

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DELSTRIGO safely and effectively. See full prescribing information for DELSTRIGO.

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

WARNING: POSTTREATMENT ACUTE EXACERBATION OF HEPATITIS B

See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B (HBV) have been reported in patients coinfecting with HIV-1 and HBV who have discontinued lamivudine or tenofovir disoproxil fumarate (TDF), two of the components of DELSTRIGO. Closely monitor hepatic function in these patients. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (5.1)

INDICATIONS AND USAGE

DELSTRIGO is a three-drug combination of doravirine (a non-nucleoside reverse transcriptase inhibitor [NNRTI]), lamivudine, and tenofovir disoproxil fumarate (both nucleoside analogue reverse transcriptase inhibitors) and is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients with no antiretroviral treatment history. (1)

DOSAGE AND ADMINISTRATION

- Testing: Prior to or when initiating DELSTRIGO, test for HBV infection. Prior to or when initiating DELSTRIGO, and during treatment with DELSTRIGO, 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 dosage: One tablet taken orally once daily with or without food in adult patients. (2.2)
- Renal impairment: Not recommended in patients with estimated creatinine clearance below 50 mL per minute. (2.3)
- Dosage adjustment with rifabutin: Take one tablet of DELSTRIGO once daily, followed by one tablet of doravirine 100 mg (PIFELTRO) approximately 12 hours after the dose of DELSTRIGO. (2.4)

DOSAGE FORMS AND STRENGTHS

- Tablets: 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate. (3)

CONTRAINDICATIONS

- DELSTRIGO is contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of DELSTRIGO. (4)
- DELSTRIGO is contraindicated in patients with a previous hypersensitivity reaction to lamivudine.

WARNINGS AND PRECAUTIONS

- New onset or worsening renal impairment: Prior to or when initiating DELSTRIGO, and during treatment with DELSTRIGO, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. Avoid administering DELSTRIGO with concurrent or recent use of nephrotoxic drugs. (5.2)
- Bone loss and mineralization defects: Consider monitoring BMD in patients with a history of pathologic fracture or other risk factors of osteoporosis or bone loss. (5.4)
- Monitor for Immune Reconstitution Syndrome. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence greater than or equal to 5%, all grades) are dizziness, nausea, and abnormal dreams. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Because DELSTRIGO is a complete regimen, co-administration with other antiretroviral medications for treatment of HIV-1 infection is not recommended. (7.1)
- Consult the full prescribing information prior to and during treatment for important potential drug-drug interactions. (4, 5.3, 7)

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)

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

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FULL PRESCRIBING INFORMATION

WARNING: POSTTREATMENT ACUTE EXACERBATION OF HEPATITIS B

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

1 INDICATIONS AND USAGE

DELSTRIGO™ is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history.

2 DOSAGE AND ADMINISTRATION

2.1 Testing When Initiating and During Treatment with DELSTRIGO

Prior to or when initiating DELSTRIGO, test patients for HBV infection [see *Warnings and Precautions* (5.1)].

Prior to or when initiating DELSTRIGO, and during treatment with DELSTRIGO, 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 Dosage

DELSTRIGO is a fixed-dose combination product containing 100 mg of doravirine (DOR), 300 mg of lamivudine (3TC), and 300 mg of TDF. The recommended dosage of DELSTRIGO in adults is one tablet taken orally once daily with or without food [see *Clinical Pharmacology* (12.3)].

2.3 Renal Impairment

Because DELSTRIGO is a fixed-dose combination tablet and the dosage of lamivudine and TDF cannot be adjusted, DELSTRIGO is not recommended in patients with estimated creatinine clearance less than 50 mL/min [see *Warnings and Precautions* (5.2) and *Use in Specific Populations* (8.6)].

2.4 Dosage Adjustment with Rifabutin

If DELSTRIGO is co-administered with rifabutin, take one tablet of DELSTRIGO once daily, followed by one tablet of doravirine 100 mg (PIFELTRO) approximately 12 hours after the dose of DELSTRIGO for the duration of rifabutin co-administration [see *Drug Interactions* (7.2) and *Clinical Pharmacology* (12.3)].

3 DOSAGE FORMS AND STRENGTHS

DELSTRIGO film-coated tablets are yellow, oval-shaped tablets, debossed with the corporate logo and 776 on one side and plain on the other side. Each tablet contains 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).

4 CONTRAINDICATIONS

- DELSTRIGO is contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of DELSTRIGO [see *Warnings and Precautions* (5.3), *Drug*

Interactions (7.2), and Clinical Pharmacology (12.3)]. These drugs include, but are not limited to, the following:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
 - the androgen receptor inhibitor enzalutamide
 - the antimycobacterials rifampin, rifapentine
 - the cytotoxic agent mitotane
 - St. John's wort (*Hypericum perforatum*)
- DELSTRIGO is contraindicated in patients with a previous hypersensitivity reaction to lamivudine.

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 HBV before initiating antiretroviral therapy.

Severe acute exacerbations of hepatitis B (e.g., liver decompensated and liver failure) have been reported in patients who are coinfecting with HIV-1 and HBV and have discontinued products containing lamivudine and/or TDF, and may occur with discontinuation of DELSTRIGO. Patients who are coinfecting with HIV-1 and HBV who discontinue DELSTRIGO should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with DELSTRIGO. If appropriate, initiation of anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

5.2 New Onset or Worsening Renal Impairment

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, a component of DELSTRIGO.

DELSTRIGO should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple nonsteroidal 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 TDF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

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

Prior to or when initiating DELSTRIGO, and during treatment with DELSTRIGO, 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. Discontinue DELSTRIGO in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

The lamivudine and TDF components of DELSTRIGO are primarily excreted by the kidney. Discontinue DELSTRIGO if estimated creatinine clearance declines below 50 mL/min as dose interval adjustment required for lamivudine and TDF cannot be achieved with the fixed-dose combination tablet [*see Use in Specific Populations (8.6)*].

5.3 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of DELSTRIGO and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to [see *Dosage and Administration* (2.4), *Contraindications* (4), and *Drug Interactions* (7.2)]:

- Loss of therapeutic effect of DELSTRIGO and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of a component of DELSTRIGO.

See Table 5 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 DELSTRIGO therapy, review concomitant medications during DELSTRIGO therapy, and monitor for adverse reactions.

5.4 Bone Loss and Mineralization Defects

Bone Mineral Density

In clinical trials in HIV-1 infected adults, TDF (a component of DELSTRIGO) was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving TDF.

The effects of TDF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for HIV-1 infected adult patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial in all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained.

Mineralization Defects

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

5.5 Immune Reconstitution Syndrome

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

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

6 ADVERSE REACTIONS

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

- Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV [see *Warnings and Precautions* (5.1)]
- New Onset or Worsening Renal Impairment [see *Warnings and Precautions* (5.2)]
- Bone Loss and Mineralization Defects [see *Warnings and Precautions* (5.4)]
- Immune Reconstitution Syndrome [see *Warnings and Precautions* (5.5)]

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.

Adverse Reactions in Adults with No Prior Antiretroviral Treatment History

The safety assessment of DELSTRIGO is based on Week 48 data from two Phase 3, randomized, international, multicenter, double-blind, active-controlled trials. A total of 747 subjects received doravirine either as the single entity in combination with other antiretroviral drugs as background regimens (n=383) or as the fixed-dose DELSTRIGO (n=364), and a total of 747 subjects were randomized to control arms.

In DRIVE-AHEAD (Protocol 021), 728 adult subjects received either DELSTRIGO (n=364) or EFV/FTC/TDF once daily (n=364). By Week 48, 3% in the DELSTRIGO group and 6% in the EFV/FTC/TDF group had adverse events leading to discontinuation of study medication.

Adverse reactions reported in greater than or equal to 5% of subjects in any treatment group in DRIVE-AHEAD are presented in Table 1.

Table 1: Adverse Reactions* (All Grades) Reported in $\geq 5\%$ [†] of Subjects in Any Treatment Group in Adults with No Antiretroviral Treatment History in DRIVE-AHEAD (Week 48)

	DELSTRIGO Once Daily N=364	EFV/FTC/TDF Once Daily N=364
Dizziness	7%	32%
Nausea	5%	7%
Abnormal Dreams	5%	9%
Insomnia	4%	5%
Diarrhea	3%	5%
Somnolence	3%	7%
Rash [‡]	2%	12%
<p>*Frequencies of adverse reactions are based on all adverse events attributed to trial drugs by the investigator.</p> <p>[†]No adverse reactions of Grade 2 or higher (moderate or severe) occurred in $\geq 2\%$ of subjects treated with DELSTRIGO.</p> <p>[‡]Rash: includes rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic.</p>		

The majority (65%) of adverse reactions associated with DELSTRIGO occurred at severity Grade 1 (mild).

Neuropsychiatric Adverse Events

For DRIVE-AHEAD, the analysis of subjects with neuropsychiatric adverse events by Week 48 is presented in Table 2. The proportion of subjects who reported one or more neuropsychiatric adverse events was 24% and 57% in the DELSTRIGO and EFV/FTC/TDF groups, respectively.

A statistically significantly lower proportion of DELSTRIGO-treated subjects compared to EFV/FTC/TDF-treated subjects reported neuropsychiatric adverse events by Week 48 in the three pre-specified categories of dizziness, sleep disorders and disturbances, and altered sensorium.

Table 2: DRIVE-AHEAD - Analysis of Subjects with Neuropsychiatric Adverse Events* (Week 48)

	DELSTRIGO Once Daily N=364	EFV/FTC/TDF Once Daily N=364	Treatment Difference (DELSTRIGO - EFV/FTC/TDF) Estimate (95% CI)[†]
Sleep disorders and disturbances [‡]	12%	26%	-13.5 (-19.1, -7.9)
Dizziness	9%	37%	-28.3 (-34.0, -22.5)
Altered sensorium [§]	4%	8%	-3.8 (-7.6, -0.3)
<p>*All causality and all grade events were included in the analysis.</p> <p>[†]The 95% CIs were calculated using Miettinen and Nurminen's method. Categories pre-specified for statistical testing were dizziness (p <0.001), sleep disorders and disturbances (p <0.001), and altered sensorium (p=0.033).</p> <p>[‡]Predefined using MedDRA preferred terms including: abnormal dreams, hyposomnia, initial insomnia, insomnia, nightmare, sleep disorder, somnambulism.</p> <p>[§]Predefined using MedDRA preferred terms including: altered state of consciousness, lethargy, somnolence, syncope.</p>			

Neuropsychiatric adverse events in the pre-defined category of depression and suicide/self-injury were reported in 4% and 7% of subjects, in the DELSTRIGO and EFV/FTC/TDF groups, respectively.

In DRIVE-AHEAD through 48 weeks of treatment, the majority of subjects who reported neuropsychiatric adverse events reported events that were mild to moderate in severity (97% [83/86] and 96% [198/207], in the DELSTRIGO and EFV/FTC/TDF groups, respectively) and the majority of subjects reported these events in the first 4 weeks of treatment (72% [62/86] in the DELSTRIGO group and 86% [177/207] in the EFV/FTC/TDF group).

Neuropsychiatric adverse events led to treatment discontinuation in 1% (2/364) and 1% (5/364) of subjects in the DELSTRIGO and EFV/FTC/TDF groups, respectively. The proportion of subjects who reported neuropsychiatric adverse events through Week 4 was 17% (62/364) in the DELSTRIGO group and 49% (177/364) in the EFV/FTC/TDF group. At Week 48, the prevalence of neuropsychiatric adverse events was 12% (44/364) in the DELSTRIGO group and 22% (81/364) in the EFV/FTC/TDF group.

Laboratory Abnormalities

The percentages of subjects with selected laboratory abnormalities (that represent a worsening from baseline) who were treated with DELSTRIGO or EFV/FTC/TDF in DRIVE-AHEAD are presented in Table 3.

Table 3: Selected Laboratory Abnormalities Reported in Adult Subjects with No Antiretroviral Treatment History in DRIVE-AHEAD (Week 48)

Laboratory Parameter Preferred Term (Unit)/Limit	DELSTRIGO Once Daily N=364	EFV/FTC/TDF Once Daily N=364
Blood Chemistry		
Total bilirubin		
1.1 - <1.6 x ULN	4%	0%

1.6 - <2.6 x ULN	2%	0%
≥2.6 x ULN	<1%	<1%
Creatinine (mg/dL)		
>1.3 - 1.8 x ULN or Increase of >0.3 mg/dL above baseline	2%	1%
>1.8 x ULN or Increase of ≥1.5 x above baseline	2%	1%
Aspartate aminotransferase (IU/L)		
2.5 - <5.0 x ULN	2%	2%
≥5.0 x ULN	<1%	2%
Alanine aminotransferase (IU/L)		
2.5 - <5.0 x ULN	3%	4%
≥5.0 x ULN	<1%	2%
Alkaline phosphatase (IU/L)		
2.5 - <5.0 x ULN	0%	<1%
≥5.0 x ULN	0%	<1%
Lipase		
1.5 - <3.0 x ULN	5%	4%
≥3.0 x ULN	1%	2%
Creatine kinase (IU/L)		
6.0 - <10.0 x ULN	2%	2%
≥10.0 x ULN	2%	3%
Cholesterol, fasted (mg/dL)		
≥300 mg/dL	<1%	<1%
LDL cholesterol, fasted (mg/dL)		
≥190 mg/dL	<1%	2%
Triglycerides, fasted (mg/dL)		
>500 mg/dL	<1%	3%
ULN = Upper limit of normal range.		

Change in Lipids from Baseline

For DRIVE-AHEAD, changes from baseline at Week 48 in LDL-cholesterol, non-HDL-cholesterol, total cholesterol, triglycerides, and HDL-cholesterol are shown in Table 4.

The LDL and non-HDL comparisons were pre-specified and are summarized in Table 4. The differences were statistically significant, showing superiority of DELSTRIGO for both parameters. The clinical benefit of these findings has not been demonstrated.

Table 4: Mean Change from Baseline in Fasting Lipids in Adult Subjects with No Antiretroviral Treatment History in DRIVE-AHEAD (Week 48)

Laboratory Parameter Preferred Term	DELSTRIGO Once Daily N=320		EFV/FTC/TDF Once Daily N=307		Difference Estimates (DELSTRIGO - EFV/FTC/TDF)
	Baseline	Change	Baseline	Change	Difference (95% CI)
LDL-Cholesterol (mg/dL)*	91.7	-2.1	91.3	8.3	-10.2 (-13.8, -6.7)
Non-HDL Cholesterol (mg/dL)*	114.7	-4.1	115.3	12.7	-16.9 (-20.8, -13.0)
Total Cholesterol (mg/dL)†	156.8	-2.2	156.8	21.1	-
Triglycerides (mg/dL)†	118.7	-12.0	122.6	21.6	-
HDL-Cholesterol (mg/dL)†	42.1	1.8	41.6	8.4	-
Subjects on lipid-lowering agents at baseline were excluded from these analyses (DELSTRIGO n=15 and EFV/FTC/TDF n=10). Subjects initiating a lipid-lowering agent post-baseline had their last fasted on-treatment value (prior to starting the agent) carried forward (DELSTRIGO n=3 and EFV/FTC/TDF n=8).					
*P-value for the pre-specified hypothesis testing for treatment difference was <0.0001.					
†Not pre-specified for hypothesis testing.					

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing experience in patients receiving lamivudine- or TDF-containing regimens. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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, posttreatment exacerbations of hepatitis B

Hypersensitivity: anaphylaxis, urticaria

Musculoskeletal: muscle weakness, CPK elevation, rhabdomyolysis

Skin: alopecia, pruritus

TDF:

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 Concomitant Use with Other Antiretroviral Medications

Because DELSTRIGO is a complete regimen for the treatment of HIV-1 infection, co-administration with other antiretroviral medications for treatment of HIV-1 infection is not recommended. Information regarding potential drug-drug interactions with other antiretroviral medications is not provided.

7.2 Effect of Other Drugs on DELSTRIGO

Co-administration of DELSTRIGO with a CYP3A inducer decreases doravirine plasma concentrations, which may reduce DELSTRIGO efficacy [see *Contraindications (4)*, *Warnings and Precautions (5.3)*, and *Clinical Pharmacology (12.3)*].

Co-administration of DELSTRIGO and drugs that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine.

Table 5 shows the significant drug interactions with the components of DELSTRIGO. The drug interactions described are based on studies conducted with either DELSTRIGO or the components of DELSTRIGO as individual agents.

Table 5: Drug Interactions with DELSTRIGO*

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Androgen Receptors		
enzalutamide	↓ doravirine	Co-administration is contraindicated with enzalutamide. At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO.
Anticonvulsants		
carbamazepine oxcarbazepine phenobarbital phenytoin	↓ doravirine	Co-administration is contraindicated with these anticonvulsants. At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO.
Antimycobacterials		
rifampin [†] rifapentine	↓ doravirine	Co-administration is contraindicated with rifampin or rifapentine. At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO.
rifabutin [†]	↓ doravirine	If DELSTRIGO is co-administered with rifabutin, one tablet of doravirine (PIFELTRO) should be taken approximately 12 hours after the dose of DELSTRIGO [see <i>Dosage and Administration (2.4)</i>]. At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO.
Cytotoxic Agents		
mitotane	↓ doravirine	Co-administration is contraindicated with mitotane. At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO.
Hepatitis C Antiviral Agents		
ledipasvir/sofosbuvir	↑ tenofovir	Monitor for adverse reactions associated with TDF.

sofosbuvir/velpatasvir		
Herbal Products		
St. John's wort	↓ doravirine	Co-administration is contraindicated with St. John's wort. At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO.
Other Agents		
sorbitol	↓ lamivudine	Co-administration 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-containing medicines.
↑ = increase, ↓ = decrease *This table is not all-inclusive †The interaction between doravirine and the concomitant drug was evaluated in a clinical study. All other drug-drug interactions shown are anticipated based on the known metabolic and elimination pathways.		

Co-administration of DELSTRIGO with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of lamivudine, tenofovir, and/or other renally eliminated drugs. Some examples of drugs that are eliminated by active tubular secretion 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)* and *Clinical Pharmacology (12.3)*].

No clinically significant changes in concentration were observed for doravirine when co-administered with the following agents: TDF, lamivudine, elbasvir and grazoprevir, ledipasvir and sofosbuvir, ritonavir, ketoconazole, aluminum hydroxide/magnesium hydroxide/simethicone containing antacid, pantoprazole, or methadone [see *Clinical Pharmacology (12.3)*].

No clinically significant changes in concentration were observed for tenofovir when co-administered with tacrolimus or entecavir [see *Clinical Pharmacology (12.3)*].

7.3 Effect of DELSTRIGO on Other Drugs

No clinically significant changes in concentration were observed for the following agents when co-administered with doravirine: lamivudine, TDF, elbasvir and grazoprevir, ledipasvir and sofosbuvir, atorvastatin, an oral contraceptive containing ethinyl estradiol and levonorgestrel, metformin, methadone, or midazolam.

No clinically significant drug interactions have been observed between TDF and the following medications: entecavir, methadone, oral contraceptives, sofosbuvir, or tacrolimus in studies conducted in healthy subjects.

Lamivudine is not significantly metabolized by CYP enzymes nor does it inhibit or induce this enzyme system; therefore, it is unlikely that clinically significant drug interactions will occur through these pathways [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 individuals exposed to DELSTRIGO during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

There is insufficient prospective pregnancy data from the APR to adequately assess the risk of birth defects and miscarriage. Doravirine use in individuals during pregnancy has not been evaluated; however, lamivudine and TDF use during pregnancy has been evaluated in a limited number of individuals reported to the APR. Available data from the APR show no difference in the overall risk of major birth defects for lamivudine and TDF compared with the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) (see *Data*). The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15-20%. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates individuals and infants from the limited geographic area, and does not include outcomes for births that occurred at less than 20 weeks gestation.

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

No adverse developmental effects were observed when doravirine and TDF were administered separately at doses/exposures ≥ 8 (doravirine) and ≥ 14 (TDF) times those of the recommended human dose (RHD) of DELSTRIGO (see *Data*).

Data

Human Data

Lamivudine: The APR has received a total of over 12,000 prospective reports with follow-up data of possible exposure to lamivudine-containing regimens; over 5,400 reports in the first trimester; over 5,500 reports in the second trimester; and over 1,800 reports in the third trimester. Birth defects occurred in 151 of 5,008 (3.0%, 95% CI: 2.6% to 3.5%) live births for lamivudine-containing regimens (first trimester exposure); and 210 of 7,356 (2.9%, 95% CI: 2.5% to 3.3%) live births for lamivudine-containing regimens (second/third trimester exposure). Among pregnant mothers in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between lamivudine and overall birth defects observed in the APR.

TDF: The APR has received a total of over 5,500 prospective reports with follow-up data of possible exposure to tenofovir disoproxil-containing regimens; over 3,900 reports in the first trimester; over 1,000 reports in the second trimester; and over 500 reports in the third trimester. Birth defects occurred in 82 of 3,535 (2.3%, 95% CI: 1.9% to 2.9%) live births for TDF-containing regimens (first trimester exposure); and 35 of 1,570 (2.2%, 95% CI: 1.6% to 3.1%) live births for TDF-containing regimens (second/third trimester exposure). Among pregnant mothers in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between tenofovir and overall birth defects observed in the APR.

Animal Data

Doravirine: Doravirine was administered orally to pregnant rabbits (up to 300 mg/kg/day on gestation days (GD) 7 to 20) and rats (up to 450 mg/kg/day on GD 6 to 20 and separately from GD 6 to lactation/postpartum day 20). No significant toxicological effects on embryo-fetal (rats and rabbits) or pre/post-natal (rats) development were observed at exposures (AUC) approximately 9 times (rats) and 8 times (rabbits) the exposure in humans at the RHD. Doravirine was transferred to the fetus through the placenta in embryo-fetal studies, with fetal plasma concentrations of up to 40% (rabbits) and 52% (rats) that of maternal concentrations observed on gestation day 20.

Lamivudine: Lamivudine was administered orally to pregnant rats (at 90, 600, and 4,000 mg per kg per day) and rabbits (at 90, 300, and 1,000 mg per kg per day and at 15, 40, and 90 mg per kg per day)

during organogenesis (on gestation Days 7 through 16 [rat] and 8 through 20 [rabbit]). No evidence of fetal malformations due to lamivudine was observed in rats and rabbits at doses producing plasma concentrations (C_{max}) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryolethality was seen in the rabbit at system exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at plasma concentrations (C_{max}) 35 times higher than human exposure at the recommended daily dose. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. In the fertility/pre- and postnatal development study in rats, lamivudine was administered orally at doses of 180, 900, and 4,000 mg per kg per day (from prior to mating through postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, was not affected by maternal administration of lamivudine.

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

8.2 Lactation

Risk Summary

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

Based on limited published data, both lamivudine and tenofovir are present in human milk. It is unknown whether doravirine is present in human milk, but doravirine is present in the milk of lactating rats (see *Data*). It is not known whether DELSTRIGO or the components of DELSTRIGO affects human milk production, or has effects on the breastfed infant. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving DELSTRIGO.

Data

Doravirine: Doravirine was excreted into the milk of lactating rats following oral administration (450 mg/kg/day) from gestation day 6 to lactation day 14, with milk concentrations approximately 1.5 times that of maternal plasma concentrations observed 2 hours post dose on lactation day 14.

8.4 Pediatric Use

Safety and efficacy of DELSTRIGO have not been established in pediatric patients less than 18 years of age.

8.5 Geriatric Use

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

8.6 Renal Impairment

Because DELSTRIGO is a fixed-dose combination tablet and the dosage of lamivudine and TDF, both components of DELSTRIGO, cannot be altered, DELSTRIGO is not recommended in patients with estimated creatinine clearance less than 50 mL/min [see *Warnings and Precautions* (5.2) and *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

No dosage adjustment of DELSTRIGO is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. DELSTRIGO has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

No data are available on overdose of DELSTRIGO in patients and there is no known specific treatment for overdose with DELSTRIGO. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required.

Doravirine: There is no known specific treatment for overdose with doravirine.

Lamivudine: Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

TDF: TDF 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

DELSTRIGO is a fixed-dose combination, film-coated tablet, containing doravirine, lamivudine, and TDF for oral administration.

Doravirine is an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI).

Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine and is an HIV-1 nucleoside analogue reverse transcriptase inhibitor.

TDF (a prodrug of tenofovir) is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. *In vivo* TDF is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir is an HIV-1 reverse transcriptase inhibitor.

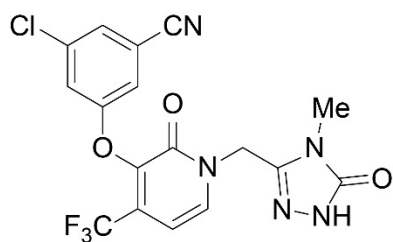
Each tablet contains 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of TDF (equivalent to 245 mg of tenofovir disoproxil) as active ingredients. The tablets include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and sodium stearyl fumarate. The tablets are film coated with a coating material containing the following inactive ingredients: hypromellose, iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin. The coated tablets are polished with carnauba wax.

Doravirine:

The chemical name for doravirine is 3-chloro-5-[[1-[(4,5-dihydro-4-methyl-5-oxo-1*H*-1,2,4-triazol-3-yl)methyl]-1,2-dihydro-2-oxo-4-(trifluoromethyl)-3-pyridinyl]oxy]benzonitrile.

It has a molecular formula of C₁₇H₁₁ClF₃N₅O₃ and a molecular weight of 425.75.

It has the following structural formula:



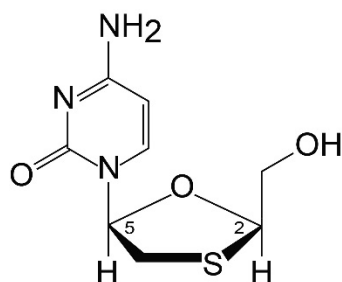
Doravirine is practically insoluble in water.

Lamivudine:

The chemical name for lamivudine is (-)-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-cytosine.

It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.26.

It has the following structural formula:



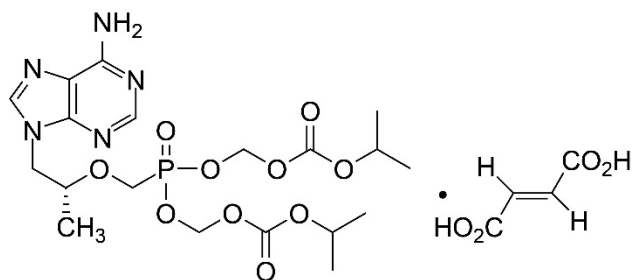
Lamivudine is soluble in water.

TDF:

The chemical name for TDF is 9-[(*R*)-2-[[bis[[[(isopropoxycarbonyl)oxy]methoxy] phosphinyl]-methoxy]propyl]adenine fumarate (1:1).

It has a molecular formula of $C_{19}H_{30}N_5O_{10} \cdot P \cdot C_4H_4O_4$ and a molecular weight of 635.52.

It has the following structural formula:



TDF is slightly soluble in water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

DELSTRIGO is a fixed-dose combination of the antiretroviral drugs doravirine, lamivudine, and TDF [see *Microbiology* (12.4)].

12.2 Pharmacodynamics

In a Phase 2 trial evaluating doravirine over a dose range of 0.25 to 2 times the recommended dose of doravirine in DELSTRIGO (in combination with FTC/TDF) in HIV-1 infected subjects with no antiretroviral treatment history, no exposure-response relationship for efficacy was identified for doravirine.

Cardiac Electrophysiology

At a doravirine dose of 1200 mg, which provides approximately 4 times the peak concentration observed following the recommended dose of doravirine in DELSTRIGO does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Single-dose administration of one DELSTRIGO tablet to healthy subjects provided comparable exposures of doravirine, lamivudine, and tenofovir to administration of doravirine tablets (100 mg) plus lamivudine tablets (300 mg) plus TDF tablets (300 mg). Doravirine pharmacokinetics are similar in healthy subjects and HIV-1-infected subjects. Pharmacokinetic properties of the components of DELSTRIGO are provided in Table 6.

Table 6: Pharmacokinetic Properties of the Components of DELSTRIGO

Parameter	Doravirine	Lamivudine	Tenofovir
General			
<i>Steady State Exposure*</i>			
AUC ₀₋₂₄ (mcg•h/mL)	16.1 (29) [†]	8.87 ± 1.83 [‡]	2.29 ± 0.69 [§]
C _{max} (mcg/mL)	0.962 (19) [†]	2.04 ± 0.54 [‡]	0.30 ± 0.09 [§]
C ₂₄ (mcg/mL)	0.396 (63) [†]	NA	NA
Absorption			
Absolute Bioavailability	64%	86%	25%
T _{max} (h)	2	NA	1
<i>Effect of Food[¶]</i>			
AUC Ratio	1.10 (1.01, 1.20)	0.93 (0.84, 1.03)	1.27 (1.17, 1.37)
C _{max} Ratio	0.95 (0.80, 1.12)	0.81 (0.65, 1.01)	0.88 (0.74, 1.04)
C ₂₄ Ratio	1.26 (1.13, 1.41)	NA	NA
Distribution			
V _{dss} [#]	60.5 L	1.3 L/kg	1.3 L/kg
Plasma Protein Binding	76%	< 36%	<0.7%
Elimination			
t _{1/2} (h)	15	5-7	17
CL/F (mL/ min)*	106 (35.2)	398.5 ± 69.1	1,043.7 ± 115.4
CL _{renal} (mL/ min)*	9.3 (18.6)	199.7 ± 56.9	243.5 ± 33.3
<i>Metabolism</i>			
Primary Pathway(s)	CYP3A	Minor	No CYP Metabolism
<i>Excretion</i>			
Major route of elimination	Metabolism	Glomerular filtration and active tubular secretion	Glomerular filtration and active tubular secretion

Urine (unchanged)	6%	71%	70-80%
Biliary/Fecal (unchanged)	Minor	NA	NA

*Presented as geometric mean (%CV: geometric coefficient of variation) or mean \pm SD.
[†]Doravirine 100 mg once daily to HIV-1 infected subjects.
[‡]Lamivudine 300 mg once daily for 7 days to 60 healthy subjects.
[§]Single 300 mg dose of TDF to HIV-1-infected subjects in the fasted state.
[¶]Geometric mean ratio [high-fat meal/fasting] and (90% confidence interval) for PK parameters. High fat meal is approximately 1000 kcal, 50% fat. The effect of food is not clinically relevant.
[#]Based on IV dose.
Abbreviations: NA=not available; AUC=area under the time concentration curve; C_{max}=maximum concentration; C₂₄=concentration at 24 hours; T_{max}=time to C_{max}; V_{dss}=apparent volume of distribution at steady state; t_{1/2}=elimination half-life; CL/F=apparent clearance; CL_{renal} = renal clearance

Specific Populations

No clinically significant differences in the pharmacokinetics of certain DELSTRIGO components were observed based on age \geq 65 years (for doravirine), sex (for doravirine, lamivudine, TDF), and race/ethnicity (for doravirine, lamivudine). The effects of age (\geq 65 years) on the pharmacokinetics of lamivudine, TDF and the effect of race on the pharmacokinetics of TDF are unknown. The pharmacokinetics of doravirine in patients <18 years of age is unknown.

Patients with Renal Impairment

Doravirine: No clinically significant difference in the pharmacokinetics of doravirine were observed in subjects with mild to severe renal impairment (creatinine clearance (CL_{cr}) >15 mL/min, estimated by Cockcroft-Gault). Doravirine has not been studied in patients with end-stage renal disease or in patients undergoing dialysis.

Lamivudine: The AUC_{inf}, C_{max}, and half-life of lamivudine increased and CL/F decreased to a clinically significant extent with diminishing renal function (CL_{cr} 111 to < 10 mL/min).

TDF: A clinically significant increase in the C_{max} and AUC of tenofovir was observed in subjects with CL_{cr} < 50 mL/min or with end stage renal disease requiring dialysis [see *Warnings and Precautions (5.2) and Use in Specific Populations (8.6)*].

Patients with Hepatic Impairment

Doravirine: No clinically significant difference in the pharmacokinetics of doravirine was observed in subjects with moderate hepatic impairment (Child-Pugh score B) compared to subjects without hepatic impairment. Doravirine has not been studied in subjects with severe hepatic impairment (Child-Pugh score C).

Lamivudine: No clinically significant differences in lamivudine pharmacokinetics were observed with diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

TDF: No clinically significant differences in tenofovir pharmacokinetics were observed between subjects with any degree of hepatic impairment and healthy subjects.

Drug Interaction Studies

DELSTRIGO is a complete regimen for the treatment of HIV-1 infection; therefore, DELSTRIGO is not recommended to be administered with other HIV-1 antiretroviral medications. Information regarding potential drug-drug interactions with other antiretroviral medications is not provided.

The drug interaction trials described were conducted with doravirine, lamivudine and/or TDF, as single entities; no drug interaction trials have been conducted using the combination of doravirine, lamivudine,

and TDF. No clinically relevant drug interactions were observed between doravirine, lamivudine, and TDF.

Doravirine: Doravirine is primarily metabolized by CYP3A, and drugs that induce or inhibit CYP3A may affect the clearance of doravirine. Co-administration of doravirine and drugs that induce CYP3A may result in decreased plasma concentrations of doravirine. Co-administration of doravirine and drugs that inhibit CYP3A may result in increased plasma concentrations of doravirine.

Doravirine is not likely to have a clinically relevant effect on the exposure of medicinal products metabolized by CYP enzymes. Doravirine did not inhibit major drug metabolizing enzymes *in vitro*, including CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, and UGT1A1 and is not likely to be an inducer of CYP1A2, 2B6, or 3A4. Based on *in vitro* assays, doravirine is not likely to be an inhibitor of OATP1B1, OATP1B3, P-glycoprotein, BSEP, OAT1, OAT3, OCT2, MATE1, and MATE2K. Drug interaction studies were performed with doravirine and other drugs likely to be co-administered or commonly used as probes for pharmacokinetic interactions. The effects of co-administration with other drugs on the exposure (C_{max} , AUC, and C_{24}) of doravirine are summarized in Table 7. A single doravirine 100 mg dose was administered in these studies unless otherwise noted.

Table 7: Drug Interactions: Changes in Pharmacokinetic Parameter Values of Doravirine in the Presence of Co-administered Drug

Co-administered Drug	Regimen of Co-administered Drug	N	Geometric Mean Ratio (90% CI) of Doravirine Pharmacokinetics with/without Co-administered Drug (No Effect=1.00)		
			AUC*	C _{max}	C ₂₄
Azole Antifungal Agents					
ketoconazole [†]	400 mg QD	10	3.06 (2.85, 3.29)	1.25 (1.05, 1.49)	2.75 (2.54, 2.98)
Antimycobacterials					
rifampin	600 mg QD	10	0.12 (0.10, 0.15)	0.43 (0.35, 0.52)	0.03 (0.02, 0.04)
rifabutin	300 mg QD	12	0.50 (0.45, 0.55)	0.99 (0.85, 1.15)	0.32 (0.28, 0.35)
HIV Antiviral Agents					
ritonavir ^{†,‡}	100 mg BID	8	3.54 (3.04, 4.11)	1.31 (1.17, 1.46)	2.91 (2.33, 3.62)
efavirenz	600 mg QD [§]	17	0.38 (0.33, 0.45)	0.65 (0.58, 0.73)	0.15 (0.10, 0.23)
	600 mg QD [¶]	17	0.68 (0.58, 0.80)	0.86 (0.77, 0.97)	0.50 (0.39, 0.64)

CI = confidence interval; QD = once daily
*AUC_{inf} for single-dose, AUC₀₋₂₄ for once daily.
[†]Changes in doravirine pharmacokinetic values are not clinically relevant.
[‡]A single doravirine 50 mg dose (0.5 times the recommended approved dose) was administered.
[§]The first day following the cessation of efavirenz therapy and initiation of doravirine 100 mg QD.
[¶]14 days following the cessation of efavirenz therapy and initiation of doravirine 100 mg QD.

Based on drug interaction studies conducted with doravirine, no clinically significant drug interactions have been observed following the co-administration of doravirine and the following drugs: dolutegravir, TDF, lamivudine, elbasvir and grazoprevir, ledipasvir and sofosbuvir, ketoconazole, ritonavir, aluminum hydroxide/magnesium hydroxide/simethicone containing antacid, pantoprazole, atorvastatin, an oral contraceptive containing ethinyl estradiol and levonorgestrel, metformin, methadone, and midazolam.

Lamivudine:

Trimethoprim/Sulfamethoxazole: Co-administration of TMP/SMX with lamivudine resulted in an increase of 43% ±23% (mean ±SD) in lamivudine AUC_∞, a decrease of 29% ±13% in lamivudine oral clearance, and a decrease of 30% ±36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by co-administration with lamivudine.

Sorbitol (Excipient): Co-administration of lamivudine with a single dose of 3.2 grams, 10.2 grams, or 13.4 grams of sorbitol resulted in dose-dependent decreases of 14%, 32%, and 36% in the AUC_∞; and 28%, 52%, and 55% in the C_{max} of lamivudine, respectively.

TDF:

No clinically significant changes in exposure were observed for tenofovir when co-administered with tacrolimus or entecavir.

No clinically significant changes in exposure were observed for the following drugs when co-administered with tenofovir: tacrolimus, entecavir, methadone, or ethinyl estradiol/norgestimate.

12.4 Microbiology

Mechanism of Action

Doravirine: Doravirine is a pyridinone non-nucleoside reverse transcriptase inhibitor of HIV-1 and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Doravirine does not inhibit the human cellular DNA polymerases α , β , and mitochondrial DNA polymerase γ .

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. Lamivudine triphosphate (3TC-TP) is a weak inhibitor of mammalian DNA polymerases α , β , and mitochondrial DNA polymerase γ .

TDF: 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. Tenofovir diphosphate inhibits the activity of HIV-1 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 in Cell Culture

Doravirine: Doravirine exhibited an EC_{50} value of 12.0 ± 4.4 nM against wild-type laboratory strains of HIV-1 when tested in the presence of 100% normal human serum (NHS) using MT4-GFP reporter cells. Doravirine demonstrated antiviral activity against a broad panel of primary HIV-1 isolates (A, A1, AE, AG, B, BF, C, D, G, H) with EC_{50} values ranging from 0.6 nM to 10.0 nM. The antiviral activity of doravirine was not antagonistic when combined with lamivudine and TDF.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and peripheral blood mononuclear cells (PBMCs) using standard susceptibility assays. EC_{50} values were in the range of 3 to 15,000 nM (1,000 nM = 230 ng per mL). The median EC_{50} values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses ($n = 3$ except $n = 2$ for clade B) respectively. Ribavirin (50 μ M) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

TDF: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} values for tenofovir were in the range of 0.04–8.5 μ M. 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 0.5–2.2 μ M).

Resistance

In Cell Culture

Doravirine: Doravirine-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes, as well as NNRTI-resistant HIV-1. Observed emergent amino acid substitutions in RT included: V106A, V106M, V106I, V108I, H221Y, F227C, F227I, F227L, F227V, M230I, L234I, P236L, and Y318F.

Lamivudine: Lamivudine-resistant variants of HIV-1 have been selected in cell culture and in subjects treated with lamivudine. Genotypic analysis showed that substitutions M184I or V cause resistance to lamivudine.

TDF: HIV-1 isolates selected by tenofovir in cell culture expressed a K65R substitution in HIV-1 RT and showed a 2–4 -fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 RT has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine, and tenofovir.

In Clinical Trials

Doravirine: In the doravirine treatment arm of the DRIVE-AHEAD trial (n=364), 9 subjects showed the emergence of doravirine-associated resistance substitutions among 20 (45%) subjects in the resistance analysis subset (subjects with HIV-1 RNA greater than 400 copies per mL at virologic failure or early study discontinuation and having resistance data). Emergent doravirine resistance-associated substitutions in RT included one or more of the following: A98G, V106I, V106A, V106M/T, V108I, E138G/K, Y188L, H221Y, P225H, F227C, F227C/R, and Y318Y/F. Six of the 9 subjects with emergent doravirine-associated resistance substitutions showed doravirine phenotypic resistance and all of them had a greater than 100-fold reduction in doravirine susceptibility (range >103 to >211). The other 3 virologic failures who had only amino acid mixtures of NNRTI resistance substitutions showed doravirine phenotypic fold-changes of less than 2-fold.

In the EFV/FTC/TDF treatment arm of the DRIVE-AHEAD trial (n=364), 12 subjects showed the emergence of efavirenz-associated resistance substitutions among 20 (60%) subjects in the resistance analysis subset.

Lamivudine and TDF: In a pooled analysis of antiretroviral-naïve subjects who received doravirine, lamivudine, and TDF, genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-1 RNA greater than 400 copies per mL at confirmed virologic failure, at Week 48, or at time of early study drug discontinuation. Genotypic resistance developed in 7 evaluable subjects. The resistance-associated substitutions that emerged were RT M41L (n=1), A62V (n=1), K65R (n=2), T69T/A (n=1) and M184V (n=4). In comparison, genotypic resistance to emtricitabine or tenofovir developed in 5 evaluable subjects who received EFV/FTC/TDF in DRIVE-AHEAD; emergent resistance-associated substitutions were RT K65R (n=1), D67G/K70E (n=1), L74V/V75M/V118I (n=1) and M184V/I (n=5).

Cross-Resistance

No significant cross-resistance has been demonstrated between doravirine-resistant HIV-1 variants and lamivudine/emtricitabine or tenofovir or between lamivudine or tenofovir-resistant variants and doravirine.

Doravirine: A panel of 96 diverse clinical isolates containing NNRTI-associated substitutions was evaluated for susceptibility to doravirine. Clinical isolates containing the Y188L substitution alone or in combination with K103N or V106I, V106A in combination with G190A and F227L, or E138K in combination with Y181C and M230L showed greater than 100-fold reduced susceptibility to doravirine.

Cross-resistance has been observed among NNRTIs. Treatment-emergent doravirine resistance associated substitutions can confer cross resistance to efavirenz, etravirine, nevirapine, and rilpivirine. Of the 6 virologic failures who developed doravirine phenotypic resistance, all had phenotypic resistance to efavirenz and nevirapine, 4 had phenotypic resistance to rilpivirine, and 3 had partial resistance to etravirine based on the Monogram PhenoSense assay.

Lamivudine: Cross-resistance has been observed among NRTIs. The M184I/V lamivudine resistance substitution confers resistance to abacavir, didanosine and emtricitabine. Lamivudine also has reduced susceptibility against the K65R substitution.

TDF: Cross-resistance has been observed among NRTIs. The K65R substitution in HIV-1 RT selected by tenofovir is also selected in some HIV-1-infected patients treated with abacavir or didanosine. HIV-1 isolates with the K65R substitution also showed reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these NRTIs may occur in patients whose virus harbors the K65R substitution. The K70E substitution selected clinically by TDF results in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir. HIV-1 isolates from patients (n=20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid 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 RT substitution without zidovudine resistance-associated substitutions (n=8) had reduced response to TDF. Limited data are available for patients whose virus expressed a Y115F

substitution (n=3), Q151M substitution (n=2), or T69 insertion (n=4) in HIV-1 RT, all of whom had a reduced response in clinical trials.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Doravirine: Doravirine was not carcinogenic in long-term oral carcinogenicity studies in mice and rats at exposures up to 6 and 7 times, respectively, the human exposures at the RHD. A statistically significant incidence of thyroid parafollicular cell adenoma and carcinoma seen only in female rats at the high dose was within the range observed in historical controls.

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) the human exposures at the RHD.

TDF: 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 RHD. At the high dose in female mice, liver adenomas were increased at exposures 16 times of that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the RHD.

Mutagenesis

Doravirine: Doravirine was not genotoxic in a battery of *in vitro* or *in vivo* assays, including microbial mutagenesis, chromosomal aberration in Chinese hamster ovary cells, and in *in vivo* rat micronucleus assays.

Lamivudine: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver. Lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg per kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection.

TDF: 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.

Impairment of Fertility

Doravirine: There were no effects on fertility, mating performance or early embryonic development when doravirine was administered to rats up to the highest dose tested. Systemic exposures (AUC) to doravirine were approximately 7 times the exposure in humans at the RHD.

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

TDF: 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 RHD based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day 7 of gestation. There was, however, an alteration of the estrous cycle in female rats.

14 CLINICAL STUDIES

14.1 Adult Subjects with No Antiretroviral Treatment History

The efficacy of DELSTRIGO is based on the analyses of 48-week data from a randomized, multicenter, double-blind, active controlled Phase 3 trial (DRIVE-AHEAD, NCT02403674) in HIV-1 infected subjects with no antiretroviral treatment history (n=728).

Subjects were randomized and received at least 1 dose of either DELSTRIGO or EFV 600 mg/FTC 200 mg/TDF 300 mg once daily. At baseline, the median age of subjects was 31 years, 15% were female, 52% were non-white, 3% had hepatitis B or C coinfection, 14% had a history of AIDS, 21% had HIV-1 RNA greater than 100,000 copies/mL, and 88% had CD4+ T-cell count greater than 200 cells/mm³; these characteristics were similar between treatment groups. Week 48 outcomes for DRIVE-AHEAD are provided in Table 8.

Mean CD4+ T-cell counts in the DELSTRIGO and EFV/FTC/TDF groups increased from baseline by 198 and 188 cells/mm³, respectively.

Table 8: Virologic Outcome in DRIVE-AHEAD at Week 48 in HIV-1 Adult Subjects with No Antiretroviral Treatment History

Outcome	DELSTRIGO Once Daily N=364	EFV/FTC/TDF Once Daily N=364
HIV-1 RNA <50 copies/mL	84%	81%
Treatment Difference (95% CI) *	3.5% (-2.0%, 9.0%)	
HIV-1 RNA ≥ 50 copies/mL [†]	11%	10%
No Virologic Data at Week 48 Window	5%	9%
Discontinued study due to AE or Death [‡]	2%	7%
Discontinued study for Other Reasons [§]	2%	2%
On study but missing data in window	0	<1%
Proportion (%) of Subjects With HIV-1 RNA <50 copies/mL at Week 48 by Baseline and Demographic Category		
Gender		
Male	84% (n = 305)	80% (n = 311)
Female	85% (n = 59)	83% (n = 53)
Race		
White	84% (n = 177)	81% (n = 170)
Non-White	84% (n = 187)	80% (n = 194)
Ethnicity		
Hispanic or Latino	83% (n = 126)	84% (n = 120)
Not Hispanic or Latino	85% (n = 236)	79% (n = 238)
Baseline HIV-1 RNA (copies/mL)		
≤100,000 copies/mL	86% (n = 291)	83% (n = 282)
>100,000 copies/mL	77% (n = 73)	72% (n = 82)
CD4+ T-cell Count (cells/mm³)		
≤200 cells/mm ³	66% (n = 44)	78% (n = 46)
>200 cells/mm ³	87% (n = 320)	81% (n = 318)
Viral Subtype[¶]		

Subtype B	84% (n = 232)	80% (n = 253)
Subtype Non-B	85% (n = 130)	83% (n = 111)
¶Viral subtype was not available for two subjects.		
*The 95% CI for the treatment difference was calculated using stratum-adjusted Mantel-Haenszel method.		
†Includes subjects who discontinued study drug or study before Week 48 for lack or loss of efficacy and subjects with HIV-1 RNA equal to or above 50 copies/mL in the Week 48 window (relative day 295-378).		
‡Includes subjects who discontinued because of adverse event (AE) or death if this resulted in no virologic data in the Week 48 window.		
§Other reasons include: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, protocol deviation, screen failure, withdrawal by subject.		

16 HOW SUPPLIED/STORAGE AND HANDLING

Each DELSTRIGO tablet contains 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil), is yellow, oval-shaped, film-coated, and is debossed with the corporate logo and 776 on one side and plain on the other side. Each bottle contains 30 tablets (NDC 0006-5007-01) and silica gel desiccants, and is closed with a child-resistant closure.

Store DELSTRIGO in the original bottle. Keep the bottle tightly closed to protect from moisture. Do not remove the desiccants.

Store DELSTRIGO at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

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

Inform patients that severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HIV-1 and HBV and have discontinued lamivudine or TDF and may occur with discontinuation of DELSTRIGO [see *Warnings and Precautions* (5.1)]. Advise patients not to discontinue DELSTRIGO without first informing their healthcare provider.

Drug Interactions

Inform patients that DELSTRIGO may interact with certain other drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort [see *Contraindications* (4), *Warnings and Precautions* (5.3), and *Drug Interactions* (7)].

For patients concomitantly receiving rifabutin, take one tablet of doravirine (PIFELTRO) 100 mg approximately 12 hours after the dose of DELSTRIGO [see *Dosage and Administration* (2.4)].

New Onset or Worsening Renal Impairment

Inform patients that renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of TDF. Advise patients to avoid DELSTRIGO with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) [see *Warnings and Precautions* (5.2)].

Bone Loss and Mineralization Defects

Inform patients that decreases in bone mineral density have been observed with the use of TDF, a component of DELSTRIGO. Assessment of bone mineral density (BMD) should be considered in patients

who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss [see *Warnings and Precautions* (5.4)].

Immune Reconstitution Syndrome

Inform patients that in some patients with advanced HIV infection (AIDS), signs and symptoms of 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* (5.5)].

Dosing Instructions

Advise patients to take DELSTRIGO every day at a regularly scheduled time with or without food. Inform patients that it is important not to miss or skip doses as it can result in development of resistance. If a patient forgets to take DELSTRIGO, tell the patient to take the missed dose right away, unless it is almost time for the next dose. Advise the patient not to take 2 doses at one time and to take the next dose at the regularly scheduled time.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant individuals exposed to DELSTRIGO [see *Use in Specific Populations* (8.1)].

Lactation

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

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