**DELSTRIGO™ (doravirine/lamivudine/tenofovir disoproxil fumarate)**
**100 mg/300 mg/300 mg**
**Film Coated Tablet**

## 1. INDICATIONS AND USAGE

DELSTRIGO is indicated for the treatment of adults infected with HIV-1 without past or present evidence of viral resistance to NNRTIs, lamivudine, or tenofovir.

## 2. DOSAGE AND ADMINISTRATION

### 2.1 General

DELSTRIGO is a fixed-dose combination product containing 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate (tenofovir DF).

### 2.2 Adult Patients

The recommended dosage regimen of DELSTRIGO in adults is one tablet taken orally once daily with or without food.

Missed Dose

If the patient misses a dose of DELSTRIGO, the patient should take DELSTRIGO as soon as possible unless it is almost time for the next dose. The patient should not take 2 doses at one time and instead take the next dose at the regularly scheduled time.

### 2.3 Pediatric Patients

Safety and efficacy of DELSTRIGO have not been established in patients younger than 18 years of age *[see Clinical Pharmacology (10.4)]*.

### 2.4 Elderly Patients

There are limited data available on the use of doravirine, lamivudine and tenofovir DF in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients *[see Use in Specific Populations (6.4) and Clinical Pharmacology (10.4)]*.

Special care is advised in this age group due to age associated changes such as decreases in renal function.

### 2.5 Renal Impairment

Because DELSTRIGO is a fixed-dose combination tablet and the dosage of lamivudine and tenofovir DF cannot be altered, patients with estimated creatinine clearance less than 50 mL/min should not receive DELSTRIGO *[see Warnings and Precautions (4.2), Use in Specific Populations (6.5) and Clinical Pharmacology (10.4)]*.

### 2.6 Hepatic Impairment

No dose 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 Use in Specific Populations (6.6) and Clinical Pharmacology (10.4)]*.

### 2.7 Co-administration with Rifabutin

If DELSTRIGO is co-administered with rifabutin, one tablet of doravirine (PIFELTRO) should be taken approximately 12 hours after the dose of DELSTRIGO *[see Drug Interactions and Other Forms of Interactions (5.2) and Clinical Pharmacology (10.5)]*.

## 3. CONTRAINDICATIONS

DELSTRIGO should not be co-administered with drugs that are strong cytochrome P450 CYP3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of DELSTRIGO *[see Clinical Pharmacology (10.5)]*. 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)*
- lumacaftor

DELSTRIGO is contraindicated in patients with a previous hypersensitivity reaction to any component of this combination.

## 4. WARNINGS AND PRECAUTIONS

### 4.1 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. DELSTRIGO is not approved for the treatment of chronic HBV infection, and the safety and efficacy of DELSTRIGO have not been established in patients coinfected with HIV-1 and HBV.

Severe acute exacerbations of hepatitis B (e.g., liver decompensated and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued lamivudine or tenofovir DF, two of the components of DELSTRIGO. Patients who are coinfected with HIV-1 and HBV 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.

### 4.2 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 tenofovir DF, 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 and Other Forms of Interactions (5.1)]*. 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 DF. 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.

It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with DELSTRIGO. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of DELSTRIGO and periodically during DELSTRIGO therapy.

The lamivudine and tenofovir DF components of DELSTRIGO are primarily excreted by the kidney. DELSTRIGO should be discontinued if estimated creatinine clearance declines below 50 mL per minute as dose interval adjustment required for lamivudine and tenofovir DF cannot be achieved with the fixed-dose combination tablet *[see Use in Specific Populations (6.5)]*.

### 4.3 Drug Interactions

Caution should be given to prescribing DELSTRIGO with drugs that may reduce the exposure of doravirine *[see Contraindications (3), Drug Interactions and Other Forms of Interactions (5.2), and Clinical Pharmacology (10.5)]*.

### 4.4 Bone Loss and Mineralization Defects

Bone Mineral Density

In clinical trials in HIV-1-infected adults, tenofovir DF (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 tenofovir DF. For additional information, consult the tenofovir DF prescribing information.

The effects of tenofovir DF-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 tenofovir DF. Arthralgias and muscle pain or weakness have also been reported in cases of

proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF.

### 4.5 Co-administration with Other Products

DELSTRIGO is a fixed-dose combination of doravirine, lamivudine, and tenofovir DF. Do not co-administer DELSTRIGO with other medicinal products containing lamivudine, or with medicinal products containing tenofovir DF or tenofovir alafenamide, or with adefovir dipivoxil. DELSTRIGO should not be administered with PIFELTRO unless needed for dose adjustment (e.g., with rifabutin) *[see Dosage and Administration (2.7) and Drug Interactions and Other Forms of Interactions (5)]*.

### 4.6 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, Guillain-Barré syndrome and autoimmune hepatitis) 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. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS

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

### 5.1 Drugs Affecting Renal Function

Because lamivudine and tenofovir are primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion, 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 (4.2) and Clinical Pharmacology (10.5)]*.

### 5.2 Established and Other Potentially Significant Drug Interactions

Doravirine is primarily metabolized by CYP3A, and drugs that induce or inhibit CYP3A may affect the clearance of doravirine. Co-administration of DELSTRIGO and drugs that induce CYP3A may result in decreased plasma concentrations of doravirine and reduce the therapeutic effect of doravirine *[see Contraindications (3), Warnings and Precautions (4.3), and Clinical Pharmacology (10.5)]*. Co-administration of DELSTRIGO and drugs that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine.

Co-administration of doravirine/lamivudine/tenofovir disoproxil with other moderate CYP3A inducers has not been evaluated, but decreased doravirine concentrations are expected. If co-administration with other moderate CYP3A inducers (e.g., debrafenib, lesinurad, bosentan, thioridazine, nafcillin, modefinil, telotristat ethyl) cannot be avoided, a 100 mg dose of doravirine should be administered daily approximately 12 hours after the administration of doravirine/lamivudine/tenofovir disoproxil dose.

Doravirine at a dose of 100 mg once daily is not likely to have a clinically relevant effect on the plasma concentrations of drugs metabolized by CYP enzymes.

Table 1 shows the established and other potentially significant drug interactions with the components of DELSTRIGO, but is not inclusive. For additional potential drug interactions with lamivudine or tenofovir DF *[see Warnings and Precautions (4.5) and Clinical Pharmacology (10.5)]*.

**Table 1: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction**

| Concomitant Drug Class: Drug Name | Effect on Concentration | Clinical Comment |
|---|---|---|
| **Antimycobacterials** | | |
| rifabutin* | ↓ doravirine<br>↔ rifabutin | Concomitant use of DELSTRIGO with rifabutin may cause a decrease in the plasma concentrations of doravirine (induction of CYP3A enzymes). |

| | | |
|---|---|---|
| | | If DELSTRIGO is co-administered with rifabutin, one tablet of PIFELTRO should be taken approximately 12 hours after the dose of DELSTRIGO *[see Dosage and Administration (2.7)]*. |
| **Azole Antifungal Agents** | | |
| fluconazole<br>itraconazole<br>ketoconazole*<br>posaconazole<br>voriconazole | ↑ doravirine<br><br>↔ azole antifungal agents | Concomitant use of DELSTRIGO with azole antifungal agents may cause an increase in the plasma concentrations of doravirine (inhibition of CYP3A enzymes).<br><br>No dose adjustment is required when DELSTRIGO is co-administered with azole antifungal agents. |
| **Hepatitis C Antiviral Agents** | | |
| ledipasvir/sofosbuvir<br>sofosbuvir/velpatasvir | ↑ tenofovir | Patients receiving DELSTRIGO concomitantly with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir should be monitored for adverse reactions associated with tenofovir DF. |
| **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 chronic use of sorbitol-containing medicines with lamivudine-containing medicines. |
| ↑ = increase, ↓ = decrease, ↔ = no change<br>*The interaction between doravirine and the drug was evaluated in a clinical study.<br>All other drug-drug interactions shown are anticipated based on the known metabolic and elimination pathways. | | |

### 5.3 Drugs with No Observed or Predicted Interactions with DELSTRIGO

Drug-drug interactions with doravirine and the following drugs were evaluated in clinical studies and no dose adjustment is needed for either drug *[see Clinical Pharmacology (10.5)]*: aluminum hydroxide/magnesium hydroxide/simethicone-containing antacid, pantoprazole, atorvastatin, an oral contraceptive containing ethinyl estradiol and levonorgestrel, metformin, methadone, midazolam, or elbasvir/grazoprevir.

No clinically relevant drug-drug interaction is expected when DELSTRIGO is co-administered with buprenorphine, naloxone, daclatasvir, simeprevir, diltiazem, verapamil, rosuvastatin, simvastatin, canagliflozin, liraglutide, sitagliptin, lisinopril, or omeprazole.

Based on the results of *in vitro* experiments and the known elimination pathways of tenofovir, the potential for CYP-mediated interactions involving tenofovir DF with other medicinal products is low *[see Clinical Pharmacology (10.5)]*.

No clinically significant drug interactions have been observed between tenofovir DF 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 (10.5)]*.

### 5.4 Lactose

The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactose deficiency or glucose-galactose malabsorption should not take this medicine.

## 6. USE IN SPECIFIC POPULATIONS

### 6.1 Pregnancy

Risk Summary

No adequate human data are available to establish whether or not DELSTRIGO poses a risk to pregnancy outcomes. Doravirine use in women during pregnancy has not been evaluated; however, lamivudine and tenofovir DF use during pregnancy has been evaluated in a limited number of women reported to the APR.

*Doravirine*: Reproduction studies performed in rats and rabbits at exposures up to approximately 9 times (rats) and 8 times (rabbits) the exposure in humans at the recommended human dose (RHD) did not indicate harmful effects of doravirine with respect to pregnancy or embryofetal development *[see Animal Toxicology (11.6)]*.

*Lamivudine*: Reproduction studies performed in rats and rabbits showed no evidence of teratogenicity. 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 32 times that of the RHD.

*Tenofovir DF*: Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the RHD based on body surface area comparisons and revealed no harm to the fetus.

Human Data

*Doravirine*: Adequate and well controlled studies with doravirine have not been conducted in pregnant women.

*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.

*Tenofovir DF*: 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.

### 6.2 Nursing Mothers

Risk Summary

Studies in humans have shown that both lamivudine and tenofovir are excreted in human milk. It is unknown whether doravirine is excreted in human milk. Because of the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving DELSTRIGO.

Data

*Human Data*

*Lamivudine*: Lamivudine is excreted in human breast milk.

*Tenofovir DF*: Samples of breast milk obtained from 5 HIV-1-infected mothers in the first postpartum week show that tenofovir is excreted in human milk. The impact of this exposure in breastfed infants is unknown.

*Animal 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.

### 6.3 Pediatric Use

Safety and efficacy of DELSTRIGO have not been established in patients younger than 18 years of age *[see Clinical Pharmacology (10.4)]*.

### 6.4 Elderly Use

There are limited data available on the use of doravirine, lamivudine and tenofovir DF in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients *[see Clinical Pharmacology (10.4)]*. Special care is advised in this age group due to age associated changes such as decreases in renal function.

### 6.5 Renal Impairment

Because DELSTRIGO is a fixed-dose combination tablet and the dosage of lamivudine and tenofovir DF cannot be altered, patients with estimated creatinine clearance less than 50 mL/min should not receive DELSTRIGO *[see Warnings and Precautions (4.2) and Clinical Pharmacology (10.4)]*.

### 6.6 Hepatic Impairment

No dose 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 (10.4)]*.

## 7. ADVERSE REACTIONS

## 7.1 Clinical Trials Experience

Summary of the safety profile

The most frequently reported adverse reactions considered possibly or probably related to doravirine were nausea (4%) and headache (3%).

Tabulated summary of adverse reactions

The adverse reactions with suspected (at least possible) relationship to treatment are listed below by body system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), or very rare (<1/10,000).

**Table 2: Tabulated summary of adverse reactions associated with doravirine/lamivudine/tenofovir disoproxil**

| Frequency | Adverse reactions |
|---|---|
| **Blood and lymphatic systems disorders** | |
| Uncommon | neutropenia*, anaemia*, thrombocytopenia* |
| Very rare | pure red cell aplasia* |
| **Infections and infestations** | |
| Rare | rash pustular |
| **Metabolism and nutrition disorders** | |
| Uncommon | hypophosphataemia, hypokalaemia* |
| Rare | hypomagnesaemia, lactic acidosis* |
| **Psychiatric disorders** | |
| Common | abnormal dreams, insomnia[1] |
| Uncommon | nightmare, depression[2], anxiety[3], irritability, confusional state, suicidal ideation |
| Rare | aggression, hallucination, adjustment disorder, mood altered, somnambulism |
| **Nervous system disorders** | |
| Common | headache, dizziness, somnolence |
| Uncommon | disturbance in attention, memory impairment, paraesthesia, hypertonia, poor quality sleep |
| Very rare | peripheral neuropathy (or paraesthesia)* |

| | |
|---|---|
| **Vascular disorders** | |
| Uncommon | hypertension |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common | cough*, nasal symptoms* |
| Rare | dyspnoea, tonsillar hypertrophy |
| **Gastrointestinal disorders** | |
| Common | nausea, diarrhoea, abdominal pain[4], vomiting, flatulence |
| Uncommon | constipation, abdominal discomfort[5], abdominal distension, dyspepsia, faeces soft[6], gastrointestinal motility disorder[7], pancreatitis* |
| Rare | rectal tenesmus |
| **Hepatobiliary disorders** | |
| Rare | hepatic steatosis*, hepatitis* |
| **Skin and subcutaneous tissue disorders** | |
| Common | alopecia*, rash[8] |
| Uncommon | pruritus |
| Rare | dermatitis allergic, rosacea, angioedema* |
| **Musculoskeletal and connective tissue disorders** | |
| Common | muscle disorders* |
| Uncommon | myalgia, arthralgia, rhabdomyolysis*† , muscular weakness*† |
| Rare | musculoskeletal pain, osteomalacia (manifested as bone pain and infrequently contributing to fractures)*, myopathy* |
| **Renal and urinary disorders** | |
| Uncommon | increased creatinine*, proximal renal tubulopathy (including Fanconi syndrome)* |
| Rare | acute kidney injury, renal disorder, calculus urinary, nephrolithiasis, acute renal failure*, renal failure*, acute tubular necrosis*, nephritis (including acute interstitial)*, nephrogenic diabetes insipidus* |
| **General disorders and administration site conditions** | |
| Common | fatigue, fever* |

| | |
|---|---|
| Uncommon | asthenia, malaise |
| Rare | chest pain, chills, pain, thirst |
| **Investigations** | |
| Common | alanine aminotransferase increased[9] |
| Uncommon | aspartate aminotransferase increased, lipase increased, amylase increased, haemoglobin decreased |
| Rare | blood creatine phosphokinase increased |

*This adverse reaction was not identified as an adverse reaction associated with doravirine from the Phase 3 clinical studies (DRIVE-FORWARD, DRIVE-AHEAD, DRIVE-SHIFT), but is included in this table as an adverse reaction based on the Summary of Product Characteristics of 3TC and/or TDF. The highest frequency category reported in the 3TC or TDF Summary of Product Characteristics is used.

† This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil in the absence of this condition.

[1]insomnia includes: insomnia, initial insomnia and sleep disorder

[2]depression includes: depression, depressed mood, major depression, and persistent depressive disorder

[3]anxiety includes: anxiety and generalized anxiety disorder

[4]abdominal pain includes: abdominal pain, and abdominal pain upper

[5]abdominal discomfort includes: abdominal discomfort, and epigastric discomfort

[6]faeces soft includes: faeces soft and abnormal faeces

[7]gastrointestinal motility disorder includes: gastrointestinal motility disorder, and frequent bowel movements

[8]rash includes: rash, rash macular, rash erythematous, rash generalized, rash maculo-papular, rash papular, and urticarial

[9]alanine aminotransferase increased includes: alanine aminotransferase increased and hepatocellular injury

Lactic acidosis

Cases of lactic acidosis have been reported with tenofovir disoproxil alone or in combination with other antiretrovirals. Patients with predisposing factors such as patients with decompensated liver disease, or patients receiving concomitant medications known to induce lactic acidosis are at increased risk of experiencing severe lactic acidosis during tenofovir disoproxil treatment, including fatal outcomes.

### 7.2 Postmarketing Experience

There are no postmarketing data available for DELSTRIGO. See the full prescribing information for lamivudine and tenofovir DF.

## 8. OVERDOSAGE

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.

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

## 9. CLINICAL STUDIES

### 9.1 Adult Subjects with No Antiretroviral Treatment History

The efficacy of DELSTRIGO is based on the analyses of 96-week data from two randomized, multicenter, double-blind, active-controlled Phase 3 trials, (DRIVE-FORWARD and DRIVE-AHEAD) in antiretroviral treatment-naïve, HIV-1-infected subjects (n=1494).

In DRIVE-FORWARD, 766 subjects were randomized and received at least 1 dose of either PIFELTRO once daily or DRV+r 800/100 mg once daily each in combination with emtricitabine/tenofovir DF (FTC/TDF) or abacavir/lamivudine (ABC/3TC) selected by the investigator. At baseline, the median age of subjects was 33 years, 16% were female, 27% were Non-White, 4% had hepatitis B and/or C virus co-infection, 10% had a history of AIDS, 20% had HIV-1 RNA greater

than 100,000 copies/mL, 86% had CD4+ T-cell count greater than 200 cells/mm$^3$, 13% received ABC/3TC and 87% received FTC/TDF; these characteristics were similar between treatment groups.

In DRIVE-AHEAD, 728 subjects were randomized and received at least 1 dose of either DELSTRIGO or EFV/FTC/TDF 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 co-infection, 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/mm$^3$; these characteristics were similar between treatment groups.

Week 96 outcomes for DRIVE-FORWARD and DRIVE-AHEAD are provided in Table 3. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

In DRIVE-FORWARD, PIFELTRO demonstrated consistent efficacy across demographic and baseline prognostic factors, including gender, race, ethnicity, NRTI background therapy, baseline HIV-1 RNA (≤ 100,000 or >100,000 copies/mL), CD4+ T-cell count, and viral subtypes. Mean CD4+ T-cell counts in the PIFELTRO and DRV+r groups increased from baseline by 224 and 207 cells/mm$^3$, respectively.

In DRIVE-AHEAD, DELSTRIGO demonstrated consistent efficacy across demographic and baseline prognostic factors, including gender, race, ethnicity, baseline HIV-1 RNA (≤ 100,000 or >100,000 copies/mL), CD4+ T-cell count, and viral subtypes. Mean CD4+ T-cell counts in the DELSTRIGO and EFV/FTC/TDF groups increased from baseline by 238 and 223 cells/mm$^3$, respectively.

**Table 3: Virologic Outcomes at Week 96 in HIV-1 Adult Subjects with No Antiretroviral Treatment History**

| Outcome | DRIVE-FORWARD | | DRIVE-AHEAD | |
|---|---|---|---|---|
| | PIFELTRO + 2 NRTIs Once Daily | DRV+r + 2 NRTIs Once Daily | DELSTRIGO Once Daily | EFV/FTC/TDF Once Daily |
| | N=379# | N=376# | N=364 | N=364 |
| HIV-1 RNA <50 copies/mL | 73% | 66% | 77% | 74% |

| | | | | |
|---|---|---|---|---|
| Treatment Differences (95% CI)* | 7.1% (0.5%, 13.7%) | | 3.8% (-2.4%, 10.0%) | |
| **HIV-1 RNA ≥ 50 copies/mL**† | 17% | 20% | 15% | 12% |
| **No Virologic Data at Week 96 Window** | 10% | 14% | 7% | 14% |
| Reasons | | | | |
| Discontinued study due to AE or Death‡ | 2% | 4% | 3% | 8% |
| Discontinued study for Other Reasons§ | 7% | 9% | 4% | 5% |
| On study but missing data in window | 1% | 1% | 1% | 1% |
| **Proportion (%) of Subjects With HIV-1 RNA <50 copies/mL at Week 96 by Baseline and Demographic Category** | | | | |
| **Gender** | | | | |
| Male | 73% (N = 315) | 68% (N = 319) | 78% (N = 305) | 73% (N = 311) |
| Female | 73% (N = 64) | 54% (N = 57) | 75% (N = 59) | 75% (N = 53) |
| **Race** | | | | |
| White | 78% (N = 277) | 69% (N = 276) | 80% (N = 176) | 74% (N = 170) |
| Non-White | 59% (N = 102) | 59% (N = 99) | 76% (N = 188) | 74% (N = 194) |
| **Ethnicity** | | | | |
| Hispanic or Latino | 78% (N = 91) | 64% (N = 85) | 81% (N = 126) | 77% (N = 119) |
| Not Hispanic or Latino | 72% (N = 283) | 67% (N = 285) | 76% (N = 238) | 72% (N = 239) |
| **NRTI Background Therapy** | | | | |
| FTC/TDF | 72% (N = 329) | 66% (N = 328) | - | - |
| ABC/3TC | 80% (N = 50) | 67% (N = 48) | - | - |
| **Baseline HIV-1 RNA (copies/mL)** | | | | |
| ≤ 100,000 copies/mL | 76% (N = 297) | 67% (N = 303) | 80% (N = 291) | 77% (N = 282) |

| | | | | |
|---|---|---|---|---|
| >100,000 copies/mL | 62% (N = 82) | 60% (N = 72) | 67% (N = 73) | 62% (N = 82) |
| **CD4+ T-cell Count (cells/mm$^3$)** | | | | |
| ≤ 200 cells/mm$^3$ | 65% (N = 40) | 52% (N = 65) | 59% (N = 44) | 70% (N = 46) |
| >200 cells/mm$^3$ | 74% (N = 339) | 69% (N = 311) | 80% (N = 320) | 74% (N = 318) |
| **Viral Subtype¶** | | | | |
| Subtype B | 72% (N = 262) | 67% (N = 266) | 80% (N = 232) | 72% (N = 253) |
| Subtype Non-B | 75% (N = 117) | 63% (N = 110) | 73% (N = 130) | 77% (N = 111) |

#For Week 96, subjects with missing HIV-1 RNA due to Abbott manufacture agent recall were excluded from the analysis.

*The 95% CIs for the treatment differences were calculated using stratum-adjusted Mantel-Haenszel method.

† Includes subjects who discontinued study drug or study before Week 96 for lack or loss of efficacy and subjects with HIV-1 RNA equal to or above 50 copies/mL in the Week 96 window.

‡ Includes subjects who discontinued because of adverse event (AE) or death if this resulted in no virologic data in the Week 96 window.

¶Viral subtype was not available for two subjects.

§Other Reasons include: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, protocol deviation, screen failure, withdrawal by subject.

Note: NRTIs = FTC/TDF or ABC/3TC.

P007 was a Phase 2b trial in antiretroviral treatment-naïve HIV-1-infected adult subjects (n=340). In Part I, subjects were randomized to receive one of 4 doses of PIFELTRO or EFV, each in combination with FTC/TDF. After Week 24, all subjects randomized to receive PIFELTRO were switched to (or maintained on) PIFELTRO 100 mg. Additional subjects were randomized in Part II to receive either PIFELTRO 100 mg or EFV, each in combination with FTC/TDF. In both parts of the trial, PIFELTRO and EFV were administered as blinded-therapy and FTC/TDF was administered open-label.

At Week 48, the proportion of subjects with HIV-1 RNA less than 50 copies/mL was 79% (85/108) and 82% (89/108) for PIFELTRO 100 mg and EFV, respectively. At Week 96, the proportion of subjects with HIV-1 RNA less than 50 copies/mL was 76% (82/108) and 76% (82/108) for PIFELTRO 100 mg and EFV, respectively. At Week 48, mean CD4+ T-cell counts in the PIFELTRO 100 mg and

EFV groups increased from baseline by 192 and 195 cells/mm$^3$, respectively. At Week 96, mean CD4+ T-cell counts in the PIFELTRO 100 mg and EFV groups increased from baseline by 259 and 264 cells/mm$^3$, respectively.

### 9.2 Virologically-Suppressed Adult Subjects

The efficacy of switching from a baseline regimen consisting of two NRTIs in combination with a ritonavir- or cobicistat-boosted PI, or cobicistat-boosted elvitegravir, or an NNRTI to DELSTRIGO was evaluated in a randomized, open-label trial (DRIVE-SHIFT), in virologically-suppressed HIV-1-infected adults. Subjects must have been virologically-suppressed (HIV-1 RNA <50 copies/mL) on their baseline regimen for at least 6 months prior to trial entry, with no history of virologic failure. Subjects were randomized to either switch to DELSTRIGO at baseline [n=447, Immediate Switch Group (ISG)], or stay on their baseline regimen until Week 24, at which point they switched to DELSTRIGO [n = 223, Delayed Switch Group (DSG)]. At baseline, the median age of subjects was 43 years, 16% were female, and 24% were Non-White.

In the DRIVE-SHIFT trial, an immediate switch to DELSTRIGO was demonstrated to be non-inferior at Week 48 compared to continuation of the baseline regimen at Week 24 as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL. Consistent results were seen for the comparison at Study Week 24 in each treatment group. Treatment results are shown in Table 4.

**Table 4: Virologic Outcomes in DRIVE-SHIFT in HIV-1 Virologically-Suppressed Subjects Who Switched to DELSTRIGO**

| Outcome | DELSTRIGO Once Daily ISG Week 48 N=447 | Baseline Regimen DSG Week 24 N=223 |
|---|---|---|
| **HIV-1 RNA <50 copies/mL** | 91% | 95% |
| ISG-DSG, Difference (95% CI)* | 3.8% (-7.9%, 0.3%)* | |
| **HIV-1 RNA ≥ 50 copies/mL†** | 2% | 2% |
| **No Virologic Data at Within the Time Window** | 8% | 4% |
| Discontinued study due to AE or Death‡ | 3% | 0 |
| Discontinued study for Other Reasons§ | 4% | 4% |

| | | |
|---|---|---|
| On study but missing data in window | 0 | 0 |
| **Proportion (%) of Subjects With HIV-1 RNA <50 copies/mL by Baseline and Demographic Category** | | |
| **Gender** | | |
| Male | 91% (N = 372) | 94% (N = 194) |
| Female | 91% (N = 75) | 100% (N = 29) |
| **Race** | | |
| White | 90% (N = 344) | 95% (N = 168) |
| Non-White | 93% (N = 103) | 93% (N = 55) |
| **Ethnicity** | | |
| Hispanic or Latino | 88% (N = 99) | 91% (N = 45) |
| Not Hispanic or Latino | 91% (N = 341) | 95% (N = 175) |
| **CD4+ T-cell Count (cells/mm$^3$)** | | |
| <200 cells/mm$^3$ | 85% (N = 13) | 75% (N = 4) |
| ≥ 200 cells/mm$^3$ | 91% (N = 426) | 95% (N = 216) |

*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 ISG or before Week 24 for DSG for lack or loss of efficacy and subjects with HIV-1 RNA ≥ 50 copies/mL in the Week 48 window for ISG and in the Week 24 window for DSG.

‡ Includes subjects who discontinued because of adverse event (AE) or death if this resulted in no virologic data on treatment during the specified window.

§Other Reasons include: lost to follow-up, non-compliance with study drug, physician decision, protocol deviation, withdrawal by subject.

Baseline Regimen = ritonavir or cobicistat-boosted PI (specifically atazanavir, darunavir, or lopinavir), or cobicistat-boosted elvitegravir, or NNRTI (specifically efavirenz, nevirapine, or rilpivirine), each administered with two NRTIs.

## 10. CLINICAL PHARMACOLOGY

### 10.1 Therapeutic Class

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

Lamivudine and Tenofovir DF are HIV-1 nucleoside analogue reverse transcriptase inhibitors (NRTI).

### 10.2 Mechanism of Action

DELSTRIGO is a fixed-dose combination of the antiviral drugs doravirine, lamivudine, and tenofovir DF *[see Clinical Pharmacology (10.3)]*.

### 10.3 Pharmacodynamics

Effects on Electrocardiogram

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

**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). The inhibitory concentration at 50% ($IC_{50}$) of doravirine for RNA-dependent DNA polymerization of recombinant wild-type HIV-1 RT in a biochemical assay was 12.2±2.0 nM (n=3). 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.

*Tenofovir DF:* Tenofovir DF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir DF 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 1.2 nM to 10.0 nM. The antiviral activity of doravirine was not antagonistic when combined with lamivudine and tenofovir DF.

*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 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median $EC_{50}$ values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B) respectively. Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

*Tenofovir DF:* 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 microM. 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 microM).

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, V106I, V106M, V108I, H221Y, F227C, F227I, F227L, F227V, M230I, L234I, P236L, and Y318F. The V106A, V106M, V108I, H221Y, F227C, M230I, P236L, and Y318F substitutions conferred 3.4-fold to 70-fold reductions in susceptibility to doravirine. Y318F in combination with V106A, V106M, V108I, and F227C conferred greater decreases in susceptibility to doravirine than Y318F alone, which conferred a 10-fold reduction in susceptibility to doravirine.

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

*Tenofovir DF:* HIV-1 isolates selected by tenofovir 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*

In Adult Subjects with No Antiretroviral Treatment History

*Doravirine*: In the doravirine treatment arms of the treatment-naïve trials DRIVE-FORWARD and DRIVE-AHEAD (n=747) through Week 48, emergent doravirine resistance-associated substitutions were observed in 7 of 30 subjects in the resistance analysis subset (subjects with HIV-1 RNA greater than 400 copies per mL at virologic failure or at early study discontinuation and having resistance data). In the DRV+r treatment arm of the DRIVE-FORWARD trial (n=383), no emergent darunavir resistance-associated substitutions were observed in the 11 subjects in the resistance analysis subset. In the EFV/FTC/TDF treatment arm of the DRIVE-AHEAD trial (n=364), emergent efavirenz resistance-associated substitutions were observed in 12 out of 24 subjects in the resistance analysis subset.

Emergent doravirine resistance-associated substitutions in RT included one or more of the following: A98G, V106A, V106I, V106M/T, Y188L, H221Y, P225H, F227C, F227C/R, and Y318Y/F.

In the doravirine treatment-arm of DRIVE-FORWARD between Weeks 48 and 96, one subject developed RT V106A and P225H doravirine resistance-associated substitutions. The resistance-associated substitutions that emerged were RT V106A and P225H and conferred >95-fold reduction in doravirine susceptibility. In the DRIVE-FORWARD trial between Weeks 48 and 96, no subjects showed the emergence of darunavir resistance-associated substitutions. In the DRIVE-AHEAD trial between Weeks 48 and 96, 3 subjects in the EFV/FTC/TDF treatment arm showed the emergence of efavirenz resistance-associated substitutions.

*Lamivudine and Tenofovir DF*: In a pooled analysis of antiretroviral-naïve subjects who received doravirine, lamivudine, and tenofovir DF, 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 or at time of

early study drug discontinuation. Genotypic resistance developed in 7 evaluable subjects who received DOR/3TC/TDF through Week 48. The resistance– associated substitutions that emerged were RT M41L (n=1), K65R (n=2), and M184V/I (n=4). Through Weeks 0 to 96, genotypic resistance to lamivudine and tenofovir developed in 1 subject who received DOR/3TC/TDF; the emergent resistance-associated substitutions was A62A/V (n=1).

In Virologically-Suppressed Adult Subjects

In the DRIVE-SHIFT clinical trial, no subject developed genotypic or phenotypic resistance to doravirine, lamivudine, or TDF during treatment with DELSTRIGO in either the immediate (n=447) or delayed switch (n=209) groups. One subject developed RT M184M/I mutation and phenotypic resistance to lamivudine and emtricitabine during treatment with their baseline regimen. None of the 24 subjects (11 immediate switch group [day 1], 13 delayed switch group [Week 24]) with baseline NNRTI mutations (RT K103N, G190A, or Y181C) experienced virologic failure through Week 48 or at time of discontinuation.

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:* Laboratory strains of HIV-1 harboring the common NNRTI-associated mutations K103N, Y181C, or K103N/Y181C substitutions in RT exhibit less than a 3-fold decrease in susceptibility to doravirine compared to wild-type virus when evaluated in the presence of 100% NHS. Doravirine was able to suppress the following NNRTI-associated substitutions: K103N, Y181C, G190A, and E138K mutants under clinically relevant concentrations.

A panel of 96 diverse clinical isolates containing NNRTI-associated mutations was evaluated for susceptibility to doravirine in the presence of 10% fetal bovine serum. Clinical isolates containing the Y188L substitution or V106 substitutions in combination with A98G, H221Y, P225H, F227C or Y318F showed greater than 100-fold reduced susceptibility to doravirine.

Treatment emergent doravirine resistance-associated substitutions may confer cross-resistance to efavirenz, rilpivirine, nevirapine, and etravirine. Of the 8 virologic failure subjects who developed doravirine phenotypic resistance, all had phenotypic resistance to nevirapine, 6 had phenotypic resistance to efavirenz, 4 had phenotypic resistance to rilpivirine, and 4 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 emtricitabine. Lamivudine-resistant HIV-1 mutants were also cross-resistant to didanosine (ddI). In some subjects treated with zidovudine plus didanosine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

*Tenofovir DF*: 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 tenofovir DF 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 tenofovir DF. 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.

### 10.4 Pharmacokinetics

Single dose administration of one DELSTRIGO tablet to healthy subjects (N=24) under fasted conditions provided comparable exposures of doravirine, lamivudine, and tenofovir to administration of doravirine tablets (100 mg) plus lamivudine tablets (300 mg) plus tenofovir DF tablets (300 mg).

*Doravirine:* The pharmacokinetics of doravirine were studied in healthy subjects and HIV-1-infected subjects. Doravirine pharmacokinetics are similar in healthy subjects and HIV-1-infected subjects. Steady state is generally achieved by day 2 of once daily dosing, with accumulation ratios of 1.2 to 1.4 for $AUC_{0-24}$, $C_{max}$, and $C_{24}$. Doravirine steady state pharmacokinetics following administration of 100 mg once daily to HIV-1-infected subjects, based on a population pharmacokinetic analysis, are provided below.

| Parameter<br>GM (%CV) | $AUC_{0-24}$<br>µ M hr | $C_{max}$<br>µ M | $C_{24}$<br>nM |
|---|---|---|---|
| Doravirine<br>100 mg<br>once daily | 37.8 (29) | 2.26 (19) | 930 (63) |

GM: Geometric mean, %CV: Geometric coefficient of variation

Absorption

Following oral dosing, peak plasma concentrations are achieved 2 hours after dosing. Doravirine has an absolute bioavailability of approximately 64% for the 100 mg tablet.

Distribution

Based on administration of an IV microdose, the volume of distribution of doravirine is 60.5 L. Doravirine is approximately 76% bound to plasma proteins.

Metabolism

Based on *in vitro* data, doravirine is primarily metabolized by CYP3A.

Elimination

Doravirine has a terminal half-life ($t_{1/2}$) of approximately 15 hours. Doravirine is primarily eliminated via oxidative metabolism. Excretion of unchanged drug via urinary excretion is minor. Biliary excretion of unchanged drug is not expected to be significant.

*Lamivudine:* Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy subjects, steady-state $C_{max}$ ($C_{max,ss}$) was 2.04 ± 0.54 mcg per mL (mean ± SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg• hour per mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours). In most single dose trials in HIV-1– infected subjects, HBV-infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours. In HIV-1– infected subjects, total clearance was 398.5 ± 69.1 mL per min (mean ± SD).

*Tenofovir DF:* Following oral administration of a single 300 mg dose of tenofovir DF to HIV-1-infected subjects in the fasted state, $C_{max}$ was achieved in one hour. $C_{max}$ and AUC values were 0.30 ± 0.09 µg per mL and 2.29 ± 0.69 µg• hr per mL, respectively. The oral bioavailability of tenofovir from tenofovir DF in fasted subjects is approximately 25%. Less than 0.7% of tenofovir binds to human plasma proteins *in vitro* over the range of 0.01 to 25 µg per mL. Approximately 70-80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine within 72 hours of dosing. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion with a

renal clearance in adults with creatinine clearance greater than 80 mL per minute of 243.5 ± 33.3 mL per minute (mean ± SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Effect of Food on Oral Absorption

The administration of a single DELSTRIGO tablet with a high-fat meal to healthy subjects resulted in a 26% increase in doravirine $C_{24}$, while AUC and $C_{max}$ were not significantly affected. Lamivudine $C_{max}$ decreased by 19% with a high-fat meal, while AUC was not significantly affected. Tenofovir $C_{max}$ decreased by 12% and AUC increased by 27% with a high-fat meal. These differences in pharmacokinetics are not clinically relevant.

Special Populations

*Renal Impairment*

*Doravirine*: Renal excretion of doravirine is minor: approximately 6% of the administered dose is excreted unchanged in urine. In a study comparing 8 subjects with severe renal impairment to 8 subjects without renal impairment, the single dose exposure of doravirine was 43% higher in subjects with severe renal impairment. In a population pharmacokinetic analysis, renal function did not have a clinically relevant effect on doravirine pharmacokinetics. No dose adjustment is required in patients with mild, moderate or severe renal impairment. Doravirine has not been studied in patients with end-stage renal disease or in patients undergoing dialysis *[see Use in Specific Populations (6.5)]*.

*Lamivudine:* The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-1– infected adults with impaired renal function (Table 5).

**Table 5: Pharmacokinetic Parameters (Mean ± SD) After a Single 300-mg Oral Dose of Lamivudine in 3 Groups of Adults with Varying Degrees of Renal Function**

| | Creatinine Clearance Criterion (Number of Subjects) | | |
|---|---|---|---|
| **Parameter** | **>60 mL/min** | **10-30 mL/min** | **<10 mL/min** |
| | **N=6** | **N=4** | **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 |
| $AUC_{\infty}$ (mcg• h/mL) | 11.0 ± 1.7 | 48.0 ± 19 | 157 ± 74 |

| | | | |
|---|---|---|---|
| Cl/F (mL/min) | 464 ± 76 | 114 ± 34 | 36 ± 11 |

*Tenofovir DF*: The pharmacokinetics of tenofovir is altered in subjects with renal impairment. In subjects with creatinine clearance below 50 mL per minute or with end stage renal disease requiring dialysis, $C_{max}$ and AUC of tenofovir were increased *[see Warnings and Precautions (4.2) and Use in Specific Populations (6.5)]*.

*Hepatic Impairment*

*Doravirine*: Doravirine is primarily metabolized and eliminated by the liver. There was no clinically relevant difference in the pharmacokinetics of doravirine in a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh score B) to 8 subjects without hepatic impairment. No dose adjustment is required in patients with mild or moderate hepatic impairment. Doravirine has not been studied in subjects with severe hepatic impairment (Child-Pugh score C) *[see Use in Specific Populations (6.6)]*.

*Lamivudine:* The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

*Tenofovir DF:* The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir DF have been studied in healthy subjects with moderate to severe hepatic impairment. No clinically relevant differences in tenofovir pharmacokinetics were observed between subjects with hepatic impairment and healthy subjects.

*Pediatric*

The pharmacokinetics and dosing recommendations of DELSTRIGO in patients younger than 18 years of age have not been established *[see Use in Specific Populations (6.3)]*.

*Elderly*

No clinically relevant differences in the pharmacokinetics of doravirine have been identified in subjects at least 65 years of age compared to subjects less than 65 years of age in a Phase 1 trial or in a population pharmacokinetic analysis. The pharmacokinetics of lamivudine and tenofovir have not been studied in subjects older than 65 years *[see Use in Specific Populations (6.4)]*.

*Race*

*Doravirine:* No clinically relevant racial differences in the pharmacokinetics of doravirine have been identified based on a population pharmacokinetic analysis of doravirine in healthy and HIV-1-infected subjects.

*Lamivudine:* There are no significant or clinically relevant racial differences in pharmacokinetics of lamivudine.

*Tenofovir DF:* There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following the administration of tenofovir DF.

*Gender*

No clinically relevant pharmacokinetic differences have been identified between men and women for doravirine, lamivudine, and tenofovir.

### 10.5 Drug Interaction Studies

DELSTRIGO is a complete regimen for the treatment of HIV-1 infection; therefore, DELSTRIGO should not 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 tenofovir DF, as single entities; no drug interaction trials have been conducted using the combination of doravirine lamivudine and tenofovir DF. No clinically relevant drug interactions were observed between doravirine, lamivudine and tenofovir DF.

*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. 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 of other drugs on the $C_{max}$, AUC, and $C_{24}$ values of doravirine are

summarized in Table 6. The effects of co-administration of doravirine on the $C_{max}$ and AUC values of other drugs are summarized in Table 7. *[See Drug Interactions and Other Forms of Interactions (5).]*

Table 6: Drug Interactions: Changes in Pharmacokinetic Parameter Values of Doravirine in the Presence of Co-administered Drug

| Co-administered Drug | Regimen of Co-administered Drug | Regimen of Doravirine | 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 | 100 mg SD | 10 | 3.06 (2.85, 3.29) | 1.25 (1.05, 1.49) | 2.75 (2.54, 2.98) |
| **Antimycobacterials** | | | | | | |
| rifampin | 600 mg SD | 100 mg SD | 11 | 0.91 (0.78, 1.06) | 1.40 (1.21, 1.63) | 0.90 (0.80, 1.01) |
| | 600 mg QD | 100 mg SD | 10 | 0.12 (0.10, 0.15) | 0.43 (0.35, 0.52) | 0.03 (0.02, 0.04) |
| rifabutin | 300 mg QD | 100 mg SD | 12 | 0.50 (0.45, 0.55) | 0.99 (0.85, 1.15) | 0.32 (0.28, 0.35) |
| **HIV Antiviral Agents** | | | | | | |
| tenofovir DF | 300 mg QD | 100 mg SD | 7 | 0.95 (0.80, 1.12) | 0.80 (0.64, 1.01) | 0.94 (0.78, 1.12) |
| lamivudine + tenofovir DF | 300 mg lamivudine SD + 300 mg tenofovir DF SD | 100 mg SD | 15 | 0.96 (0.87, 1.06) | 0.97 (0.88, 1.07) | 0.94 (0.83, 1.06) |
| **Hepatitis C Antiviral Agents** | | | | | | |
| elbasvir + grazoprevir | 50 mg elbasvir QD + 200 mg grazoprevir QD | 100 mg QD | 12 | 1.56 (1.45, 1.68) | 1.41 (1.25, 1.58) | 1.61 (1.45, 1.79) |
| ledipasvir + sofosbuvir | 90 mg ledipasvir SD + 400 mg sofosbuvir SD | 100 mg SD | 14 | 1.15 (1.07, 1.24) | 1.11 (0.97, 1.27) | 1.24 (1.13, 1.36) |
| **Acid-Reducing Agents** | | | | | | |
| antacid (aluminum and magnesium hydroxide oral suspension) | 20 mL SD | 100 mg SD | 14 | 1.01 (0.92, 1.11) | 0.86 (0.74, 1.01) | 1.03 (0.94, 1.12) |
| pantoprazole | 40 mg QD | 100 mg SD | 13 | 0.83 (0.76, 0.91) | 0.88 (0.76, 1.01) | 0.84 (0.77, 0.92) |
| **Opioid Analgesics** | | | | | | |
| methadone | 20-200 mg QD | 100 mg QD | 14 | 0.74 (0.61, 0.90) | 0.76 (0.63, 0.91) | 0.80 (0.63, 1.03) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | individualized dose | | | | | |
| CI = Confidence interval; SD = Single Dose; QD = Once Daily<br>*$AUC_{0-\infty}$ for single dose, $AUC_{0-24}$ for once daily. | | | | | | |

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

| Co-administered Drug | Regimen of Co-administered Drug | Regimen of Doravirine | N | Geometric Mean Ratio [90% CI] Drug Pharmacokinetics with/without Co-administered Doravirine (No Effect=1.00) | | |
|---|---|---|---|---|---|---|
| | | | | AUC* | $C_{max}$ | $C_{24}$ |
| **CYP3A Substrate** | | | | | | |
| midazolam | 2 mg SD | 120 mg QD | 7 | 0.82 (0.70, 0.97) | 1.02 (0.81, 1.28) | - |
| **HIV-Antiviral Agents** | | | | | | |
| lamivudine | 300 mg lamivudine SD + 300 mg tenofovir DF SD | 100 mg SD | 15 | 0.94 (0.88, 1.00) | 0.92 (0.81, 1.05) | - |
| tenofovir DF | | | | 1.11 (0.97, 1.28) | 1.17 (0.96, 1.42) | - |
| **HCV-Antiviral Agents** | | | | | | |
| elbasvir | 50 mg elbasvir QD + 200 mg grazoprevir QD | 100 mg QD | 12 | 0.96 (0.90, 1.02) | 0.96 (0.91, 1.01) | 0.96 (0.89, 1.04) |
| grazoprevir | | | | 1.07 (0.94, 1.23) | 1.22 (1.01, 1.47) | 0.90 (0.83, 0.96) |
| ledipasvir | 90 mg ledipasvir SD + 400 mg sofosbuvir SD | 100 mg SD | 14 | 0.92 (0.80, 1.06) | 0.91 (0.80, 1.02) | -- |
| sofosbuvir | | | | 1.04 (0.91, 1.18) | 0.89 (0.79, 1.00) | -- |
| GS-331007 | | | | 1.03 (0.98, 1.09) | 1.03 (0.97, 1.09) | -- |
| **Oral Contraceptives** | | | | | | |
| ethinyl estradiol | 0.03 mg ethinyl estradiol + 0.15 mg levonorgestrel (Nordette®-28) SD | 100 mg QD | 19 | 0.98 (0.94, 1.03) | 0.83 (0.80, 0.87) | -- |
| levonorgestrel | | | | 1.21 (1.14, 1.28) | 0.96 (0.88, 1.05) | -- |
| **Statins** | | | | | | |
| atorvastatin | 20 mg SD | 100 mg QD | 14 | 0.98 (0.90, 1.06) | 0.67 (0.52, 0.85) | - |
| **Antidiabetics** | | | | | | |
| metformin | 1000 mg SD | 100 mg QD | 14 | 0.94 (0.88, 1.00) | 0.94 (0.86, 1.03) | - |
| **Opioid Analgesics** | | | | | | |
| methadone (R-methadone) | 20-200 mg QD individualized dose | 100 mg QD | 14 | 0.95 (0.90, 1.01) | 0.98 (0.93, 1.03) | 0.95 (0.88, 1.03) |
| methadone (S- | | | | 0.98 (0.90, 1.06) | 0.97 (0.91, 1.04) | 0.97 (0.86, 1.10) |

| | | | | | | |
|---|---|---|---|---|---|---|
| methadone) | | | | | | |
| CI = Confidence interval; SD = Single Dose; QD = Once Daily.<br>*$AUC_{0-\infty}$ for single dose, $AUC_{0-24}$ for once daily. | | | | | | |

*Lamivudine*

*Trimethoprim/Sulfamethoxazole:* Lamivudine and trimethoprim/sulfamethoxazole (TMP/SMX) were co-administered to 14 HIV-positive patients in a single-center, open-label, randomized, crossover study. Each patient received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design. Co-administration of TMP/SMX with lamivudine resulted in an increase of 43%±23% (mean ±SD) in lamivudine $AUC_{\infty}$ , 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.

*Tenofovir DF*

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, co-administration of tenofovir DF with drugs that are eliminated by active tubular secretion may increase concentrations of tenofovir, and/or the co-administered drug *[see Warnings and Precautions (4.2) and Drug Interactions and Other Forms of Interactions (5.1)]*.

Drug interaction studies were performed for tenofovir DF and the following medications: entecavir, methadone, oral contraceptives (ethinyl estradiol/norgestimate), and tacrolimus. Tacrolimus increased the $C_{max}$ of tenofovir by 13% (90% CI: [↑ 1% to ↑ 27%]) and had no effect on the tenofovir AUC and $C_{min}$. Tenofovir had no effect on the $C_{max}$, AUC, and $C_{min}$ of tacrolimus.

The $C_{max}$, AUC, and $C_{min}$ of tenofovir were not affected in the presence of entecavir. Tenofovir increased the AUC of entecavir by 13% (90% CI: [↑ 11% to ↑ 15%]) and had no effect on the entecavir $C_{max}$ and $C_{min}$.

Tenofovir had no effect on the $C_{max}$, AUC, and $C_{min}$ of methadone or ethinyl estradiol/norgestimate.

## 11. ANIMAL TOXICOLOGY

No animal studies have been conducted with DELSTRIGO. The following data are based on findings in separate studies with the individual components of DELSTRIGO (doravirine, lamivudine, and tenofovir disoproxil fumarate).

### 11.1 Acute Toxicity

*Doravirine:* No acute toxicity studies were performed.

*Lamivudine:* Acute toxicity studies with lamivudine have been performed in the mouse and rat. There were no deaths and no evidence of target organ toxicity following acute oral administration of very high doses of lamivudine (two doses of 2000 mg/kg) in mice. Intravenous single dose administration of lamivudine at 2000 mg/kg was well tolerated by both mice and rats, with only non-specific clinical signs of relatively short duration observed, and was not associated with any target organ toxicity.

*Tenofovir DF:* Following single doses, the no-effect-level (NOEL) in rats was 1500 mg/kg. Following single doses in dogs (up to 270 mg/kg), mild renal tubular karyomegaly and/or basophilia were the only effects observed. An assessment of effects on renal function after a single dose demonstrated increased urinary electrolyte excretion and urine volume in rats administered tenofovir DF 500 mg/kg; no effect was observed at 50 mg/kg. When rats were administered tenofovir DF (0, 50, or 500 mg/kg) to evaluate effects on the gastrointestinal transit of a charcoal meal, there was reduced gastric emptying at 500 mg/kg/day, but no effect at 50 mg/kg/day.

### 11.2 Chronic Toxicity

*Doravirine:* In repeat-dose oral toxicity studies, doravirine was very well tolerated in all animal species up to the highest doses tested. There were no adverse effects or target organs of toxicity identified in rats dosed for 6 months with 450 mg/kg/day, or in dogs dosed with 1000 mg/kg/day for 9 months (approximately 7 times and 18 times, respectively, above the exposure at the RHD).

*Lamivudine:* In repeat-dose toxicity studies, lamivudine was very well tolerated in the rat at oral doses up to 2000 mg/kg b.i.d. for 6 months and in dogs up to 1000 mg/kg/b.i.d for up to 12 months. In dogs, deaths were seen in females dosed with 1500 mg/kg b.i.d. in a 3-month study. Treatment-related effects in chronic toxicity studies were restricted to minor hematological (mainly red cell parameters), clinical chemistry and urinalysis changes, and mucosal hyperplasia of the cecum (in rats). Hematological changes included reductions in red cell counts at all dose levels, associated with increased MCV and MCH, and reductions in total leucocyte, neutrophil and lymphocyte counts in high-dose animals, but with no effect on bone marrow cytology. The no (toxicologically important)

effect level was 450 mg/kg b.i.d in rats and 45 mg/kg/day in dog, which is approximately 17-fold and 9-fold respectively above the human exposure at the RHD.

*Tenofovir DF:* Tenofovir and tenofovir DF 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 the 4 animal species tested. 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.

### 11.3 Carcinogenesis

*Doravirine:* Long-term oral carcinogenicity studies of doravirine in mice and rats showed no evidence of carcinogenic potential at exposures up to 6 times (mice) and 7 times (rats) the human exposures at the RHD.

*Lamivudine:* Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 12 times (mice) and 57 times (rats) the human exposures at the RHD.

*Tenofovir DF:* Long-term oral carcinogenicity studies of tenofovir DF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the RHD. At the high-dose in female mice, liver adenomas were increased at exposures 10 times of that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 4 times that observed in humans at the RHD.

### 11.4 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.

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

### 11.5 Reproduction

*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:* Lamivudine did not affect male or female fertility in rats at doses associated with exposures approximately 112 times higher than the exposures in humans at the RHD.

*Tenofovir DF:* There were no effects on fertility, mating performance or early embryonic development when tenofovir DF 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.

### 11.6 Development

*Doravirine:* Reproduction studies with orally administered doravirine have been performed in rats and rabbits at exposures approximately 9 times (rats) and 8 times (rabbits) the exposure in humans at the RHD with no effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development. Doravirine was administered orally at up to 300 mg/kg/day to pregnant rabbits on gestation days 7 to 20, and up to 450 mg/kg/day to rats on gestation days 6 to 20, and also to rats on gestation day 6 to lactation/postpartum day 20. Studies in pregnant rats and rabbits showed that doravirine is transferred to the fetus through the placenta, with fetal plasma concentrations of up to 40% (rabbits) and 52% (rats) that of maternal concentrations observed on gestation day 20.

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.

*Lamivudine:* Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses producing plasma levels up to approximately 32 times the human at the RHD. No evidence of teratogenicity due to lamivudine 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 plasma levels up to 32 times those in humans. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta.

*Tenofovir DF:* 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.

## 12. NAME OF THE DRUG

DELSTRIGO (doravirine, lamivudine, and tenofovir disoproxil fumarate).

## 13. PHARMACEUTICAL FORM

DELSTRIGO is available as a yellow, oval-shaped, film-coated tablet, 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).

## 14. PHARMACEUTICAL PARTICULARS

DELSTRIGO is a fixed-dose combination, film-coated tablet, containing doravirine, lamivudine, and tenofovir DF 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.

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

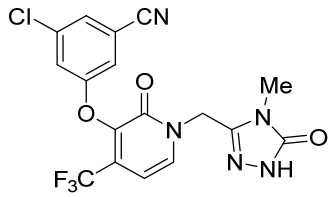
## 14.1 Chemistry

*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 $C_{17}H_{11}ClF_3N_5O_3$ and a molecular weight of 425.75.

It has the following structural formula:



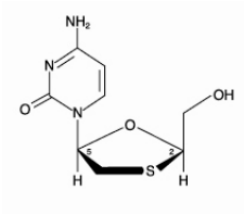

Doravirine is practically insoluble in water.

*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:



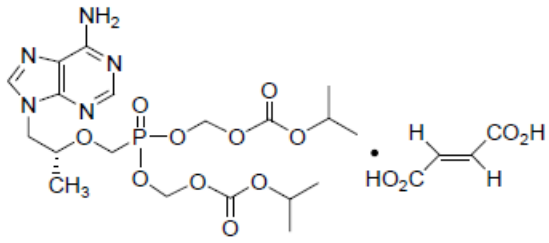
Lamivudine is soluble in water.

*Tenofovir DF*

The chemical name for 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 slightly soluble in water.

## 14.2 Composition

### Active Ingredient

Each tablet contains 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir DF (equivalent to 245 mg of tenofovir disoproxil) as active ingredients.

### Inactive Ingredients (List of Excipients)

Each tablet includes the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, sodium stearyl fumarate, and carnauba wax. The tablets are film coated with a coating material containing the following inactive ingredients: hypromellose, iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin.

### 14.3 Storage

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

Store DELSTRIGO below 30°C.

### 14.4 Shelf Life

Refer to outer carton.

### 14.5 Availability (a.k.a. Nature and Contents of Container)

DELSTRIGO is supplied in a high-density polyethylene (HDPE) bottle containing 30 tablets with silica gel desiccant and is closed with a polypropylene child-resistant closure.

**Product Owner:**
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MSD