PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PR DELSTRIGO®

doravirine/lamivudine/tenofovir disoproxil fumarate tablets

Tablets, 100 mg/300 mg/300 mg, oral

Antiviral Agent

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RECENT MAJOR LABEL CHANGES

Serious Warnings and Precautions Box (3)	(Approved date 08/2019)
Warnings and Precautions (7)	(Approved date 08/2019)

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DELSTRIGO® (doravirine/lamivudine/tenofovir disoproxil fumarate) is indicated as a complete regimen for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults without past or present evidence of viral resistance to doravirine, lamivudine, or tenofovir.

1.1 Pediatrics (< 18 years of age)

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

1.2 Geriatrics (≥ 65 years of age)

There are limited data available on the use of doravirine, lamivudine and tenofovir disoproxil fumarate (tenofovir DF) in patients aged 65 years and over.

2 CONTRAINDICATIONS

DELSTRIGO® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS. COMPOSITION AND PACKAGING**.

DELSTRIGO® is contraindicated 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 **DRUG INTERACTIONS, Drug-Drug Interactions**). 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[1];
- the cytotoxic agent mitotane;
- St. John's wort (*Hypericum perforatum)*.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- 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 (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

- **Nephrotoxicity**
  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 (see **WARNINGS AND PRECAUTIONS, Renal**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

As with all antiretroviral drugs, therapy should be initiated by a healthcare professional experienced in the management of HIV-1 infection.

Testing

DELSTRIGO® contains lamivudine and tenofovir DF, and therefore, test for hepatitis B virus infection prior to or when initiating DELSTRIGO® (see **WARNINGS AND PRECAUTIONS, Special Populations**).

DELSTRIGO® contains tenofovir DF and therefore, all patients should be assessed for creatinine clearance, prior to initiation of DELSTRIGO® and periodically during DELSTRIGO® therapy; patients at risk of renal dysfunction should additionally be tested for serum phosphorus, urine glucose, and urine protein (see **WARNINGS AND PRECAUTIONS, Renal**).

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose
Adults
The recommended dosage regimen of DELSTRIGO® is one tablet taken orally once daily with or without food.

Pediatrics (< 18 years of age)
Safety and efficacy of DELSTRIGO® have not been established in patients younger than 18 years of age (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Geriatrics (≥ 65 years of age)
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 **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics** **and** **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**). Special care is advised in this age group due to age associated changes such as decreases in renal function.

Dosage Adjustment
Renal Impairment
As 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, Special Populations, Renal Impairment** **and** **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

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). It is not known whether the exposure to doravirine will increase in patients with severe hepatic impairment. Therefore, caution is advised when DELSTRIGO® is administered to patients with severe hepatic impairment (see **WARNINGS AND PRECAUTIONS, Special Populations, Hepatic Impairment** **and** **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Coadministration with Moderate CYP3A Inducers
If DELSTRIGO® is coadministered with rifabutin, one tablet of doravirine 100 mg (PIFELTRO®) should be taken approximately 12 hours after the dose of DELSTRIGO® (see **WARNINGS AND PRECAUTIONS, Use with CYP3A Inducers** **and** **DRUG INTERACTIONS, Drug-Drug Interactions**).

Co-administration of DELSTRIGO® with other moderate CYP3A inducers (e.g. dabrafenib, bosentan, modafinil) has not been evaluated and should be avoided. If coadministration cannot be avoided, one tablet of doravirine 100 mg (PIFELTRO®) should be taken approximately 12 hours after the dose of DELSTRIGO® (see **WARNINGS AND PRECAUTIONS, Use with CYP3A Inducers** **and** **DRUG INTERACTIONS, Drug-Drug Interactions**).

4.3 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.

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Active Ingredients:
DELSTRIGO® is a fixed-dose combination. 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.

Table 1 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/Strength/Composition	Non-medicinal Ingredients
oral	Film-coated tablet 100 mg doravirine / 300 mg lamivudine / 300 mg tenofovir DF	Carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and sodium stearyl fumarate. Film coating: hypromellose, iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin.

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 bottle contains 30 tablets and desiccants.

7 WARNINGS AND PRECAUTIONS

See the SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information.

General

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.

DELSTRIGO® has not been evaluated in patients with previous virologic failure to any other antiretroviral therapy. In the Phase 3 study in patients with no antiretroviral treatment history, NNRTI-associated mutations detected at screening were part of exclusion criteria. In the Phase 3 study in virologically suppressed patients, data in patients with a past history of NNRTI resistance were limited (see MICROBIOLOGY).

DELSTRIGO® should not be used in antiretroviral-experienced patients with HIV-1 harboring NNRTI resistance-associated mutations which may confer resistance to doravirine, or lamivudine or tenofovir resistance associated-mutations, or with suspected NNRTI, lamivudine, or tenofovir resistance in virologically suppressed patients if no genotype is available (see MICROBIOLOGY).

DELSTRIGO® should not be administered with adefovir dipivoxil (see **DRUG INTERACTIONS**).

DELSTRIGO® should not be administered with doravirine as a single agent (PIFELTRO®) unless needed for doravirine dose adjustment when DELSTRIGO® is coadministered with rifabutin or other moderate CYP3A inducers (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment** **and** **DRUG INTERACTIONS**).

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 decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide), suggesting increased bone turnover. 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.

Driving and Operating Machinery
Patients should be informed that fatigue, dizziness, and somnolence have been reported during treatment with DELSTRIGO® (see **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**). Patients should be instructed that, if they experience any of these symptoms, they should avoid potentially hazardous tasks such as driving or operating machinery.

Drug Interactions
Use with CYP3A Inducers
Doravirine is a substrate of cytochrome P 450 (CYP)3A. Drugs that are inducers of CYP3A may significantly reduce the exposure to doravirine and may lead to loss of therapeutic effect and possible development of resistance.

The coadministration of DELSTRIGO® with strong CYP3A inducers is contraindicated (see **CONTRAINDICATIONS**).

If DELSTRIGO® is coadministered with rifabutin, a moderate CYP3A inducer, one tablet of doravirine 100 mg (PIFELTRO®) should be taken approximately 12 hours after the dose of DELSTRIGO®. Coadministration of DELSTRIGO® with other moderate CYP3A inducers (e.g. dabrafenib, bosentan, modafinil) should be avoided. If coadministration cannot be avoided, one tablet of doravirine 100 mg (PIFELTRO®) should be taken approximately 12 hours after the dose of DELSTRIGO® (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment** **and** **DRUG INTERACTIONS, Drug-Drug Interactions**).

Use with Certain Hepatitis C Virus (HCV) Regimens
Tenofovir exposure is increased when tenofovir DF is coadministered with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, or sofosbuvir/velpatasvir/voxilaprevir. Patients receiving a regimen containing tenofovir DF concomitantly with these medicinal products, particularly patients at increased risk for renal dysfunction, should be monitored for tenofovir DF-associated adverse reactions (see **DRUG INTERACTIONS**).

Endocrine and Metabolism
Serum Lipids and Blood Glucose
Serum lipid and blood glucose levels may increase during antiretroviral therapy (ART). Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations should be managed as clinically appropriate.

Hematologic
Very rare occurrences of pure red cell aplasia have been reported with lamivudine use. Discontinuation of lamivudine has resulted in normalization of hematologic parameters in patients with suspected lamivudine-induced pure red cell aplasia.

Hepatic/Biliary/Pancreatic
Lactic Acidosis/Severe Hepatomegaly with Steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including lamivudine and tenofovir DF, the

components of DELSTRIGO®, alone or in combination with other antiretrovirals. Treatment with DELSTRIGO® should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Immune

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory 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, autoimmune hepatitis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution syndrome; however, the time to onset is more variable and can occur many months after initiation of treatment.

Angioedema

Cases of angioedema have been reported in patients taking tenofovir DF (**see ADVERSE REACTIONS, Post-Market Adverse Reactions**).

Renal

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, Drug-Drug Interactions**). 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 **WARNINGS AND PRECAUTIONS, Renal Impairment**).

Sexual Health

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant patients exposed to DELSTRIGO®, an International Antiretroviral Pregnancy Registry (APR) has been established.

Physicians are encouraged to report pregnancy cases for inclusion in the registry:
http://www.apregistry.com/
Telephone: 1-800-258-4263
Fax: 1-800-800-1052

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.

Skin

Severe skin and hypersensitivity reactions have been reported with use of other NNRTIs. Drug related rash of moderate to severe intensity occurred in 0.3% of patients in DRIVE-AHEAD. Discontinue DELSTRIGO® immediately if signs or symptoms of severe skin or hypersensitivity reactions develop.

7.1 Special Populations

7.1.1 Pregnant Women

DELSTRIGO® has not been studied in pregnant women. DELSTRIGO® should not be used in pregnant women unless the potential benefits outweigh the potential risks to the fetus.

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.

In pregnant rats and rabbits, doravirine was able to cross the placenta.

Lamivudine: Reproduction studies performed in rats and rabbits showed no evidence of teratogenicity. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 32 times that of the RHD. 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 RHD based on body surface area comparisons and revealed no harm to the fetus.

7.1.2 Breast-feeding

HIV-1 infected mothers should not breastfeed their infants to avoid risking postnatal transmission of HIV.

Doravirine: Doravirine was excreted into the milk of lactating rats.

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®.

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.

7.1.3 Pediatrics (< 18 years of age)

Safety and efficacy of DELSTRIGO® have not been established in patients younger than 18 years of age (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

7.1.4 Geriatrics (≥ 65 years of age)

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 **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**). Special care is advised in this age group due to age associated changes such as decreases in renal function.

7.1.5 Renal Impairment

Because DELSTRIGO® is a fixed-dose combination tablet and the dosage of lamivudine and tenofovir DF cannot be altered, DELSTRIGO® is not recommended in patients with estimated creatinine clearance less than 50 mL/min (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

7.1.6 Hepatic Impairment

DELSTRIGO® has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). It is not known whether the exposure to doravirine will increase in patients with severe hepatic impairment. Therefore, caution is advised when DELSTRIGO® is administered to patients with severe hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**). No dose adjustment of DELSTRIGO® is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

Patients Co-Infected with HIV-1 and HBV or HCV
Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at increased risk for severe hepatic adverse events.

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 HBV and HIV-1 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. In patients with advanced liver disease or cirrhosis, post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Therefore, in these patients, discontinuation of treatment without initiation of alternative anti-hepatitis B therapy is not recommended.

Emergence of Lamivudine-Resistant HBV
In non–HIV-1-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see full Product Monograph for Heptovir* for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview
The safety assessment of DELSTRIGO® in antiretroviral treatment-naïve, HIV-1 infected subjects, is based on the analyses of data through 48-and 96 Weeks from a Phase 3, randomized, international, multicenter, double-blind, active-controlled trial, DRIVE-AHEAD (Protocol 021).

In subjects receiving DELSTRIGO®, the serious adverse reactions of nausea, vomiting, asthenia, insomnia, and nightmares were reported, and these reactions were reported by <1% subjects. The most frequently reported adverse reaction with DELSTRIGO® was dizziness (7 %). There were no adverse reactions of moderate to severe intensity with an incidence of

greater than or equal to 2%.

The following adverse drug reactions are discussed in the WARNINGS AND PRECAUTIONS section:

- Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV
- New Onset or Worsening Renal Impairment
- Bone Loss and Mineralization Defects
- Immune Reconstitution Inflammatory Syndrome
- Lactic Acidosis/Severe Hepatomegaly with Steatosis

In addition to the events reported here, please consult the lamivudine and tenofovir DF product monographs.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical Trials in Antiretroviral Treatment-Naïve Adults

In DRIVE-AHEAD, 728 adult subjects received either DELSTRIGO® (n=364) or efavirenz/emtricitabine/tenofovir DF (EFV/FTC/TDF) once daily (n=364). By Week 48, 3.0% in the DELSTRIGO® group and 6.6% in the EFV/FTC/TDF group had adverse events leading to discontinuation of study medication.

Adverse reactions reported in greater than or equal to 2% of subjects in any treatment group in adults with no antiretroviral treatment history in DRIVE-AHEAD are presented in Table 2.

Table 2: Adverse Reactions (All Grades) Reported in ≥2%† 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
Gastrointestinal disorders		
Nausea	5%	7%
Diarrhea	3%	5%
Vomiting	2%	3%
General disorders and administration site conditions		
Fatigue	4%	3%
Nervous System disorders		
Dizziness	7%	32%
Headache	4%	4%
Somnolence	3%	7%
Sleep disorder	<1%	2%
Psychiatric disorders		
Abnormal dreams	5%	9%
Insomnia	4%	5%
Nightmare	2%	4%
Skin and subcutaneous tissue disorders		
Rash	2%	9%

** Frequencies of adverse reactions are based on all adverse events attributed to trial drugs by the investigator.
† No adverse reactions of Grade 2 or higher (moderate or severe) occurred in ≥ 2% of subjects treated with DELSTRIGO®.

Overall, the clinical adverse experiences at Week 96 were consistent with those observed at Week 48.

Clinical Trials in Virologically-Suppressed Adults

The safety of DELSTRIGO® in virologically-suppressed adults was based on Week 48 data from 670 subjects in the DRIVE-SHIFT trial (**Clinical Trials, Trial Design and Study Demographics**). Overall, the safety profile in virologically-suppressed adult subjects was similar to that in subjects with no antiretroviral treatment history.

8.3 Less Common Clinical Trial Adverse Reactions

Other adverse reactions reported in <2% of patients in the DRIVE-AHEAD or DRIVE-SHIFT trials through Week 96 and Week 48 respectively are listed below.

Blood and Lymphatic Systems Disorders: lymph node pain.

Cardiac Disorders: palpitations

Ear and Labyrinth Disorders: motion sickness, vertigo.

Eye Disorders: vision blurred.

Gastrointestinal Disorders: abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, abnormal feces, change in bowel habits, constipation, dry mouth, dyspepsia, feces soft, epigastric discomfort, flatulence, frequent bowel movements, gastritis, irritable bowel syndrome.

General Disorders and Administration Site Conditions: asthenia, chest discomfort, chest pain, generalized oedema, malaise, pyrexia, thirst.

Hepatobiliary Disorders: hepatitis, hepatocellular injury, hyperbilirubinemia.

Immune System Disorders: immune reconstitution inflammatory syndrome.

Infections and Infestations: angular cheilitis, lymphogranuloma venereum, oral herpes, nasopharyngitis.

Investigations: alanine aminotransferase increased*, amylase increased. aspartate aminotransferase increased, blood triglycerides increased, bone density decreased, gastric pH decreased, lipase increased, neutrophil count decreased, weight increased.

Metabolism and Nutrition Disorders: alcohol intolerance, decreased appetite, hypertriglyceridemia, hypomagnesemia, hypophosphatemia, obesity, vitamin D deficiency.

Musculoskeletal and Connective Tissue Disorders: arthralgia, back pain, muscle spasms, myalgia.

Nervous System Disorders: burning sensation, cognitive disorder, disturbance in attention, dysgeusia, hyperesthesia, hypertonia, memory impairment, mental impairment, migraine, paresthesia, poor quality sleep, presyncope.

Psychiatric Disorders: adjustment disorder, aggression, anxiety, confusional state, depressed mood, depression, generalized anxiety disorder, hallucination, irritability, libido disorder, major depression, persistent depressive disorder, somnambulism, suicidal ideation.

Renal and Urinary Disorders: acute kidney injury, pollakiuria, polyuria, renal disorder, renal failure, renal pain.

Reproductive and Breast Disorders: erectile dysfunction.

Skin and Subcutaneous Tissue Disorders: alopecia, hyperhidrosis, pruritus, rash macular, rash papular, rosacea, urticaria.

Vascular Disorders: hypertension.

*Reported in 2.1% in DRIVE-SHIFT

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

The percentages of subjects with selected Grade 2 to 4 laboratory abnormalities (that represent a worsening Grade from baseline) who were treated with DELSTRIGO® or EFV/FTC/TDF in DRIVE-AHEAD are presented in Table 3.

Table 3 - Selected Grade 2 to 4 Laboratory Abnormalities Reported in DRIVE-AHEAD (Week 48)

Laboratory Parameter Preferred Term (Unit)	Limit	DELSTRIGO® Once Daily	EFV/FTC/TDF Once Daily
		N=364	N=364
Blood Chemistry			
Total bilirubin			
Grade 2	1.6 - <2.6 x ULN	2%	0%
Grade 3-4	≥2.6 x ULN	<1%	<1%
Creatinine (micromol/L)			
Grade 2	>1.3 - 1.8 x ULN or Increase of > 26.5 micromol/L above baseline	2%	1%
Grade 3-4	>1.8 x ULN or Increase of ≥1.5 x above baseline	2%	1%
Aspartate aminotransferase (IU/L)			
Grade 2	2.5 - <5.0 x ULN	2%	2%
Grade 3-4	≥5.0 x ULN	<1%	2%
Alanine aminotransferase (IU/L)			
Grade 2	2.5 - <5.0 x ULN	3%	4%
Grade 3-4	≥5.0 x ULN	<1%	2%
Alkaline phosphatase (IU/L)			
Grade 2	2.5 - <5.0 x ULN	0%	<1%
Grade 3-4	≥5.0 x ULN	0%	<1%
Lipase			
Grade 2	1.5 - <3.0 x ULN	5%	4%
Grade 3-4	≥3.0 x ULN	1%	2%
Creatine kinase (IU/L)			
Grade 2	6.0 - <10.0 x ULN	2%	2%
Grade 3-4	≥10.0 x ULN	2%	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. Changes from baseline at Week 96 were similar to findings at Week 48.

DELSTRIGO® had a neutral effect on LDL- and non-HDL-cholesterol, total cholesterol, and triglycerides, as indicated by the differences in the mean change from baseline at Week 48. The LDL and non-HDL comparisons were pre-specified and the differences were statistically significant, showing superiority of DELSTRIGO® for both parameters.

For DRIVE-SHIFT, improvements in LDL- and non-HDL-cholesterol, total cholesterol, and triglycerides from baseline were observed in virologically suppressed subjects who switched to DELSTRIGO® from a ritonavir boosted PI regimen as shown in Table 4.

Table 4 - Mean Change from Baseline in Fasting Lipids in DRIVE-AHEAD and DRIVE-SHIFT

	DRIVE-AHEAD (No antiretroviral treatment history) Week 48		DRIVE-SHIFT (Virologically Suppressed) Week 24	
Laboratory Parameter Preferred Term	**DELSTRIGO®- Once Daily**	**EFV/FTC/TDF Once Daily**	**DELSTRIGO® (Week 0-24) Once Daily**	**PI+ritonavir (Week 0-24) Once Daily**
	N=320	**N=307**	**N=244**	**N=124**
LDL-Cholesterol (mmol/L)[Þ]	-0.05	0.21	-0.42	-0.07
Non-HDL Cholesterol (mmol/L)[Þ]	-0.11	0.33	-0.64	-0.05
Total Cholesterol (mmol/L)	-0.06	0.55	-0.68	-0.01
Triglycerides (mmol/L)	-0.14	0.24	-0.50	-0.00
HDL-Cholesterol (mmol/L)	0.05	0.22	-0.03	0.05
Subjects on lipid-lowering agents at baseline were excluded from these analyses (in DRIVE-AHEAD DELSTRIGO® n=15 and EFV/FTC/TDF n=10, and in DRIVE-SHIFT DELSTRIGO® n=26 and PI+ritonavir n=13). Subjects initiating a lipid-lowering agent post-baseline had their last fasted on-treatment value (prior to starting the agent) carried forward (in DRIVE-AHEAD DELSTRIGO® n=3 and EFV/FTC/TDF n=8, and in DRIVE-SHIFT DELSTRIGO® n=4 and PI+ritonavir n=2). [Þ] P-values for the pre-specified hypothesis testing for treatment difference were <0.0001.				

Adverse Reactions from Clinical Trials of the Components of DELSTRIGO®
For information on the safety profiles of lamivudine and tenofovir DF, consult the Product Monographs for 3TC* (lamivudine) and Viread* (tenofovir DF).

8.5 Clinical Trial Adverse Reactions (Pediatrics)

The clinical trials have not been conducted in a pediatric population.

8.6 Post-Market Adverse Reactions

There are no postmarketing data available for doravirine.

Lamivudine
The following additional adverse experiences have been reported in post-marketing experience without regard to causality. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to lamivudine, or a combination of these factors.

Body as a whole: anaphylaxis, fatigue, fever, malaise, weakness

Digestive: stomatitis

Endocrine/Metabolic: hyperglycemia, hyperlactatemia, lactic acidosis and hepatic steatosis (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism** and **Hepatic/Biliary/Pancreatic**)

Gastrointestinal Disorders: diarrhea, nausea, pancreatitis, rises in serum amylase, upper abdominal pain, vomiting

Hematological: pure red cell aplasia (see **WARNINGS AND PRECAUTIONS, Hematologic**)

Hepatic: transient rises in liver enzymes

Hemic and Lymphatic: anemia, lymphadenopathy, neutropenia, splenomegaly, thrombocytopenia

Immune System Disorders: Immune Reconstitution Inflammatory Syndrome (see **WARNINGS AND PRECAUTIONS, Immune**)

Musculoskeletal and Connective Tissue Disorders: arthralgia, muscle disorders including very rarely rhabdomyolysis

Nervous System Disorders: headache, paresthesia, peripheral neuropathy

Other: alopecia

Skin and Subcutaneous Tissue Disorders: pruritus, rash, urticarial

Tenofovir DF
The following adverse reactions have been identified during post-approval use of tenofovir DF. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been considered possible adverse reactions due to a combination of their seriousness, frequency of reporting or potential causal relationship with tenofovir DF.

Immune System Disorders: allergic reaction (including angioedema) (see **WARNINGS AND PRECAUTIONS, Immune**)

Metabolism and Nutrition Disorders: lactic acidosis, hypokalemia, hypophosphatemia (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**)

Respiratory, Thoracic and Mediastinal Disorders: dyspnea

Gastrointestinal Disorders: pancreatitis, increased amylase, abdominal pain

Blood and Lymphatic System Disorders: thrombocytopenia

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

Skin and Subcutaneous Tissue Disorders: rash

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing 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 (see **WARNINGS AND PRECAUTIONS, Renal**)

General Disorders and Administration Site Conditions: asthenia
The following adverse reactions, listed under the body system headings above, sometimes appeared to be concurrent with proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalemia, muscular weakness, myopathy, hypophosphatemia.

There have been three post marketing reports of acute renal failure in patients on concomitant NSAIDS therapy where a relationship to tenofovir DF could not be excluded.

These events mostly occurred in medically complex patients, where underlying disease processes confound interpretation.

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy an inflammatory reaction to infectious pathogens (active or inactive) may arise (see **WARNINGS and PRECAUTIONS**).

In HBV infected patients, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of HBV therapy (see **WARNINGS AND PRECAUTIONS, Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV**).

See the full product monograph for lamivudine and tenofovir DF for postmarketing information on these products.

9 DRUG INTERACTIONS

9.1 Overview

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.

9.2 Drug-Drug Interactions

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.

Drugs Affecting Renal Function
Because lamivudine and tenofovir are primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion, coadministration 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, amphotericin B, cidofovir, foscarnet[1], ganciclovir, interleukin-2, pentamidine, valacyclovir, valganciclovir, vancomycin, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs (see **WARNINGS AND PRECAUTIONS**).

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. Coadministration of DELSTRIGO® and drugs that induce CYP3A may result in decreased plasma concentrations of doravirine and reduce the therapeutic effect of doravirine (see **CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS**). Coadministration of DELSTRIGO® and drugs that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine.

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 5 shows the established and other potentially significant drug interactions with the components of DELSTRIGO®, but is not inclusive.

Table 5 - 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[Þ]	↓ doravirine ↔ rifabutin	Concomitant use of DELSTRIGO® with rifabutin may cause a decrease in the plasma concentrations of doravirine (induction of CYP3A enzymes). If DELSTRIGO® is coadministered with rifabutin, one tablet of doravirine 100 mg (PIFELTRO®) should be taken approximately 12 hours after the dose of DELSTRIGO® (see **DOSAGE AND ADMINISTRATION Recommended Dose and Dosage Adjustment**).
Azole Antifungal Agents		
fluconazole itraconazole ketoconazole[Þ] posaconazole voriconazole	↑ doravirine ↔ azole antifungal agents	Concomitant use of DELSTRIGO® with azole antifungal agents may cause an increase in the plasma concentrations of DELSTRIGO® (inhibition of CYP3A enzymes). No doravirine dose adjustment is required when DELSTRIGO® is coadministered with azole antifungal agents.
Endothelin Receptor Antagonists		
bosentan	Interaction not studied with doravirine or DELSTRIGO®. Expected: ↓ doravirine (Induction of CYP3A)	Coadministration should be avoided. If coadministration cannot be avoided, an additional 100 mg dose of doravirine (PIFELTRO®) should be taken 12 hours following the initial dose of DELSTRIGO®.
Hepatitis B Antiviral Agents		
adefovir dipivoxil	Expected: ↔ tenofovir	DELSTRIGO® should not be coadministered with adefovir dipivoxil as both adefovoir and tenofovir DF (a component of DELSTRIGO®) may reduce renal function (see **WARNINGS AND PRECAUTIONS**).
Hepatitis C Antiviral Agents		
ledipasvir/sofosbuvir sofosbuvir/velpa-tasvir	↑ tenofovir	Patients receiving DELSTRIGO® concomitantly with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir should be monitored for adverse reactions associated with tenofovir DF (see **WARNINGS AND PRECAUTIONS, Drug Interactions**).
Kinase Inhibitors		
dabrafenib	Interaction not studied with doravirine or DELSTRIGO®. Expected: ↓ doravirine (Induction of CYP3A)	Coadministration should be avoided. If coadministration cannot be avoided, an additional 100 mg dose of doravirine (PIFELTRO®) should be taken 12 hours following the initial dose of DELSTRIGO®.

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Laxatives, Osmotic		
sorbitol solution (3.2 g, 10.2 g, 13.4 g)	Single dose lamivudine oral solution 300 mg Lamivudine: AUC↓ 14%; 32%; 36% Cmax↓ 28%; 52%; 55%	Co-administration of single doses of lamivudine and sorbitol resulted in a sorbitol dose-dependent reduction in lamivudine exposures. When possible, avoid chronic coadministration of sorbitol-containing medicines with lamivudine. Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.
Psychostimulants		
modafinil	Interaction not studied with doravirine or DELSTRIGO®. Expected: ↓ doravirine (Induction of CYP3A)	Coadministration should be avoided. If coadministration cannot be avoided, an additional 100 mg dose of doravirine (PIFELTRO®) should be taken 12 hours following the initial dose of DELSTRIGO®.
↑ = increase, ↓ = decrease, ↔ = no change Þ The interaction between doravirine and the drug was evaluated in a clinical study. All other drug-drug interactions shown are anticipated based on the known metabolic and elimination pathways.		

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*:* 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 doravirine is coadministered 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.

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.

Assessment of Drug Interactions
Doravirine
Doravirine is primarily metabolized by CYP3A, and drugs that induce or inhibit CYP3A may affect the clearance of doravirine. Coadministration of doravirine and drugs that induce CYP3A may

result in decreased plasma concentrations of doravirine. Coadministration 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 coadministered or commonly used as probes for pharmacokinetic interactions. The effects of coadministration of other drugs on the C_{max}, AUC, and C_{24} values of doravirine are summarized in Table 6. The effects of coadministration of doravirine on the C_{max} and AUC values of other drugs are summarized in Table 7.

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

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Doravirine	N	Geometric Mean Ratio (90% CI) of Doravirine Pharmacokinetics with/without Coadministered Drug (No Effect=1.00)		
				AUC[Þ]	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)

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Doravirine	N	Geometric Mean Ratio (90% CI) of Doravirine Pharmacokinetics with/without Coadministered Drug (No Effect=1.00)		
				AUC[Þ]	C_{max}	C_{24}
Opioid Analgesics						
methadone	20-200 mg QD individualized dose	100 mg QD	14	0.74 (0.61, 0.90)	0.76 (0.63, 0.91)	0.80 (0.63, 1.03)
CI = Confidence interval; SD = Single Dose; QD = Once Daily [Þ] $AUC_{0-\infty}$ for single-dose, AUC_{0-24} for once daily.						

Table 7 - Drug Interactions: Changes in Pharmacokinetic Parameter Values for Coadministered 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[b]	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)	-
Hepatitis C 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[2]				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 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-methadone)				0.98 (0.90, 1.06)	0.97 (0.91, 1.04)	0.97 (0.86, 1.10)

CI = Confidence interval; SD = Single Dose; QD = Once Daily.
[b] $AUC_{0-\infty}$ for single-dose, AUC_{0-24} for once daily.
[2] The predominant circulating nucleoside metabolite of sofosbuvir.

Lamivudine

Trimethoprim/Sulfamethoxazole: An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40% increase in lamivudine AUC_{∞} at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment.

Tenofovir DF

Table 8 - Established Drug-Drug Interactions for Tenofovir[1] in the Presence of the Coadministered Drug

			% Change of Tenofovir Pharmacokinetic Parameters[2] (90% CI)		
Coadministered Drug	**Dose of Coadministered Drug (mg)**	**N**	**C_{max}**	**AUC**	**C_{min}**
Entecavir	1 mg once daily x 10 days	28	NA	NA	NA
Ledipasvir/ Sofosbuvir[3,4]	90/400 once daily x 10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑ 42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/ Sofosbuvir[3,5]		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/ Sofosbuvir[6]	90/400 once daily x 10 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑123)	↑ 163 (↑ 132 o↑ 197)
Ledipasvir/ Sofosbuvir[7]		14	↑ 32 (↑ 25 to ↑ 39)	↑ 40 (↑ 31 to ↑50)	↑ 91 (↑ 74 to ↑ 110)
Ledipasvir/ Sofosbuvir[8]	90/400 once daily x 10 days	29	↑ 61 (↑ 51 to ↑ 72)	↑ 65 (↑ 59 to ↑ 71)	↑115 (↑ 105 to ↑ 126)
Sofosbuvir/ Velpatasvir[9]	400/100 once daily	24	↑ 55 (↑ 43 to ↑ 68)	↑ 30 (↑ 24 to ↑ 36)	↑ 39 (↑ 31 to ↑ 48)
Sofosbuvir/ Velpatasvir[10]		29	↑ 55 (↑ 45 to ↑ 66)	↑ 39 (↑ 33 to ↑ 44)	↑ 52 (↑ 45 to ↑ 59)
Sofosbuvir/ Velpatasvir[11]		15	↑ 77 (↑ 53 to ↑ 104)	↑ 81 (↑ 68 to 94)	↑ 121 (↑ 100 to ↑ 143)
Sofosbuvir/ Velpatasvir[12]		24	↑ 44 (↑ 33 to ↑55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑76 to ↑ 92)
Sofosbuvir/ Velpatasvir[13]		24	↑ 36 (↑ 25 to ↑ 47)	↑ 35 (↑ 29 to ↑ 42)	↑ 45 (↑ 39 to ↑ 51)
Sofosbuvir/ Velpatasvir[14]		30	↑ 46 (↑ 39 to ↑ 54)	↑40 (↑ 34 to ↑ 45)	↑ 70 (↑ 61 to ↑ 79)

1. Patients received tenofovir DF 300 mg once daily
2. Increase = ↑; NA = Not Available.
3. Data generated from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provides similar results.
4. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF coadministered with ledipasvir/sofosbuvir.
5. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF coadministered with ledipasvir/sofosbuvir.
6. Study conducted with efavirenz/emtricitabine/tenofovir DF coadministered with ledipasvir/sofosbuvir.
7. Study conducted with emtricitabine/rilpivirine/tenofovir DF coadministered with ledipasvir/sofosbuvir.
8. Study conducted with emtricitabine/tenofovir DF + dolutegravir coadministered with ledipasvir/sofosbuvir.
9. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF coadministered with sofosbuvir/velpatasvir.
10. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF coadministered with sofosbuvir/velpatasvir.

11. Study conducted with efavirenz/emtricitabine/tenofovir DF coadministered with sofosbuvir/velpatasvir.
12. Study conducted with emtricitabine/rilpivirine/tenofovir DF coadministered with sofosbuvir/velpatasvir.
13. Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir DF coadministered with sofosbuvir/velpatasvir.
14. Administered as raltegravir +emtricitabine/tenofovir DF coadministered with sofosbuvir/velpatasvir.

Table 9 - Established Drug-Drug Interactions for Coadministered Drug in the Presence of Tenofovir DF

			% Change of Coadministered Drug Pharmacokinetic Parameters[1] (90% CI)		
Coadministered Drug	**Dose of Coadministered Drug (mg)**	**N**	**C_{max}**	**AUC**	**C_{min}**
Entecavir	1 mg once daily x 10 days	28	NA	↑ 13 (↑ 11 to ↑ 15)	NA
Ledipasvir	Ledipasvir/ Sofosbuvir 90/400 once daily x 10 days[3,4]	24	↑ 68 (↑ 54 to ↑ 84)	↑ 96 (↑ 74 to ↑ 121)	↑ 118 (↑ 91 to ↑ 150)
Sofosbuvir			↑ 1 (↓ 12 to ↑15)	↑ 11 (↑ 2 to ↑ 21)	NC
GS-331007[2]			↑ 17 (↑12 to ↑23)	↑ 31 (↑ 25 to ↑ 36)	↑ 42 (↑ 34 to ↑ 49)
Ledipasvir	Ledipasvir/ Sofosbuvir 90/400 once daily x 10 days[3,5]	23	↑ 11 (↓ 1 to ↑ 24)	↑ 12 (0 to ↑ 25)	↑ 17 (↑ 4 to ↑ 31)
Sofosbuvir			↓ 37 (↓ 48 to ↓ 25)	↓ 27 (↓ 35 to ↓ 18)	NC
GS-331007[2]			↑ 10 (↑ 4 to ↑ 16)	↑ 20 (↑ 16 to ↑ 24)	↑ 26 (↑ 20 to ↑ 32)
Ledipasvir	Ledipasvir/ Sofosbuvir 90/400 once daily x 10 days[6]	15	↓ 34 (↓ 41 to ↓ 25)	↓ 34 (↓ 41 to ↓ 25)	↓ 34 (↓ 43 to ↓ 24)
Sofosbuvir			↑ 3 (↓ 13 to ↑ 23)	↓ 6 (↓ 19 to ↑ 10)	NC
GS-331007[2]			↓ 14 (↓ 24 to ↓ 4)	↓ 10 (↓ 17 to ↓ 3)	↑ 7 (↑ 2 to ↑ 13)
Ledipasvir	Ledipasvir/ Sofosbuvir 90/400 once daily x 10 days[7]	14	↑ 1 (↓ 5 to ↑ 7)	↑ 8 (↑ 2 to ↑ 15)	↑ 16 (↑ 8 to ↑ 25)
Sofosbuvir			↑ 5 (↓ 7 to ↑ 20)	↑ 10 (↑ 1 to ↑ 21)	NC
GS-331007[2]			↑ 6 (↑1 to ↑ 11)	↑ 15 (↑ 11 to ↑ 19)	↑ 18 (↑ 13 to ↑ 23)
Sofosbuvir	400/100 once daily[8]	24	↑ 12 (↓ 3 to ↑ 29)	↑ 22 (↑ 12 to ↑33)	NC
GS-331007[2]			↑ 21 (↑12 to ↑ 29)	↑ 32 (↑ 27 to ↑ 36)	↑ 42 (↑ 37 to ↑ 49)
Velpatasvir			↑ 55 (↑ 41 to ↑ 71)	↑ 142 (↑ 123 to ↑ 164)	↑ 301 (↑ 257 to ↑ 350)
Sofosbuvir	400/100 once daily[9]	29	↓ 38 (↓ 46 to ↓ 29)	↓ 28 (↓ 34 to ↓20)	NC
GS-331007[2]			↑ 4 (↓ 1 to ↑ 8)	↑ 13 (↑ 8 to ↑18)	↑ 13 (↑ 6 to ↑ 19)
Velpatasvir			↓ 24 (↓ 35 to ↓ 11)	↓ 16 (↓ 28 to ↓ 2)	↑ 1 (↓ 13 to ↑ 18)

Sofosbuvir	400/100 once daily[10]	14	↑ 38 (↑ 14 to ↑ 67)	↓ 3 (↓ 17 to ↑ 14)	NC
GS-331007[2]			↓ 14 (↓ 20 to ↓ 7)	↓ 10 (↓ 15 to ↓ 4)	↑ 1 (↓ 5 to ↑ 7)
Velpatasvir			↓ 47 (↓ 57 to ↓ 36)	↓ 53 (↓ 61 to ↓43)	↓ 57 (↓ 64 to ↓ 48)
Sofosbuvir	400/100 once daily[11]	24	↑ 9 (↓ 5 to ↑ 25)	↑ 16 (↑ 9 to ↑ 24)	NC
GS-331007[2]			↓ 4 (↓ 10 to ↑ 1)	↑ 4 (0 to ↑ 7)	↑ 12 (↑ 7 to ↑ 17)
Velpatasvir			↓ 4 (↓ 15 to ↑ 10)	↓ 1 (↓ 12 to ↑ 11)	↑ 2 (↓ 9 to ↑ 15)
Sofosbuvir	400/100 once daily[12]	24	↑ 1 (↓ 15 to ↑ 19)	↑ 24 (↑ 13 to ↑ 37)	NC
GS-331007[2]			↑ 13 (↑ 7 to ↑ 18)	↑ 35 (↑ 30 to ↑ 40)	↑ 45 (↑ 38 to ↑ 52)
Velpatasvir			↑ 5 (↓ 7 to ↑19)	↑ 19 (↑ 7 to ↑ 34)	↑ 37 (↑ 22 to ↑ 54)
Sofosbuvir	400/100 once daily[13]	30	↑ 9 (↓ 3 to ↑ 23)	↑ 16 (↑ 7 to ↑ 25)	NC
GS-331007[2]			↓ 5 (↓ 9 to ↓ 2)	↑ 3 (0 to ↑ 6)	↑ 8 (↑ 4 to ↑ 13)
Velpatasvir			↓ 3 (↓ 13 to↑ 8)	↓ 2 (↓ 12 to ↑ 10)	↓ 3 (↓ 13 to ↑ 7)

1. Increase = ↑; Decrease =↓; NA = Not Available; NC = Not Calculated.
2. The predominant circulating nucleoside metabolite of sofosbuvir.
3. Data generated from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provides similar results.
4. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF coadministered with ledipasvir/sofosbuvir.
5. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF coadministered with ledipasvir/sofosbuvir.
6. Study conducted with efavirenz/emtricitabine/tenofovir DF coadministered with ledipasvir/sofosbuvir.
7. Study conducted with emtricitabine/rilpivirine/tenofovir DF coadministered with ledipasvir/sofosbuvir.
8. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF coadministered with sofosbuvir/velpatasvir).
9. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF coadministered with sofosbuvir/velpatasvir.
10. Study conducted with efavirenz/emtricitabine/tenofovir DF coadministered with sofosbuvir/velpatasvir.
11. Study conducted with emtricitabine/rilpivirine/tenofovir DF) coadministered with sofosbuvir/velpatasvir.
12. Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir DF coadministered with sofosbuvir/velpatasvir.
13. Comparison based on exposures when administered as raltegravir + emtricitabine/tenofovir DF coadministered with sofosbuvir/velpatasvir.

9.3 Drug-Food Interactions

The single dose administration of the DELSTRIGO® tablet with a high-fat meal to healthy subjects increased doravirine C_{24} (26%) and AUC (10%), while C_{max} was not significantly affected in comparison to fasting. A decrease in lamivudine C_{max} (-19%) and no significant change in AUC were observed with a high fat meal, while a decrease in tenofovir C_{max} (-12%) and increase in AUC (27%) was observed with a high fat meal. These differences in pharmacokinetics are not clinically relevant.

DELSTRIGO® can be taken with or without food.

9.4 Drug-Herb Interactions

Coadministration of St. John's wort, a potent CYP3A inducer, may significantly decrease doravirine plasma concentrations, which may result in loss of therapeutic effect and possible development of resistance.

Coadministration of DELSTRIGO® with St. John's wort is contraindicated.

9.5 Drug-Laboratory Test Interactions

Interactions with clinical laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

DELSTRIGO® is a fixed-dose combination of the antiviral drugs doravirine, lamivudine, and tenofovir DF (see **ACTION and PHARMACOLOGY, Pharmacodynamics**).

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, ß, 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.

10.2 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.

10.3 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 GM (%CV)	AUC_{0-24} µM hr	C_{max} µM	C_{24} nM
Doravirine 100 mg 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 multiple dose oral administration of lamivudine 300 mg once daily for seven days the mean steady-state C_{max} is 2.04 µg/mL and the mean AUC_{24} is 8.87 µg•h/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. The observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 L/h/kg.

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.

Special Populations and Conditions

Pediatrics: The pharmacokinetics and dosing recommendations of DELSTRIGO® in patients younger than 18 years of age have not been established (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

Geriatrics: Limited data showed no clinically relevant differences in the pharmacokinetics of doravirine 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 **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

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

Ethnic Origin:
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 differences in pharmacokinetics properties of lamivudine among races.

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

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 **WARNINGS AND PRECAUTIONS, Special Populations, Hepatic Impairment**).

Lamivudine: The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Data obtained for lamivudine in patients with moderate to severe hepatic impairment show that the pharmacokinetics are not significantly affected by hepatic dysfunction.

Tenofovir DF: The pharmacokinetics of tenofovir following a 300 mg single dose of tenofovir DF have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects.

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 **WARNINGS AND PRECAUTIONS, Special Populations, Renal Impairment**).

Lamivudine: Studies with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. Based on the lamivudine data, DELSTRIGO® is not recommended for patients with CrCl of < 50 mL/min.

Tenofovir DF: The pharmacokinetics of tenofovir are altered in subjects with renal impairment (see **WARNINGS AND PRECAUTIONS, Renal, New Onset or Worsening 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.

11 STORAGE, STABILITY AND DISPOSAL

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

Store DELSTRIGO® at room temperature (15°C to 30°C).

[1] Not marketed in Canada

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

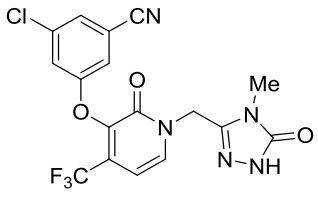
Doravirine:

Common name: doravirine

Chemical name: 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

Molecular formula and molecular mass: $C_{17}H_{11}ClF_3N_5O_3$, 425.75

Structural formula:



Physicochemical properties: Doravirine is practically insoluble in water.

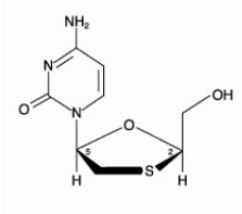
Lamivudine:

Proper name: lamivudine

Chemical name: (-)-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-cytosine

Molecular formula and molecular mass: $C_8H_{11}N_3O_3S$, 229.26.

Structural formula:



Physicochemical properties: Lamivudine is soluble in water.

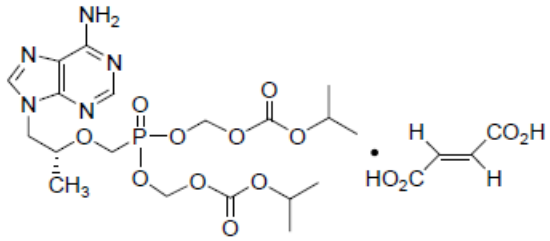
Tenofovir DF:

Proper name: tenofovir disoproxil fumarate

Chemical name: 9-[(R)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy] phosphinyl]-methoxy]propyl]adenine fumarate (1:1)

Molecular formula and molecular mass: $C_{19}H_{30}N_5O_{10}\ P \cdot C_4H_4O_4$; 635.52

Structural formula:



Physicochemical properties: Tenofovir DF is slightly soluble in water.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

The efficacy and safety of DELSTRIGO® (doravirine/lamivudine/tenofovir disoproxil fumarate) were evaluated in the study summarized in Table 10.

Table 10 - Summary of subject demographics for clinical trials in HIV-1-infected patients

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
P021 (DRIVE-AHEAD)	Randomized, international, multicenter, double-blind, active-controlled trial in treatment-naive patients	DELSTRIGO® or EFV/FTC/TDF Oral, once daily 48 Weeks and 96 Weeks	728	33.1 (18 to 70 years)	Male: 616 Female: 112
P024 (DRIVE-SHIFT)	Randomized, international, multicenter, open-label, active-controlled trial in virologically suppressed patients	Immediate switch group (ISG): DELSTRIGO® Oral, once daily for 48 Weeks Delayed switch group (DSG): Ritonavir- or cobicistat-boosted PI or cobicistat-boosted EVG or an NNRTI each administered with 2 NRTIs Oral, dose and frequency determined by baseline regimen 24 Weeks followed by DELSTRIGO® Oral, once daily Weeks 24 to 48	670	43.3 (21 to 71 years)	Male: 566 Female: 104

13.2 Study Results

Treatment Naïve patients

The demographic and baseline characteristics of patients in DRIVE-AHEAD are summarized in Table 11.

Table 11 – Demographic and Baseline Characteristics in DRIVE-AHEAD at Week 48 in HIV-1 Adult Subjects with No Antiretroviral Treatment History

	DELSTRIGO® **Once Daily** **(N = 364)**	**Comparator** **Once Daily** **(N = 364)**
Gender n (%)		
Male	305 (83.8)	311 (85.4)
Female	59 (16.2)	53 (14.6)
Race n (%)		
American Indian or Alaska Native	10 (2.7)	6 (1.6)
Asian	59 (16.2)	65 (17.9)
Black or African American	67 (18.4)	68 (18.7)
Multiple	51 (14.0)	55 (15.1)
Native Hawaiian or Other Pacific Islander	-	-
White	177 (48.6)	170 (46.7)
Ethnicity n (%)		
Hispanic or Latino	126 (34.6)	120 (33.0)
Not Hispanic or Latino	236 (64.8)	238 (65.4)
Unknown	2 (0.5)	6 (1.6)
Region n (%)		
Africa	37 (10.2)	27 (7.4)
Asia / Pacific	59 (16.2)	62 (17.0)
Europe	88 (24.2)	94 (25.8)
Latin America	89 (24.5)	87 (23.9)
North America	91 (25.0)	94 (25.8)
Age (years)		
18 to 64	362 (99.5)	362 (99.5)
≥ 65	2 (0.5)	2 (0.5)
Mean (SD)	33.6 (10.5)	32.7 (9.9)
Median (min, max)	32.0 (18, 70)	30.0 (18, 69)
Baseline CD4+ T-Cell Count (cells/mm^3)		
N†	364	364
Mean (SD)	434,9 (217.9)	415,5 (210.6)
Median (min, max)	413,5 (19, 1399)	388.0 (19, 1452)
Baseline CD4+ T-Cell Count n (%)		
≤ 50 cells/mm^3	9 (2.5)	10 (2.7)
> 50 cells/mm^3 and ≤ 200 cells/mm^3	35 (9.6)	35 (9.9)
> 200 cells/mm^3	320 (87.9)	318 (87.4)
Baseline Plasma HIV-1 RNA (log_{10} copies/mL)		
N†	364	364
Mean (SD)	4,4 (0.7)	4,4 (0.7)
Median (min, max)	4.4 (2.4, 6.1)	4,5 (2.6, 6.4)

Baseline Plasma HIV-1 RNA (copies/mL)		
N†	364	364
Geometric Mean	23760.4	29087.1
Median (min, max)	22438.5 (259, 1268560)	25467.5 (403, 2692740)
Baseline Plasma HIV-1 RNA n (%)		
≤ 100,000 copies/mL	291(79.9)	282 (77.5)
> 100,000 copies/mL	73 (20.1)	82 (22.5)
History of AIDS n (%)		
Yes	46 (12.6)	53 (14.6)
No	318 (87.4)	311 (85.4)
Stratum n (%)		
Screening HIV RNA ≤ 100,000	275 (75.5)	274 (75.3)
Screening HIV RNA > 100,000	89 (24.5)	90 (24.7)
Hepatitis B and/or C Positive	19 (5.2)	18 (4.9)
Hepatitis B and C Negative	345 (94.8)	346 (95.1)
Baseline Hepatitis Status††		
Hepatitis B and/or C Positive	11 (3.0)	9 (2.5)
Hepatitis B Positive Only	9 (2.5)	8 (2.2)
Hepatitis C Positive Only	2 (0.5)	1 (0.3)
Viral Subtype n (%)		
Subtype B	232 (63.7)	253 (69.5)
Non-Subtype B	130 (35.7)	111 (30.5)
Missing	2 (0.5)	0 (0.0)

† Subjects with missing results excluded.
†† Evidence of hepatitis B surface antigen or evidence of HCV RNA by polymerase chain reaction (PCR) quantitative test for hepatitis C virus.
N = Number of subjects randomized and treated in each treatment group.
n (%) = Number (percent) of subjects in each sub-category.

21 subjects previously classified as hepatitis B and/or C positive were subsequently identified based on lab tests as being hepatitis B and C negative. 4 subjects previously classified as hepatitis B and C negative were subsequently identified based on lab tests as being hepatitis B and/or C positive.

The efficacy of DELSTRIGO® in antiretroviral treatment-naïve adult, HIV-1 infected subjects, was assessed at 48-Weeks in a Phase 3, randomized, international, multicenter, double-blind, active-controlled trial DRIVE-AHEAD (Protocol 021).

In DRIVE-AHEAD, 728 subjects were randomized and received at least 1 dose of either DELSTRIGO® or efavirenz/emtricitabine/tenofovir disoproxil (EFV/FTC/TDF) once daily. At baseline, the median age of subjects was 31 years (range 18-70 years), 85 % were male, 52 % were non-white, 3 % had hepatitis B or C co-infection, 14 % had a history of AIDS, 21 % had HIV-1 RNA > 100,000 copies per mL, and 12 % had CD4+ T-cell count < 200 cells per mm^3; these characteristics were similar between treatment groups.

At Week 96, efficacy in the DELSTRIGO® treatment group was similar to that in the EFV/FTC/TDF treatment group with regard to the proportion of participants with HIV-1 RNA <50 copies/mL, using the FDA snapshot approach; this supports the non-inferiority of DELSTRIGO® to EFV/FTC/TDF previously established at Week 48. Specifically, 77.5% and 73.6% of participants in the DELSTRIGO® and EFV/FTC/TDF treatment groups, respectively, achieved HIV-1 RNA <50 copies/mL, with an estimated treatment difference of 3.8% (95%CI: -2.4, 10.0).

Week 48 outcomes for DRIVE-AHEAD are provided in Table 12.

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 198 and 188 cells/mm^3, respectively.

Table 12 - Virologic Outcome in DRIVE-AHEAD at Week 48 in HIV-1 Adult Subjects with No Antiretroviral Treatment History

Outcome	DRIVE-AHEAD	
	DELSTRIGO® Once Daily	**Comparator Once Daily**
	N=364	**N=364**
	n (%)	n (%)
HIV-1 RNA <50 copies/mL	307 (84%)	294 (81%)
Treatment Differences (95% CI) [Þ]	3.5% (-2.0%, 9.0%)	
HIV-1 RNA ≥ 50 copies/mL [†]	39 (11%)	37 (10%)
No Virologic Data at Week 48 Window	18 (5%)	33 (9%)
Reasons		
Discontinued study due to AE or Death [‡]	9 (2%)	24 (7%)
Discontinued study for Other Reasons [§]	9 (2%)	8 (2%)
On study but missing data in window	0 (0%)	1(<1%)
Proportion (%) of Subjects With HIV-1 RNA <50 copies/mL at Week 48 by Baseline and Demographic Category		
	n / N (%)	**n / N (%)**
Gender		
Male	257/305 (84%)	250/311 (80%)
Female	50/59 (85%)	44/53 (83%)
Race		
White	149/177 (84%)	138/170 (81%)
Non-White	158/187 (84%)	156/194 (80%)
Ethnicity		
Hispanic or Latino	105/126 (83%)	101/120 (84%)
Not Hispanic or Latino	200/236 (85%)	189/238 (79%)
Baseline HIV-1 RNA (copies/mL)		
≤ 100,000 copies/mL	251/291 (86%)	235/282 (83%)
> 100,000 copies/mL	56/73 (77%)	59/82 (72%)
CD4+ T-cell Count (cells/mm^3)		
≤ 200 cells/mm^3	29/44 (66%)	36/46 (78%)
> 200 cells/mm^3	278/320 (87%)	258/318 (81%)
Viral Subtype [¶]		
Subtype B	195/232 (84%)	202/253 (80%)
Subtype Non-B	110/130 (85%)	92/111 (83%)
¶Viral subtype was not available for two subjects.		

[Þ] 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 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.

Virologically suppressed patients

The demographic and baseline characteristics of patients in DRIVE-SHIFT are summarized in Table13.

Table 13 – Demographic and Baseline Characteristics in DRIVE-SHIFT in HIV-1 Virologically-Suppressed Subjects

	DELSTRIGO® ISG Once Daily (N = 447)	Baseline Regimen DSG (N = 223)
Gender n (%)		
Male	372 (83.2)	194 (87.0)
Female	75 (16.8)	29 (13.0)
Race n (%)		
American Indian or Alaska Native	5 (1.1)	2 (0.9)
Asian	17 (3.8)	8 (3.6)
Black or African American	56 (12.5)	34 (15.2)
Multiple	24 (5.4)	11 (4.9)
Native Hawaiian or Other Pacific Islander	1 (0.2)	0 (0.0)
White	344 (77.0)	168 (75.3)
Ethnicity n (%)		
Hispanic or Latino	99 (22.1)	45 (20.2)
Not Hispanic or Latino	341 (76.3)	175 (78.5)
Unknown	7 (1.6)	3 (1.3)
Region n (%)		
Asia / Pacific	19 (4.3)	12 (5.4)
Europe	268 (60.0)	137 (61.4)
Latin America	49 (11.0)	24 (10.8)
North America	111 (24.8)	50 (22.4)
Age (years)		
18 to 64	438 (98.0)	214 (96.0)
≥ 65	9 (2.0)	9 (4.0)
Mean (SD)	43.1 (10.1)	43.7 (10.6)
Median (min, max)	43.0 (21,71)	42.0 (22,71)
Baseline CD4+T-Cell Count (cells/mm^3)		
N†	439	220
Mean (SD)	664.9 (295.3)	649.9 (279.2)
Median (min, max)	633.0 (82, 1928)	624.5 (140, 1687)
Baseline CD4+T-Cell Count n (%)		
< 200 cells/mm^3	13 (2.9)	4 (1.8)
≥ 200 cells/mm^3	426 (95.3)	216 (96.9)
Missing	8 (1.8)	3 (1.3)
Baseline Plasma HIV-1 RNA n (%)		
<50 copies/mL	436 (97.5)	222 (99.6)
<40 copies/mL	436 (97.5)	220 (98.7)
≥40 copies/mL	11 (2.5)	3 (1.3)
≥50 copies/mL	11 (2.5)	1 (0.4)

	DELSTRIGO® ISG Once Daily (N = 447)	Baseline Regimen DSG (N = 223)
History of AIDS n (%)		
Yes	80 (17.9)	35 (15.7)
No	367 (82.1)	188 (84.3)
Stratum n (%)		
Ritonavir-boosted PI	312 (69.8)	155 (69.5)
Lipid-lowering therapy	31 (6.9)	12 (5.4)
Non-Lipid-lowering therapy	281 (62.9)	143 (64.1)
Cobicistat-boosted PI	4 (0.9)	2 (0.9)
Cobicistat-boosted elvitegravir or an NNRTI	131 (29.3)	66 (29.6)
Duration of ART Regimen Prior to Enrollment (%)		
<1 year	26 (5.8)	12 (5.4)
≥1 year	421 (94.2)	211 (94.6)
Duration of ART Regimen Prior to Enrollment (months)		
N†	447	223
Mean (SD)	56.6 (38.4)	58.6 (37.0)
Median (min, max)	48.4 (6.9, 264.9)	50.5 (7.2, 181.1)
Baseline Hepatitis Status††		
Hep B and/or C Positive	14 (3.1)	9 (4.0)
Hep B Positive Only	12 (2.7)	7 (3.1)
Hep C Positive Only	2 (0.4)	2 (0.9)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen		
N	340 (76.1)	168 (75.3)
K103N, Y181C, and/or G190A	11 (2.5)	13 (5.8)

† Subjects with missing results excluded.

†† Evidence of hepatitis B surface antigen or evidence of hepatitis C virus (HCV) RNA by polymerase chain reaction (PCR) quantitative test for HCV.

Baseline Regimen = ritonavir or cobicistat-boosted PI, or cobicistat-boosted elvitegravir, or NNRTI, each administered with two NRTIs.

Note: The DSG continues their baseline regimen until the time of the switch to DELSTRIGO® QD at Study Week 24.

N = Number of subjects randomized and treated in each treatment group.

n (%) = Number (percent) of subjects in each sub-category.

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, ISG], or stay on their baseline regimen until Week 24, at which point they switched to DELSTRIGO® [n = 223, DSG].

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 14.

Table 14 - Virologic Outcomes in DRIVE-SHIFT in HIV-1 Virologically-Suppressed Subjects Who Switched to DELSTRIGO®

Outcome	DELSTRIGO® Once Daily ISG Week 48	Baseline Regimen DSG Week 24
	N=447	N=223
	n (%)	n (%)
HIV-1 RNA <50 copies/mL	406 (91%)	211 (95%)
ISG-DSG, Difference (95% CI)**	3.8% (-7.9%, 0.3%)**	
HIV-1 RNA ≥ 50 copies/mL†	7 (2%)	4 (2%)
No Virologic Data at Within the Time Window	34 (8%)	8 (4%)
Discontinued study due to AE or Death‡	14 (3%)	0 (0%)
Discontinued study for Other Reasons§	20 (4%)	8 (4%)
On study but missing data in window	0 (0%)	0 (0%)
Proportion (%) of Subjects With HIV-1 RNA <50 copies/mL by Baseline and Demographic Category		
	n / N (%)	**n / N (%)**
Gender		
Male	338/372 (91%)	182/194 (94%)
Female	68/75 (91%)	29/29 (100%)
Race		
White	310/344 (90%)	160/168 (95%)
Non-White	96/103 (93%)	51/55 (93%)
Ethnicity		
Hispanic or Latino	87/99 (88%)	41/45 (91%)
Not Hispanic or Latino	312/341 (91%)	167/175 (95%)
CD4+ T-cell Count (cells/mm^3)		
<200 cells/mm^3	11/13 (85%)	3/4 (75%)
≥200 cells/mm^3	388/426 (91%)	205/216 (95%)

** 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.

14 MICROBIOLOGY

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. IC_{50} values were in the range of 0.003 µM to 2 µM (1 µM = 0.23 mcg/mL). The IC_{50} values of lamivudine against different HIV-1 clades (A to G) ranged from 0.001 to 0.120 µM, and against HIV-2 isolates from 0.002 to 0.041 µM in PBMCs. 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.

3TC-TP shows significantly less affinity for host cell DNA polymerases and is a weak inhibitor of mammalian α, β, and γ DNA polymerases.

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, V106M, V106I, V108I, F227L, F227C, F227V, H221Y, 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 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 arm of the treatment-naïve trial DRIVE-AHEAD (n=364), through 48 Weeks, emergent doravirine-associated resistance substitutions were observed in 6 of 20 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 doravirine treatment-arm of DRIVE-AHEAD between Weeks 48 and 96, no subjects developed genotypic or phenotypic resistance to doravirine. In the EFV/FTC/TDF treatment arm of the DRIVE-AHEAD trial (n=364) through 48 Weeks, emergent efavirenz-associated resistance substitutions were observed in 12 out of 20 subjects in the resistance analysis subset. In DRIVE-AHEAD between Weeks 48 and 96, 3 additional subjects in the EFV/FTC/TDF treatment arm showed the emergence of efavirenz-associated resistance substitutions.

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

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 DELSTRIGO® through Week 48. The resistance–associated substitutions that emerged were RT M41L (n=1), K65R (n=2), and M184V/I (n=4). Between Weeks 48 and 96, genotypic resistance to lamivudine and tenofovir developed in 2 subjects who received DELSTRIGO®; the emergent resistance-associated substitutions were V118I (n=1) and A62A/V (n=1). Between Weeks 48 and 96, genotypic resistance to emtricitabine or tenofovir developed in 1 subject who received EFV/FTC/TDF; the emergent resistance-associated substitution in this subject was V118I.

In DRIVE-AHEAD, no additional genotypic or phenotypic resistance to doravirine, lamivudine or TDF was identified in subjects in the doravirine treatment arm between Week 48 and Week 96.

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. 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 substitutions was evaluated for susceptibility to doravirine. Isolates that showed potentially clinically meaningful reduced (>100-fold) susceptibility to doravirine contained the following substitutions: Y188L alone or in combination with K103N or V106I; V106A in combination with G190A and F227L; and E138K in combination with Y181C and M230L.

In phase 3 trials, the following amino acid substitutions were observed in clinical isolates obtained from patients with treatment failure who had both genotypic and phenotypic resistance data available: Y188L alone, F227C in combination with A98G, A98G/V106I/H221Y, V106I, V106I/H221Y or V106M; and V106A in combination with P225H and Y318F. Clinical isolates with these substitutions showed a 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 6 virologic failures who developed doravirine phenotypic resistance, all had phenotypic resistance to EFV 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 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.

15 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute 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.

Chronic Toxicity
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-times 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.

Carcinogenicity
Doravirine: Long-term oral carcinogenicity studies of doravirine in transgenic RasH2 mice (6 months, 6 times the RHD exposure) and rats (2 years, 7 times the RHD exposure) showed no evidence of carcinogenic potential.

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.

Genotoxicity
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.

Fertility

Reproduction

Doravirine: There were no effects of doravirine on fertility, mating performance or early embryonic development up to systemic exposures that 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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

℞ DELSTRIGO®

doravirine/lamivudine/tenofovir disoproxil fumarate tablets

Read this carefully before you start taking **DELSTRIGO® (doravirine/lamivudine/tenofovir disoproxil fumarate)** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **DELSTRIGO®**.

Serious Warnings and Precautions

- **Worsening of hepatitis B virus in people who have HIV-1 infection:**
  If you have both HIV and hepatitis B virus infection, your hepatitis B virus infection may get worse (flare up) if you stop taking DELSTRIGO®. If you have both HIV and hepatitis B virus infection and stop taking DELSTRIGO®, talk to your doctor immediately if have a flare up of your hepatitis B virus infection. Symptoms of a flare up can include the following: jaundice (skin or the white part of eyes turns yellow) urine turns dark, bowel movements (stools) turn light in color, loss of appetite for several days or longer, feeling sick to your stomach (nausea), lower stomach pain. Your doctor will closely monitor your health after you stop treatment. You may require blood tests for several months after stopping treatment. DELSTRIGO® is not approved for the treatment of hepatitis B virus infection, so you must discuss your hepatitis B virus infection therapy with your doctor.

- The most serious possible side effect is harm to the kidneys, including damage to kidney cells, kidney tissue inflammation and kidney failure. Your doctor may monitor your kidney function before beginning and while receiving DELSTRIGO®. Some patients treated with tenofovir disoproxil fumarate (one of the medicines in DELSTRIGO®) have had kidney problems. Your doctor may need to perform additional blood tests if you have had kidney problems in the past or need to take another drug that can cause kidney problems.

What is DELSTRIGO® used for?

- DELSTRIGO® is used to treat Human Immunodeficiency Virus-1 (HIV-1) infection in adults. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).
- DELSTRIGO® is for people who do not have HIV virus that is resistant to doravirine, lamivudine or tenofovir.

How does DELSTRIGO® work?

- Doravirine is a type of medicine called an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI).
- Lamivudine is a type of medicine called an HIV-1 nucleoside analogue reverse transcriptase inhibitor.
- Tenofovir disoproxil fumarate is a type of medicine called an HIV-1 nucleoside analogue reverse transcriptase inhibitor.
- The medicines in DELSTRIGO® block an enzyme that HIV needs in order to make more virus.
- DELSTRIGO® can help lower the amount of HIV in your blood (called your "viral load") and increase your CD4+ T cell count which can make your immune system stronger. This may reduce your risk of death or getting infections that can happen when your immune system is weak.
- DELSTRIGO® does not cure HIV or AIDS. It is important to keep taking DELSTRIGO® to control your HIV infection.

What are the ingredients in DELSTRIGO®?
Each tablet has the following medicines: doravirine, lamivudine, and tenofovir disoproxil fumarate.

Each tablet has the following ingredients that are not medicines: Carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose and sodium stearyl fumarate.

Each tablet is covered with the following ingredients that are not medicines: Hypromellose, iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin.

DELSTRIGO® comes in the following dosage form:
As tablets containing 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).

Do not use DELSTRIGO® if you:

- are allergic to doravirine, lamivudine or tenofovir disoproxil fumarate.
- are allergic to any of the other ingredients in DELSTRIGO® or any part of the container.
- **are taking any of the following medicines:**
    - carbamazepine, oxcarbazepine, phenobarbital, phenytoin which are used to treat seizures
    - enzalutamide, used to treat prostate cancer
    - rifampin, used to treat tuberculosis
    - mitotane, used to treat cancer
    - St. John's wort which is an herbal product used to treat depression
    - adefovir dipivoxil, used to treat hepatitis B infection.

It is not known if DELSTRIGO® is safe and effective in children under 18 years of age.

There is very little information on the combination use of doravirine, lamivudine and tenofovir disoproxil fumarate in patients 65 years of age and over.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DELSTRIGO®. Talk about any health conditions or problems you may have, including if you:

- have hepatitis B virus infection.
- have hepatitis C virus infection.
- have kidney problems.
- have severe liver problems.
- have a history of bone fractures due to your bone problems, or are at risk for bone softening or thinning.
- have or had any allergies.
- are pregnant or planning to become pregnant.
- are breastfeeding or planning to breastfeed.
- are taking any of the following combination of medicines to treat your hepatitis C infection: ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir.

Other warnings you should know about:

Pregnancy:
Tell your doctor if you are pregnant or planning to become pregnant. It is not known if DELSTRIGO® can harm your unborn baby. Tell your doctor if you become pregnant while you are taking DELSTRIGO®.

Pregnancy Registry:
There is a pregnancy registry for women who take antiretroviral medicines while they are pregnant. The purpose of this registry is to collect information about the health of you and your baby. If you do become pregnant while taking DELSTRIGO®, talk to your doctor about taking part in this registry.

Breastfeeding:
You should not breastfeed if you are taking DELSTRIGO®. You should also not breastfeed a baby if you are infected with HIV. This is because you can pass HIV to your baby. If you breastfeed a baby they can get HIV from you.

HIV Transmission:
DELSTRIGO® does not reduce the risk of passing HIV to others through sexual contact, sharing needles or being exposed to your blood. Always practice safe sex. Use latex or polyurethane condoms or other barrier methods to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Never re-use or share needles. Ask your doctor if you have any questions about safe sex or how to prevent passing HIV to other people.

Driving and using machines:
DELSTRIGO® may make you tired, dizzy or sleepy. This may affect your ability to drive and use machines. Before driving or using machines, wait until you are feeling well again.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

- Do not take other medicines that contain tenofovir disoproxil fumarate, tenofovir alafenamide, lamivudine, emtricitabine or adefovir dipivoxil.

The following may interact with DELSTRIGO®:

- The medicine rifabutin used to treat some bacterial infections such as tuberculosis.
    - If you also take the medicine rifabutin, take one tablet of doravirine (PIFELTRO®) about 12 hours after DELSTRIGO®, as prescribed by your doctor.
- Medicines that modify a system called CYP3A that removes medicines from your body. If you are not sure whether a medicine you take affects this system, ask your doctor.
- Medicines that reduce how well your kidney works or are removed by the kidney using the same route as DELSTRIGO® may change the blood levels of some components of DELSTRIGO®. Examples of these medicines include cidofovir, ganciclovir, vancomycin or aminoglycosides. If you are not sure if your medicine affects your kidneys or removal of medicine by the kidney, ask your doctor.

Avoid taking the following medicines with DELSTRIGO®:

- bosentan, a medicine used to treat high blood pressure in the lungs.
- dabrafenib, a medicine used to treat cancer.
- modafinil, a medicine used to treat sleep disorders.

If you cannot avoid taking these medicines with DELSTRIGO®, take one tablet of doravirine (PIFELTRO®) 12 hours after DELSTRIGO®, as prescribed by your doctor.

- Sorbitol-containing medicines (usually liquids): regular use should be avoided as these medicines can decrease blood levels of a component of DELSTRIGO®.

How to take DELSTRIGO®:

- Take DELSTRIGO® exactly as your doctor tells you.
- Your treatment with DELSTRIGO® will be initiated by a doctor with experience in the management of HIV infection.
- Do not change your dose or stop taking this or any other HIV medicine without talking to your doctor. Stay under a doctor's care when taking DELSTRIGO®.

Usual adult dose:

- Take 1 tablet once a day by mouth at about the same time every day with or without food.
- DELSTRIGO® is taken by itself (not with other HIV medicines).

Overdose:

If you think you have taken too much DELSTRIGO®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- It is important that you do not miss or skip doses of DELSTRIGO®.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is almost time for your next dose, skip the missed dose and take the next dose at your regular time.
- Do not take two doses of DELSTRIGO® at the same time.
- If you are not sure what to do, call your doctor or pharmacist.

What are possible side effects from using DELSTRIGO®?
These are not all the possible side effects you may feel when taking DELSTRIGO®. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects include:
- dizziness
- abnormal dreams, difficulty in sleeping (insomnia), nightmares
- headache
- sleepiness
- feeling sick (nausea), diarrhea, vomiting
- feeling tired

Other side effects include:
- feeling weak
- depression

Serious side effects may include:

See "Serious Warnings and Precautions box"

Bone problems can happen in some people who take DELSTRIGO®. Bone problems include bone pain, softening, or thinning (which may lead to fractures). Your doctor may need to do additional tests to check your bones.

Immune Reconstitution Inflammatory Syndrome:
Changes to your immune system can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time (Immune Reconstitution Inflammatory Syndrome).

Autoimmune disorders (when the immune system attacks healthy body tissue), may also occur after you start taking medicines for HIV infection. Examples include: Grave's disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the nervous system), polymyositis (which affects the muscles), or autoimmune hepatitis (which affects the liver). Autoimmune disorders may occur many months after the start of treatment. Look for symptoms such as:
- high temperature (fever), redness, rash or swelling
- fatigue
- joint or muscle pain
- numbness or weakness beginning in the hands and feet and moving up towards the trunk of the body
- palpitations (chest pain) or rapid heart rate

If you notice these or any symptoms of inflammation or infection, tell your doctor immediately.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE **Bone problems:** • bone pain • bone fracture • pain in arms or legs • muscle pain or weakness		✓	
RARE **Lactic acidosis** (high level of lactic acid in the body): • feeling very weak or tired • unusual muscle pain • stomach pain with nausea and vomiting • feeling cold, especially in arms and legs • feeling dizzy or lightheaded • fast or irregular heart rate		✓	
RARE **Anemia** (decreased red blood cells): • fatigue • loss of energy • shortness of breath • weakness		✓	
RARE **Kidney problems:** • increased or decreased urination as well as increased thirst • swelling of legs and feet • feeling tired • lack of energy		✓	

VERY RARE **Flare-ups of hepatitis B virus infection following drug discontinuation:** • jaundice (skin or the white part of eyes turns yellow) • urine turns dark • bowel movements (stools) turn light in color • loss of appetite for several days or longer • feeling sick to your stomach (nausea) • lower stomach pain		✓	
VERY RARE **Severe allergic reactions:** • swollen face, lips, mouth, tongue or throat, which may lead to difficulty swallowing or breathing			✓
VERY RARE **Severe skin rash:** • mouth sores or blisters on your body			✓
VERY RARE **Severe Hepatomegaly with Steatosis** (swollen and fatty liver): • jaundice (skin or the white part of eyes turns yellow) • urine turns dark • bowel movements (stool) turns light in color • loss of appetite for several days or longer • feeling sick to your stomach (nausea) • lower stomach pain.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

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

Store DELSTRIGO® at room temperature (15°C to 30°C).

Keep out of reach and sight of children.

If you want more information about DELSTRIGO®:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php) or the Merck Canada website (www.merck.ca) or by calling 1-800-567-2594.

To report an adverse event related to DELSTRIGO®, please contact 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

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