑ tenofovir	Monitor patients receiving TEMIXYS concomitantly with EPCLUSA® (sofosbuvir/velpatasvir) for adverse reactions associated with TDF.
ledipasvir/sofosbuvir		Monitor patients receiving TEMIXYS concomitantly with HARVONI® (ledipasvir/sofosbuvir) without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination for adverse reactions associated with TDF. In patients receiving TEMIXYS concomitantly with HARVONI® and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofovir concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with TDF.

a. This table is not all inclusive.
b. ↑=Increase, ↓=Decrease

7.3 Drugs Inhibiting Organic Cation Transporters

3TC, a component of TEMIXYS, is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim) *[see Clinical Pharmacology (12.3)]*. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of 3TC.

7.4 Sorbitol

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

Lamivudine: Available data from the APR show no difference in the risk of overall major birth defects for 3TC compared to the background rate for major birth defects of 2.7% in U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) (*see Data*).

3TC produced embryonic toxicity in rabbits at a dose the produced similar human exposures as the recommended clinical dose. The relevance of animal findings to human pregnancy registry data is not known.

Tenofovir Disoproxil Fumarate: Available data from the APR show no increase in the overall risk of major birth defects with first trimester exposure for tenofovir disoproxil fumarate (TDF) (2.1%) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data).* The rate of miscarriage for individual drugs is not reported in the APR. In the U.S. general population, the estimated background risk of miscarriage in clinically recognized pregnancies is 15–20%.

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

Data

Human Data

Lamivudine: Based on prospective reports from the APR of over 11,000 exposures to 3TC during pregnancy resulting in live births (including over 4,500 exposed in the first trimester), there was no difference between lamivudine and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in the first trimester was 3.1% (95% CI: 2.6% to 3.6%).

3TC pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks gestation using 150 mg 3TC twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using 3TC 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. 3TC pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. 3TC concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that 3TC crosses the placenta in humans. Amniotic fluid concentrations of 3TC were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg per mL (150 mg twice daily) and 2.1 to 5.2 mcg per mL (300 mg twice daily).

Tenofovir Disoproxil Fumarate: Based on prospective reports from the APR exposures to TDF-containing regimens during pregnancy resulting in live births (including 3,342 exposed in the first trimester and 1,475 exposed in the second/third trimester), there was no increase in overall major birth defects with TDF compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP. The prevalence of major birth defects in live births was 2.3% (95% CI: 1.8% to 2.8%) with first trimester exposure to TDF-containing regimens, and 2.1% (95% CI: 1.4% to 3.0%) with the second/third trimester exposure to TDF-containing regimens.

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

Animal Data

Lamivudine: Studies in pregnant rats showed that 3TC is transferred to the fetus through the placenta. Reproduction studies with orally administered 3TC have been performed in rats and rabbits at doses producing plasma levels up to approximately 35 times that for the recommended adult HIV dose. No evidence of teratogenicity due to 3TC was observed. Evidence of early embryo-lethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans.

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

8.2 Lactation

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

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

Lamivudine: 3TC is excreted into human milk. Samples of breast milk obtained from 20 mothers receiving 3TC monotherapy 300 mg twice daily (2 times the dose in TEMIXYS) had measurable concentrations of 3TC. There is not information on the effects of 3TC on the breastfed infant or the effects of 3TC on milk production.

Tenofovir Disoproxil Fumarate: Based on published data, tenofovir has been shown to be present in human breast milk. It is not known if tenofovir affects milk production or has effects on the breastfed child.

8.4 Pediatric Use

The safety and effectiveness of TEMIXYS as a fixed dose formulation in pediatric patients infected with HIV-1 and weighing at least 35 kg have been established based on clinical studies using the individual components (lamivudine and tenofovir disoproxil fumarate).

8.5 Geriatric Use

Clinical trials of lamivudine and tenofovir disoproxil fumarate did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, caution

should be exercised in administration of TEMIXYS in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

8.6 Renal Impairment

TEMIXYS is not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis because it is a fixed-dose combination formulation that cannot be adjusted *[see Dosage and Administration (2.3)]*.

10 OVERDOSAGE

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

Lamivudine: There is no known specific treatment for overdose with 3TC. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. Because a negligible amount of 3TC was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a 3TC overdose event.

Tenofovir Disoproxil Fumarate: Limited clinical experience at doses higher than the therapeutic dose of TDF is available.

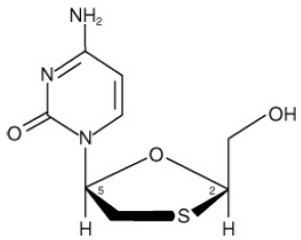
Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of TDF, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

11 DESCRIPTION

TEMIXYS is for oral administration. Each film coated tablet contains 300 mg of Lamivudine USP (also known as 3TC) and 300 mg of tenofovir disoproxil fumarate or tenofovir DF, a fumaric acid salt of bis-isopropoxycabonyloxymethyl ester prodrug of tenofovir (equivalent to 245 mg of tenofovir disoproxil), as active ingredients. In addition, each tablet contains the following inactive ingredients: cellactose 80 (lactose monohydrate and powdered cellulose), colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, and a film-coating which contains hypromellose, polyethylene glycol and titanium dioxide.

Lamivudine

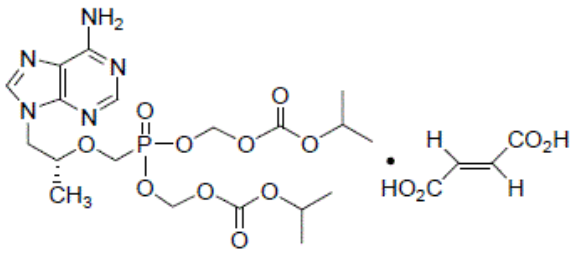
Lamivudine, a synthetic nucleoside analogue with activity against HIV-1 and HBV. The chemical name of lamivudine is (-)-1-[(2*R*,5*S*)-2-Hydroxymethyl-1,3-oxathiolan-5-yl]cytosine. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.26 g per mol. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid with solubility of approximately 70 mg per mL in water at 20 °C.

Tenofovir Disoproxil Fumarate

The chemical name of tenofovir DF is 9-[(R)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy] phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



Tenofovir DF is a white to off-white crystalline powder with a solubility of 13.4 mg per mL in distilled water at 25°C. It has an octanol/phosphate buffer (pH 6.5) partition coefficient (log p) of 1.25 at 25°C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TEMIXYS is fixed dose combination of antiviral drugs, 3TC, 300 mg and TDF, 300 mg with antiviral activity against HIV-1 *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Lamivudine: After oral administration of 2 mg/kg of 3TC twice a day to 9 adults with HIV-1, the peak serum 3TC concentration (C_{max}) was 1.5 ± 0.5 mcg/mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0.25 to 10 mg/kg and absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the 150-mg tablet and 87% ± 13% for the oral solution. Binding of 3TC to human plasma proteins is low (< 36%). Within 12 hours after a single oral dose of 3TC in 6 HIV-1-infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. The majority of 3TC is eliminated unchanged in urine by active organic cationic secretion and the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours in most single-dose studies with serum sampling for 24 hours after dosing.

Tenofovir disoproxil fumarate: Following oral administration of a single 300 mg dose of TDF to HIV-1 infected subjects in the fasted state, maximum serum concentrations (C_{max}) were achieved in 1.0 ± 0.4 hrs (mean ± SD) and C_{max} and AUC values were 296 ± 90 ng/mL and 2287 ± 685 ng•hr/mL, respectively. The oral bioavailability of tenofovir from TDF in fasted subjects is approximately 25%. Less than 0.7% of tenofovir binds to human plasma proteins *in vitro* and the binding is independent of concentration over the range of 0.01 to 25 mcg/mL. Approximately 70 to 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine.

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 243 ± 33 mL/min (mean ± SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Specific Populations

Geriatric Patients: The pharmacokinetics of lamivudine and tenofovir disoproxil fumarate have not been studied in patients over 65 years of age.

Gender: There are no significant or clinically relevant gender differences in the pharmacokinetics of lamivudine and tenofovir.

Race

Lamivudine: There are no significant or clinically relevant racial differences in 3TC pharmacokinetics.

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

Patients with Renal Impairment: [see Use in Specific Populations (8.6)].

Lamivudine: The pharmacokinetic of lamivudine are altered in subjects with impaired renal function (Table 4).

Table 4: Pharmacokinetic Parameters (Mean ± SD) after a Single 300-mg Oral Dose of 3TC in Subjects with Varying Degrees of Renal Function

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

Tenofovir Disoproxil Fumarate: The pharmacokinetics of tenofovir are altered in subjects with renal impairment *[see Warnings and Precautions (5.2)]*. In subjects with creatinine clearance below 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and $AUC_{0-\infty}$ of tenofovir were increased (Table 5).

Table 5: Pharmacokinetic Parameters (Mean ± SD) of Tenofovir in Subjects after a Single 300 mg Oral Dose of TDF in Subjects with Varying Degrees of Renal Function

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

Patients with Hepatic Impairment

Lamivudine: The pharmacokinetics of lamivudine were not altered by diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Tenofovir Disoproxil Fumarate: The pharmacokinetics of tenofovir following a 300 mg single dose of TDF have been studied in non-HIV infected subjects with moderate to severe (Child-Pugh B to C) hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects.

Assessment of Drug Interactions**:** *[see Drug Interactions (7)]*

Lamivudine

Effect of Lamivudine on the Pharmacokinetics of Other Agents: Based on *in vitro* study results, 3TC at therapeutic drug exposures is not expected to affect the pharmacokinetics of drugs that are substrates of the following

transporters: organic anion transporter polypeptide 1B1/3 (OATP1B1/3), breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K, organic cation transporter 1 (OCT1), OCT2, or OCT3.

Effect of Other Agents on the Pharmacokinetics of 3TC: 3TC is a substrate of MATE1, MATE2-K, and OCT2 *in vitro*. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase 3TC plasma concentrations. This interaction is not considered clinically significant as no dose adjustment of 3TC is needed.

3TC is a substrate of P-gp and BCRP; however, considering its absolute bioavailability (87%), it is unlikely that these transporters play a significant role in the absorption of 3TC. Therefore, coadministration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of 3TC.

Interferon Alfa: There was no significant pharmacokinetic interaction between 3TC and interferon alfa in a trial of 19 healthy male subjects *[see Warnings and Precautions (5.7)]*.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of 3TC, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and 3TC (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects *[see Warnings and Precautions (5.7)]*.

Sorbitol (Excipient): 3TC and sorbitol solutions were coadministered to 16 healthy adult subjects in an open-label, randomized-sequence, 4-period, crossover trial. Each subject received a single 300-mg dose of 3TC oral solution alone or coadministered with a single dose of 3.2 grams, 10.2 grams, or 13.4 grams of sorbitol in solution. Coadministration of 3TC with sorbitol resulted in dose-dependent decreases of 20%, 39%, and 44% in the $AUC_{(0-24)}$, 14%, 32%, and 36% in the $AUC_{(\infty)}$, and 28%, 52%, and 55% in the C_{max} of 3TC, respectively.

Trimethoprim/Sulfamethoxazole: 3TC and TMP/SMX were coadministered to 14 HIV-1-positive subjects in a single-center, open-label, randomized, crossover trial. Each subject received treatment with a single 300-mg dose of 3TC and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of 3TC 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with 3TC resulted in an increase of 43% ± 23% (mean ± SD) in lamivudine AUC_{∞}, a decrease of 29% ±13% in lamivudine oral clearance, and a decrease of 30% ± 36% in 3TC renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with 3TC. There is no information regarding the effect on 3TC pharmacokinetics of higher doses of TMP/SMX such as those used in treat PCP.

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

TDF has been evaluated in healthy volunteers in combination with other antiretroviral and potential concomitant drugs. Tables 6 and 7 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of TDF on the pharmacokinetics of coadministered drug.

TDF is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. When TDF is coadministered with an inhibitor of these transporters, an increase in absorption may be observed.

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

Table 6: Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[a] in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[b] (90% CI)		
			C_{max}	AUC	C_{min}
Atazanavir[c]	400 once daily × 14 days	33	↑14 (↑8 to ↑20)	↑24 (↑21 to ↑28)	↑22 (↑15 to ↑30)
Atazanavir/ Ritonavir [c]	300/100 once daily	12	↑34 (↑20 to ↑51)	↑37 (↑30 to ↑45)	↑29 (↑21 to ↑36)
Darunavir/ Ritonavir[d]	300/100 twice daily	12	↑24 (↑8 to ↑42)	↑22 (↑10 to ↑35)	↑37 (↑19 to ↑57)
Indinavir	800 three times daily × 7 days	13	↑14 (↓3 to ↑33)	⇔	⇔
Ledipasvir/ Sofosbuvir[e,f]	90/400 once daily × 10 days	24	↑47 (↑37 to ↑58)	↑35 (↑29 to ↑42)	↑47 (↑38 to ↑57)
Ledipasvir/ Sofosbuvir[e,g]		23	↑64 (↑54 to ↑74)	↑50 (↑42 to ↑59)	↑59 (↑49 to ↑70)
Ledipasvir/ Sofosbuvir[h]	90/400 once daily × 14 days	15	↑79 (↑56 to ↑104)	↑98 (↑77 to ↑123)	↑163 (↑132 to ↑197)
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[i]	400 single dose	16	↑25 (↑8 to ↑45)	⇔	⇔
Sofosbuvir/ Velpatasvir[j]	400/100 once daily	24	↑44 (↑33 to ↑55)	↑ 40 (↑34 to ↑ 46)	↑84 (↑76 to ↑92)
Sofosbuvir/ Velpatasvir[k]	400/100 once daily	30	↑46 (↑39 to ↑54)	↑40 (↑34 to ↑45)	↑70 (↑61 to ↑79)
Sofosbuvir/ Velpatasvir/ Voxilaprevir[l]	400/100/100 + Voxilaprevir[m] 100 once daily	29	↑48 (↑36 to ↑61)	↑39 (↑32 to ↑46)	↑47 (↑38 to ↑56)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↑13 (↑1 to ↑27)	⇔	⇔
Tipranavir/ Ritonavir[n]	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 VIREAD® 300 mg once daily.
[b] Increase = ↑; Decrease = ↓; No Effect = ⇔

[c] Reyataz® (atazanavir) Prescribing Information.
[d] Prezista® (darunavir) Prescribing Information.
[e] Data generated from simultaneous dosing with HARVONI® (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provided similar results.
[f] Comparison based on exposures when administered as atazanavir/ritonavir + FTC/TDF.
[g] Comparison based on exposures when administered as darunavir/ritonavir + FTC/TDF.
[h] Study conducted with ATRIPLA® (EFV/FTC/TDF) coadministered with HARVONI®; coadministration with HARVONI® also results in comparable increases in tenofovir exposure when tenofovir DF is administered as COMPLERA® (FTC/rilpivirine/TDF), or TRUVADA® + dolutegravir.
[i] Study conducted with ATRIPLA® coadministered with SOVALDI® (sofosbuvir).
[j] Study conducted with COMPLERA® coadministered with EPCLUSA®; coadministration with EPCLUSA® also results in comparable increases in tenofovir exposures when TDF is administered as ATRIPLA®, STRIBILD® (elvitegravir/cobicistat/FTC/TDF), TRUVADA® + atazanavir/ritonavir, or TRUVADA® + darunavir/ritonavir.
[k] Administered as raltegravir + FTC/TDF.
[l] Comparison based on exposures when administered as darunavir/ritonavir + FTC/TDF.
[m] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.
[n] Aptivus® (tipranavir) Prescribing Information.

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

Table 7: Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of TDF

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[a] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑12 (↓1 to ↑26)	⇔	NA
Atazanavir[b]	400 once daily × 14 days	34	↓21 (↓27 to ↓14)	↓25 (↓30 to ↓19)	↓40 (↓48 to ↓32)
Atazanavir[b]	Atazanavir/ Ritonavir 300/100 once daily × 42 days	10	↓28 (↓50 to ↑5)	↓25[c] (↓42 to ↓3)	↓23[c] (↓46 to ↑10)
Darunavir[d]	Darunavir/Ritonavir 300/100 once daily	12	↑ 16 (↓6 to ↑42)	↑21 (↓ 5 to ↑54)	↑24 (↓10 to ↑69)
Didanosine[e]	250 once, simultaneously with tenofovir and a light meal[f]	33	↓20[g] (↓32 to ↓7)	⇔ [g]	NA
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	↑20 (↑12 to ↑29)
Entecavir	1 mg once daily × 10 days	28	⇔	↑13 (↑11 to ↑15)	⇔
Indinavir	800 three times daily × 7 days	12	↓11 (↓30 to ↑12)	⇔	⇔
Lamivudine	150 twice daily × 7 days	15	↓24 (↓34 to ↓12)	⇔	⇔
Lopinavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	⇔	⇔	⇔
Ritonavir			⇔	⇔	⇔
Saquinavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑22 (↑6 to ↑41)	↑29[h] (↑12 to ↑48)	↑47[h] (↑23 to ↑76)
Ritonavir			⇔	⇔	↑ 23 (↑3 to ↑46)
Tacrolimus	0.05 mg/kg twice daily 7 days	21	⇔	⇔	⇔
Tipranavir[i]	Tipranavir/Ritonavir 500/100 twice daily	22	↓17 (↓26 to ↓6)	↓ 18 (↓25 to ↓9)	↓21 (↓30 to ↓10)
	Tipranavir/Ritonavir 750/200 twice daily (23 doses)	20	↓11 (↓16 to ↓4)	↓9 (↓15 to ↓3)	↓ 12 (↓22 to 0)

[a] Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable
[b] Reyataz® (atazanavir) Prescribing Information.
[c] In HIV-infected subjects, addition of TDF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
[d] Prezista® (darunavir) Prescribing Information.
[e] Videx® EC (didanosine) Prescribing Information. Subjects received didanosine enteric-coated capsules.
[f] 373 kcal, 8.2 g fat
[g] Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions.

[h] Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when TDF and ritonavir-boosted saquinavir are coadministered.
[i] Aptivus® (tipranavir) Prescribing Information.

12.4 Microbiology

Mechanism of Action

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

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

Antiviral Activity

Lamivudine: The antiviral activity of 3TC against HIV-1 was assessed in a number of cell lines including monocytes and fresh human peripheral blood lymphocytes (PBMCs) using standard susceptibility assays. EC_{50} values were in the range of 3 to 15,000 nM. (1 μM = 0.23 mcg/mL). The median EC_{50} values of 3TC were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B) respectively. The EC_{50} values against HIV-2 isolates (n = 4) ranged from 3 to 120 nM in PBMCs. 3TC was not antagonistic to all tested anti-HIV agents. Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of 3TC by 3.5-fold in MT-4 cells.

Tenofovir disoproxil fumarate: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} (50% effective concentration) values for tenofovir were in the range of 0.04 μM to 8.5 μM. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5 μM to 2.2 μM) and strain-specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 5.5 μM). Please see the full prescribing information for VIREAD® for information regarding the inhibitory activity of TDF against HBV.

Resistance

Lamivudine: 3TC-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that resistance was predominantly due to a methionine to valine or isoleucine (M184V/I).

Tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in reverse transcriptase and showed a 2- to 4- fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir. K65R substitutions developed in some subjects failing a TDF regimen.

Cross-Resistance

Lamivudine: Cross-resistance among certain reverse transcriptase inhibitors has been observed. 3TC-resistant HIV-1 isolate were cross-resistant in cell culture to didanosine (ddI). Cross-resistance is also expected with abacavir and emtricitabine as these select M184V substitutions.

Tenofovir disoproxil fumarate: Cross resistance among certain reverse transcriptase inhibitors has been recognized. The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1 infected subjects treated with abacavir or didanosine. HIV-1 isolates with the K65R also showed reduced susceptibility to emtricitabine and 3TC. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated reverse transcriptase substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), showed a 3.1-fold decrease in the susceptibility to tenofovir.

Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N=8) had reduced response to VIREAD®. Limited data are available for patients whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lamivudine: Long-term carcinogenicity studies with 3TC in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) the human exposures at the recommended dose of 300 mg.

3TC was not mutagenic in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in assay for unscheduled DNA synthesis in rat liver. 3TC showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2000 mg per kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection.

In a study of reproductive performance, 3TC administered to rats at doses up to 4,000 mg per kg per day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

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

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

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

13.2 Animal Toxicology and/or Pharmacology

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

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

14 CLINICAL STUDIES

14.1 Clinical Trial Results in Adults with HIV-1 Infection

Treatment-Naïve Subjects: Trial 903

Data through 144 weeks are reported for Trial 903, a double-blind, active-controlled multicenter trial comparing TDF 300 mg + 3TC 300 mg + EFV 600 mg vs stavudine (d4T) 40 mg + 3TC 300 mg + and EFV 600 mg 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/mm^3 (range 3−956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 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/mm^3. Treatment outcomes through 48 and 144 weeks are presented in Table 8.

Table 8: Outcomes of Randomized Treatment at Week 48 and 144 (Trial 903)

Outcomes	At Week 48		At Week 144	
	TDF + 3TC + EFV (N=299)	d4T + 3TC + EFV (N=301)	TDF + 3TC + EFV (N=299)	d4T + 3TC + EFV (N=301)
Responder[a]	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%

[a] Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 and 144.
[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 < 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 ≤100,000 copies/mL) and CD4+ cell count (< or ≥200 cells/mm^3). Through 144 weeks of therapy, 62% and 58% of subjects in the TDF and d4T arms, respectively, achieved and maintained confirmed HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4+ cell count was 263 cells/mm^3 for the TDF arm and 283 cells/mm^3 for the d4T arm.

Through 144 weeks, 11 subjects in the TDF group and 9 subjects in the d4T group experienced a new CDC Class C event.

16 HOW SUPPLIED/STORAGE AND HANDLING

TEMIXYS (lamivudine and tenofovir disoproxil fumarate) tablets 300 mg/300 mg are white, oblong shape, film-coated tablets debossed with "C 0" on one side and plain on the other side.

They are supplied as follows:

Bottles of 30 tablets with a desiccant and closed with a child-resistant closure NDC 72606-002-01

Store below 30°C (86 ºF).

Keep bottles tightly closed to protect from moisture.

Dispense and store only in original bottle.

17 PATIENT COUNSELING INFORMATION

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

Patients with Hepatitis B or C-infection

Inform patients co-infected with HIV-1 and HBV that deterioration of liver disease has occurred in some cases when treatment with lamivudine and tenofovir disoproxil fumarate were discontinued. Advise patients to discuss any changes in regimen with their healthcare provider *[see Warnings and Precautions (5.1)]*.

Inform patients with HIV-1/HCV co-infection that hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions (5.7)]*.

New Onset or Worsening Renal Impairment

Inform patients that renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. Advise patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis to avoid TEMIXYS with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) for patients *[see Dosage and Administration (2.3), Warnings and Precautions (5.2)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs and symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy *[see Warnings and Precautions (5.3)]*.

Bone Loss and Mineralization Defects

Inform patients that decreases in bone mineral density have been observed with the use of lamivudine and tenofovir disoproxil fumarate. Bone mineral density monitoring should be considered in patients who have a history of pathologic bone fracture or at risk for osteopenia *[see Warnings and Precautions (5.4)]*.

Lactic Acidosis and Severe Hepatomegaly

Inform patients that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. TEMIXYS should be suspended in any patients who develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *[see Warnings and Precautions (5.5)]*.

Drug Interactions

Advise patients that TEMIXYS may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other medication, including other HIV drugs and drugs for treatment of hepatitis C virus.

Do not administer TEMIXYS with HEPSERA *[see Warnings and Precautions (5.6) and Drug Interactions (7.1)]*.

Risk of Pancreatitis

Advise parents or guardians to monitor pediatric patients for signs and symptoms of pancreatitis *[see Warnings and Precautions (5.8)]*.

Pregnancy Registry

Advise patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in women exposed to lamivudine and tenofovir disoproxil fumarate tablets *[see Use in Specific Populations (8.1)]*.

Storage

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

Lactation

Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *[see Use in Specific Populations (8.2)]*.

Missed Dosage

Instruct patients that if they miss a dose of TEMIXYS, to take it as soon as they remember. Advise patients not to double their next dose or take more than the prescribed dose.

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