PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PIFELTRO®

doravirine tablets

Tablets, 100 mg, oral

Antiviral Agent

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS	04/2023
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PIFELTRO® (doravirine) is indicated, in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older and weighing at least 35kg without past or present evidence of viral resistance to doravirine.

1.1 Pediatrics

Pediatrics (≥ 12 to < 18 years of age): The safety and efficacy of PIFELTRO® in pediatric patients ≥ 12 years of age and weighing at least 35 kg receiving doravirine 100 mg once daily has been established (see **8.2.1 Clinical Trial Adverse Reactions – Pediatrics** and **14CLINICAL TRIALS**).

Safety and efficacy of PIFELTRO® have not been established in patients younger than 12 years of age and weighing less than 35 kg.

1.2 Geriatrics

Geriatric (≥ 65 years of age): There are limited data available on the use of doravirine in patients aged 65 years and over.

2 CONTRAINDICATIONS

PIFELTRO® 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 **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

PIFELTRO® is contraindicated with drugs that are strong cytochrome P450 CYP3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of PIFELTRO® (see **9.4 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*).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- PIFELTRO® is a tablet containing 100 mg of doravirine.
- PIFELTRO® can be taken with or without food.

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

4.2 Recommended Dose and Dosage Adjustment

Recommended Dosage

Adults and Pediatric Patients 12 Years and older and Weighing at Least 35 kg

The recommended dosage regimen of PIFELTRO® is one 100 mg tablet taken orally once daily.

Pediatrics (< 12 years of age)

Safety and efficacy of PIFELTRO® have not been established in patients younger than 12 years of age and weighing less than 35 kg.

Geriatrics (≥ 65 years of age)

There are limited data available on the use of doravirine in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients (see **10.3 Pharmacokinetics**). No dose adjustment of PIFELTRO® is needed in elderly patients.

Dosage Adjustment in Adults

Renal Impairment

No dose adjustment of PIFELTRO® is required in patients with mild, moderate or severe renal impairment. PIFELTRO® has not been adequately studied in patients with end-stage renal disease and has not been studied in dialysis patients (see **10.3 Pharmacokinetics**).

Hepatic Impairment

No dose adjustment of PIFELTRO® is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. PIFELTRO® has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see **10.3 Pharmacokinetics**).

Co-administration with Rifabutin

If PIFELTRO® is co-administered with rifabutin, one tablet of PIFELTRO® should be taken twice daily (approximately 12 hours apart) (see **9.4 Drug-drug interactions**).

4.5 Missed Dose

If the patient misses a dose of PIFELTRO®, the patient should take PIFELTRO® 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 PIFELTRO®. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

PIFELTRO® is a film-coated tablet containing doravirine for oral administration.

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 100 mg	Carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose. Film coating: hypromellose, lactose monohydrate, titanium dioxide, and triacetin.

PIFELTRO® 100 mg tablet is a white oval-shaped, film-coated tablet, debossed with the corporate logo and 700 on one side and plain on the other side.

PIFELTRO® tablets are available in bottles of 30.

7 WARNINGS AND PRECAUTIONS

General

History of treatment failure and resistance

PIFELTRO® 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 **15 MICROBIOLOGY**).

PIFELTRO® should not be used in antiretroviral-experienced patients with HIV-1 harboring NNRTI resistance-associated mutations which may confer resistance to doravirine or with suspected NNRTI resistance in virologically-suppressed patients if no genotype is available (see **15 MICROBIOLOGY**).

Driving and Operating Machinery

Patients should be informed that fatigue, dizziness, and somnolence have been seen during treatment with doravirine (see **8.2 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

Caution should be given to prescribing PIFELTRO® with drugs that may reduce the exposure of doravirine (see **2 CONTRAINDICATIONS**, **9.4 Drug-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.

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.

Reproductive Health: Female and Male Potential

- **Fertility**

  No human data on the effect of doravirine on fertility are available. Animal studies do not indicate harmful effects of doravirine on fertility at systemic exposures that were approximately 7 times higher than the exposure in humans at the recommended clinical dose (see section **16 NON-CLINICAL TOXICOLOGY**).

Skin

In clinical trial data, drug related rash of moderate to severe intensity occurred in 0.3% of patients in DRIVE-FORWARD and DRIVE-AHEAD, respectively.

Severe skin reactions, including toxic epidermal necrolysis (TEN), have been reported during the postmarketing experience with doravirine-containing regimens (see section 8.5 Post-Market Adverse Reactions). Discontinue PIFELTRO®, and other medications known to be associated with severe skin reactions, immediately if a painful rash with mucosal involvement or a progressive severe rash, or hypersensitivity reactions develop. Clinical status should be closely monitored, and appropriate therapy should be initiated.

7.1 Special Populations

7.1.1 Pregnant Women

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

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.

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

Physicians are encouraged to report pregnancy cases for inclusion in the registry. SM_APR@APRegistry.com (www.apregistry.com)
Telephone: 1-800-258-4263
Fax: 1-800-800-1052

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

Pediatrics (≥ 12 years to < 18 years): The safety and efficacy of PIFELTRO® for the treatment of HIV-1 infection have been established in pediatric patients 12 years of age and older and weighing at least 35 kg (see **1.1 Pediatrics** and **14 CLINICAL TRIALS**).

Use of PIFELTRO® in pediatric patients 12 years and older and weighing at least 35 kg is supported by evidence from adequate and well-controlled trials in adults and an open-label trial in virologically-suppressed or treatment-naïve pediatric subjects. The safety, efficacy, and exposure of doravirine in these pediatric subjects were similar to that in adults (see **10.3 Pharmacokinetics**).

Pediatrics (< 12 years of age): The safety and efficacy of PIFELTRO® have not been established in patients younger than 12 years of age and weighing less than 35 kg.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): There are limited data available on the use of doravirine in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients (see **10.3 Pharmacokinetics**). No dose adjustment of PIFELTRO® is needed in elderly patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety assessment of PIFELTRO® in antiretroviral treatment-naïve, HIV-1-infected subjects, is based on the analyses of data through 48- and 96 Weeks from two Phase 3, randomized, international, multicenter, double-blind, active-controlled trials (DRIVE-FORWARD (Protocol 018) and DRIVE-AHEAD (Protocol 021)).

In subjects receiving PIFELTRO®, 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 doravirine was nausea (6 %). There were no adverse reactions of moderate to severe intensity with an incidence of greater than or equal to 2%.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, 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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Clinical Trials in Antiretroviral Treatment-Naïve Adults

In DRIVE-FORWARD, 766 adult subjects received either PIFELTRO® 100 mg (n=383) or darunavir 800 mg + ritonavir 100 mg (DRV+r) (n=383) once daily in a double-blind design, each in combination with emtricitabine/tenofovir DF (FTC/TDF) or abacavir/lamivudine (ABC/3TC). By Week 48, 1.6% in the PIFELTRO® group and 3.1% in the DRV+r group had adverse events leading to discontinuation of study medication.

In DRIVE-AHEAD, 728 adult subjects received either DELSTRIGO® (doravirine/lamivudine/tenofovir DF) (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-FORWARD and DRIVE-AHEAD are presented in Table 2.

Table 2 - Adverse Reactions[Þ] (All Grades) Reported in ≥2%[†] of Subjects in Any Treatment Group in Adults with No Antiretroviral Treatment History in DRIVE-FORWARD and DRIVE-AHEAD (Week 48)

	DRIVE-FORWARD		DRIVE-AHEAD	
	PIFELTRO® +2 NRTIs Once Daily	DRV+r +2 NRTIs Once Daily	DELSTRIGO® Once Daily	EFV/FTC/TDF Once Daily
	N=383	N=383	N=364	N=364
Gastrointestinal Disorders				
Abdominal pain upper	2%	<1%	<1%	<1%
Diarrhea	5%	13%	3%	5%
Nausea	7%	8%	5%	7%
Vomiting	2%	1%	2%	3%
General Disorders and Administration Site Conditions				
Fatigue	5%	2%	4%	3%
Nervous System Disorders				
Dizziness	3%	2%	7%	32%
Headache	6%	3%	4%	4%
Sleep disorder	2%	<1%	<1%	2%
Somnolence	0%	<1%	3%	7%
Psychiatric Disorders				
Abnormal dreams	1%	<1%	5%	9%
Insomnia	1%	2%	4%	5%
Nightmare	<1%	<1%	2%	4%
Skin and Subcutaneous Disorders				
Rash	<1%	<1%	2%	9%

[Þ] 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 doravirine.
NRTIs = nucleoside reverse transcriptase inhibitors
NRTIs = FTC/TDF or ABC/3TC.

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 PIFELTRO® in virologically-suppressed adults was based on Week 48 data from 670 subjects in the DRIVE-SHIFT trial (see **Virologically-Suppressed Adult Subjects**). Overall, the safety profile in virologically-suppressed adult subjects was similar to that in subjects with no antiretroviral treatment history.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The safety of doravirine as a component of DELSTRIGO® was evaluated in 45 HIV-1-infected virologically-suppressed or treatment-naïve pediatric patients 12 to less than 18 years of age through Week 24 in an open-label trial (IMPAACT 2014 (Protocol 027)) (see **Pediatric Subjects**). The safety profile in pediatric subjects was similar to that in adults. There were no serious or Grade 3 or 4 adverse reactions. No subjects discontinued due to an adverse event.

8.3 Less Common Clinical Trial Adverse Reactions

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

Blood and Lymphatic Systems Disorders: lymph node pain, neutropenia.

Cardiac Disorders: palpitations.

Ear and Labyrinth Disorders: motion sickness, vertigo.

Eye Disorders: vision blurred.

Gastrointestinal Disorders: abdominal discomfort, abdominal distension, abdominal pain, abnormal feces, change in bowel habits, constipation, dry mouth, dyspepsia, dysphagia, epigastric discomfort, feces soft, flatulence, frequent bowel movements, gastritis, gastrointestinal motility disorder, gastroesophageal reflux disease, irritable bowel syndrome, rectal tenesmus.

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

Hepatobiliary Disorders: hepatitis, hepatocellular injury, hyperbilirubinemia.

Immune System Disorders: immune reconstitution inflammatory syndrome.

Infections and Infestations: acute sinusitis, angular cheilitis, conjunctivitis, folliculitis, gastroenteritis, lymphogranuloma venereum, oral herpes, nasopharyngitis, rash pustular.

Investigations: alanine aminotransferase increased*, amylase increased, aspartate aminotransferase increased, blood creatinine phosphokinase increased, blood triglycerides increased, bone density decreased, gastric pH decreased, hemoglobin decreased, lipase increased, weight decreased, 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, musculoskeletal pain, 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, mood altered, mood swings, persistent depressive disorder, somnambulism, suicidal ideation.

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

Reproductive and Breast Disorders: erectile dysfunction.

Respiratory, Thoracic and Mediastinal Disorders: cough, dyspnea, tonsillar hypertrophy.
Skin and Subcutaneous Tissue Disorders: acne, alopecia, dermatitis allergic, hyperhidrosis, pruritus, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rosacea, seborrheic dermatitis, skin lesion, 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 PIFELTRO® or DRV+r in DRIVE-FORWARD, or 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-FORWARD and DRIVE-AHEAD (Week 48)

		DRIVE-FORWARD		DRIVE-AHEAD	
Laboratory Parameter Preferred Term (Unit)	**Limit**	**PIFELTRO® +2 NRTIs Once Daily**	**DRV+r +2 NRTIs Once Daily**	**DELSTRIGO® Once Daily**	**EFV/FTC/TDF Once Daily**
		N=383	**N=383**	**N=364**	**N=364**
Blood Chemistry					
Total bilirubin (mg/dL)					
Grade 2	1.6 - <2.6 x ULN	2%	<1%	2%	0%
Grade 3-4	≥2.6 x ULN	0%	0%	<1%	<1%
Creatinine (micromol/L)					
Grade 2	>1.3 - 1.8 x ULN or Increase of > 26.5 micromol/L above baseline	3%	4%	2%	1%
Grade 3-4	>1.8 x ULN or Increase of ≥1.5 x above baseline	2%	3%	2%	1%
Aspartate aminotransferase (IU/L)					
Grade 2	2.5 - <5.0 x ULN	4%	3%	2%	2%
Grade 3-4	≥5.0 x ULN	<1%	2%	<1%	2%
Alanine aminotransferase (IU/L)					
Grade 2	2.5 - <5.0 x ULN	3%	2%	3%	4%
Grade 3-4	≥5.0 x ULN	1%	2%	<1%	2%
Alkaline phosphatase (IU/L)					
Grade 2	2.5 - <5.0 x ULN	<1%	<1%	0%	<1%
Grade 3-4	≥5.0 x ULN	0%	0%	0%	<1%
Lipase					
Grade 2	1.5 - <3.0 x ULN	4%	5%	5%	4%
Grade 3-4	≥3.0 x ULN	3%	2%	1%	2%
Creatine kinase (IU/L)					
Grade 2	6.0 - <10.0 x ULN	2%	3%	2%	2%
Grade 3-4	≥10.0 x ULN	3%	4%	2%	3%

ULN = Upper limit of normal range.
Note: NRTIs = FTC/TDF or ABC/3TC.

Change in Lipids from Baseline

For DRIVE-FORWARD and 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 those seen at Week 48.

PIFELTRO® 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 for doravirine 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-FORWARD, DRIVE-AHEAD and DRIVE-SHIFT

Laboratory Parameter Preferred Term	DRIVE-FORWARD (No antiretroviral treatment history) Week 48		DRIVE-AHEAD (No antiretroviral treatment history) Week 48		DRIVE-SHIFT (Virologically-Suppressed) Week 24	
	PIFELTRO® +2 NRTIs Once Daily	DRV+r +2 NRTIs Once Daily	DELSTRIGO® Once Daily	EFV/FTC/ TDF Once Daily	DELSTRIGO® (Week 0-24) Once Daily	PI+Ritonavir (Week 0-24) Once Daily
	N=320	N=311	N=320	N=307	N=244	N=124
LDL Cholesterol (mmol/L)[Þ]	-0.12	0.25	-0.05	0.21	-0.42	-0.07
Non-HDL Cholesterol (mmol/L)[Þ]	-0.14	0.36	-0.11	0.33	-0.64	-0.05
Total Cholesterol (mmol/L)	-0.04	0.47	-0.06	0.55	-0.68	-0.01
Triglycerides (mmol/L)	-0.03	0.28	-0.14	0.24	-0.50	-0.00
HDL Cholesterol (mmol/L)	0.10	0.11	0.05	0.22	-0.03	0.05

Subjects on lipid-lowering agents at baseline were excluded from these analyses (in DRIVE-FORWARD: PIFELTRO® n=12 and DRV+r n=14; 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-FORWARD: PIFELTRO® n=6 and DRV+r n=4; 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.

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

8.5 Post-Market Adverse Reactions

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

Skin and Subcutaneous Tissue Disorders: toxic epidermal necrolysis (TEN)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Established and Other Potentially Significant Drug Interactions

Doravirine is primarily metabolized by CYP3A, and drugs that induce or inhibit CYP3A may affect the clearance of doravirine. Co-administration of PIFELTRO® and drugs that induce CYP3A may result in decreased plasma concentrations of doravirine and reduce the therapeutic effect of doravirine (see **2 CONTRAINDICATIONS**, **7 WARNINGS AND PRECAUTIONS**, and **9.4 Drug-Drug Interactions**). Co-administration of PIFELTRO® and drugs that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine.

9.4 Drug-Drug Interactions

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 PIFELTRO® 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
HIV-Antiviral Agents		
efavirenz[Þ] etravirine nevirapine	↓ doravirine	Concomitant use of PIFELTRO® with efavirenz, etravirine and nevirapine may decrease plasma concentrations of doravirine (CYP3A induction).
ritonavir[†]- boosted PIs (atazanavir, darunavir, fosamprenavir, indinavir[1], lopinavir, saquinavir, tipranavir)	↑ doravirine	Concomitant use of PIFELTRO® with ritonavir-boosted PIs or ritonavir-boosted elvitegravir may cause an increase in the plasma concentrations of doravirine (inhibition of CYP3A enzymes).
ritonavir-boosted elvitegravir	↔ boosted PIs ↔ elvitegravir	No dose adjustment is required when PIFELTRO® is co-administered with ritonavir-boosted PIs or ritonavir-boosted elvitegravir.
cobicistat-boosted PIs (darunavir, atazanavir)	↑ doravirine	Concomitant use of PIFELTRO® with cobicistat-boosted PIs or cobicistat-boosted elvitegravir may cause an increase in the plasma concentrations of doravirine (inhibition of CYP3A enzymes).
cobicistat-boosted elvitegravir	↔ boosted PIs ↔ elvitegravir	

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
		No dose adjustment is required when PIFELTRO® is co-administered with cobicistat-boosted PIs or cobicistat-boosted elvitegravir.
unboosted PIs (atazanavir, fosamprenavir, indinavir[1], nelfinavir)	↑ doravirine	Concomitant use of PIFELTRO® with unboosted PIs may cause an increase in the plasma concentrations of doravirine (inhibition of CYP3A enzymes).
	↔ unboosted PIs	No dose adjustment is required when PIFELTRO® is co-administered with unboosted PIs.
Antimycobacterials		
rifabutin[Þ]	↓ doravirine	Concomitant use of PIFELTRO® with rifabutin may cause a decrease in the plasma concentrations of doravirine (induction of CYP3A enzymes).
	↔ rifabutin	If PIFELTRO® is co-administered with rifabutin, one tablet of PIFELTRO® should be taken twice daily (approximately 12 hours apart) (see **4.2 Recommended Dose and Dose Adjustment**)
Azole Antifungal Agents		
fluconazole itraconazole ketoconazole[Þ] posaconazole voriconazole	↑ doravirine	Concomitant use of PIFELTRO® with azole antifungal agents may cause an increase in the plasma concentrations of PIFELTRO® (inhibition of CYP3A enzymes).
	↔ azole antifungal agents	No doravirine dose adjustment is required when PIFELTRO® is co-administered with azole antifungal agents.

↑ = increase, ↓ = decrease, ↔ = no change, PIs = Protease Inhibitors
[Þ] The interaction between PIFELTRO® and the drug was evaluated in a clinical study.
[†] The interaction was evaluated with ritonavir only.
All other drug-drug interactions shown are anticipated based on the known metabolic and elimination pathways.
[1] Not marketed in Canada

Drugs with No Observed or Predicted Interactions with PIFELTRO®

Drug-drug interactions with PIFELTRO® and the following drugs were evaluated in clinical studies and no dose adjustment is needed for either drug (see section below Drug Interaction Studies)*:* aluminum hydroxide/magnesium hydroxide/simethicone-containing antacid, pantoprazole, atorvastatin, an oral contraceptive containing ethinyl estradiol and levonorgestrel, metformin, methadone, midazolam, sofosbuvir/ledipasvir, elbasvir/grazoprevir, dolutegravir, lamivudine, or tenofovir DF.

No clinically relevant drug-drug interaction is expected when PIFELTRO® is co-administered with abacavir, emtricitabine, enfuvirtide, raltegravir, maraviroc, tenofovir alafenamide, buprenorphine, naloxone, daclatasvir, simeprevir, diltiazem, verapamil, rosuvastatin, simvastatin, canagliflozin, liraglutide, sitagliptin, lisinopril, or omeprazole.

Drug Interaction Studies

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

Doravirine is not likely to have a clinically relevant effect on the exposure of medicinal products metabolized by CYP enzymes. Drug interaction studies were performed with doravirine and other drugs likely to be co-administered or commonly used as probes for pharmacokinetic interactions. The effects of co-administration of other drugs on the C_{max}, AUC, and C_{24} values of doravirine are summarized in Table 6. The effects of co-administration of doravirine on the C_{max} and AUC values of other drugs are summarized in Table 7.

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

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Doravirine	N	Geometric Mean Ratio (90% CI) of Doravirine Pharmacokinetics with/without Co-administered Drug (No Effect=1.00)		
				AUC[b]	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						
ritonavir	100 mg BID	50 mg SD	8	3.54 (3.04, 4.11)	1.31 (1.17, 1.46)	2.91 (2.33, 3.62)
dolutegravir	50 mg QD	200 mg QD	11	1.00 (0.89, 1.12)	1.06 (0.88, 1.28)	0.98 (0.88, 1.09)
efavirenz[†]	600 mg QD	100 mg QD day 1	17	0.38 (0.33, 0.45)	0.65 (0.58, 0.73)	0.15 (0.10, 0.23)
	600 mg QD	100 mg QD Steady State	17	0.68 (0.58, 0.80)	0.86 (0.77, 0.97)	0.50 (0.39, 0.64)
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 +	100 mg SD	15	0.96 (0.87, 1.06)	0.97 (0.88, 1.07)	0.94 (0.83, 1.06)

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Doravirine	N	Geometric Mean Ratio (90% CI) of Doravirine Pharmacokinetics with/without Co-administered Drug (No Effect=1.00)		
				AUC[Þ]	C_{max}	C_{24}
	300 mg tenofovir DF SD					
Hepatitis C Antiviral Agents						
elbasvir + grazoprevir	50 mg elbasvir QD + 200 mg grazoprevir QD	100 mg QD	12	1.56 (1.45, 1.68)	1.41 (1.25, 1.58)	1.61 (1.45, 1.79)
ledipasvir + sofosbuvir	90 mg ledipasvir SD + 400 mg sofosbuvir SD	100 mg SD	14	1.15 (1.07, 1.24)	1.11 (0.97, 1.27)	1.24 (1.13, 1.36)
Acid-Reducing Agents						
antacid (aluminum and magnesium hydroxide oral suspension)	20 mL SD	100 mg SD	14	1.01 (0.92, 1.11)	0.86 (0.74, 1.01)	1.03 (0.94, 1.12)
pantoprazole	40 mg QD	100 mg SD	13	0.83 (0.76, 0.91)	0.88 (0.76, 1.01)	0.84 (0.77, 0.92)
Opioid Analgesics						
methadone	20-200 mg QD 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; BID = Twice Daily

[Þ] $AUC_{0-\infty}$ for single dose, AUC_{0-24} for once daily.

[†] Interaction was assessed following the cessation of efavirenz therapy.

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

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Doravirine	N	Geometric Mean Ratio [90% CI] Drug Pharmacokinetics with/without Co-administered Doravirine (No Effect=1.00)		
				AUC[Þ]	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						
dolutegravir	50 mg QD	200 mg QD	11	1.36 (1.15, 1.62)	1.43 (1.20, 1.71)	1.27 (1.06, 1.53)
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. [Þ] $AUC_{0-\infty}$ for single dose, AUC_{0-24} for once daily.
[2]The predominant circulating nucleoside metabolite of sofosbuvir.

9.5 Drug-Food Interactions
The single dose administration of the 100 mg PIFELTRO® tablet with a high-fat meal to healthy subjects resulted in a 16% and 36% increase in doravirine AUC and C_{24}, respectively, and C_{max} was not significantly affected (3% increase), in comparison to fasting.

PIFELTRO® can be taken with or without food.

9.6 Drug-Herb Interactions
Co-administration 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.

Co-administration of PIFELTRO® with St. John's wort is contraindicated.

9.7 Drug-Laboratory Test Interactions
Interactions with clinical laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action
PIFELTRO® contains the antiviral drug doravirine, which is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1 (see **15 MICROBIOLOGY**).

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
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 AUC0-24, Cmax, and C24. 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} (mcg•h/mL)	C_{max} mcg/mL	C_{24} mcg/mL
Doravirine 100 mg once daily	16.1 (29)	0.962 (19)	0.396 (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 (t1/2) 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.

Special Populations and Conditions

- **Pediatrics**

Mean doravirine exposures were similar in 54 pediatric patients aged 12 to less than 18 years and weighing at least 35 kg in IMPAACT 2014 (Protocol 027) relative to adults following administration of a single dose of 100 mg doravirine or once daily DELSTRIGO®.

Table 8: Steady State Pharmacokinetics for Doravirine Following Administration of a Single 100 mg Dose of Doravirine or Once Daily DELSTRIGO® in HIV-1-Infected Pediatric Patients Aged 12 to Less than 18 Years and Weighing at Least 35 kg

Parameter GM (%CV)*	AUC_{0-24} (mcg•h/mL)	C_{max} (mcg/mL)	C_{24} (mcg/mL)
Doravirine[†]	16.4 (24)	1.03 (16)	0.379 (42)
* Presented as geometric mean (GM) (%CV: geometric coefficient of variation) [†]From population PK analysis (n=53 weighing ≥ 45 kg, n=1 weighing ≥ 35 kg to <45 kg) Abbreviations: AUC=area under the time concentration curve; C_{max}=maximum concentration; C_{24}=concentration at 24 hours			

The pharmacokinetics and dosing recommendations of PIFELTRO® in patients younger than 12 years of age and weighing less than 35 kg have not been established.

- **Geriatrics**
  No clinically relevant differences in the pharmacokinetics of doravirine have been identified in subjects at least 65 years of age compared to subjects less than 65 years of age in a Phase 1 trial or in a population pharmacokinetic analysis.
- **Sex**
  No clinically relevant pharmacokinetic differences have been identified between men and women for doravirine.

- **Ethnic Origin**
  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.
- **Hepatic Insufficiency**
  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).
- **Renal Insufficiency**
  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

11 STORAGE, STABILITY AND DISPOSAL

Store PIFELTRO® in the original bottle. Keep the bottle tightly closed to protect from moisture. Do not remove the desiccant.
Store PIFELTRO® at room temperature (15°C to 30°C).

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

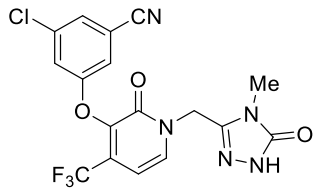
Drug Substance

Proper 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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Table 9 - Summary of Subject Demographics for Clinical Trials in HIV-I-Infected Patients

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
P018 (DRIVE-FORWARD)	Randomized, international, multicenter, double-blind, active-controlled trial which also had a placebo (4 pills for each arm) in treatment naïve patients	PIFELTRO® 100 mg or DRV+r 800mg/100mg each in combination with FTC/TDF or ABC/3TC Oral, once daily 48 Weeks and 96 Weeks	766	35.2 years (18 to 69 years)	Male: 645 Female: 121

P021 (DRIVE-AHEAD)	Randomized, international, multicenter, double-blind, active-controlled trial in treatment naïve patients	DELSTRIGO® (doravirine/lamivudine/ tenofovir DF) or EFV/FTC/TDF Oral, once daily 48 Weeks and 96 Weeks	728	33.1 years (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

Adult Subjects with No Antiretroviral Treatment History

The efficacy of PIFELTRO® (doravirine) is based on the analyses of 48-Week data from two randomized, multicenter, double-blind, active-controlled Phase 3 trials (DRIVE-FORWARD and DRIVE-AHEAD), in antiretroviral treatment-naïve, HIV-1 infected subjects (n=1494).

In DRIVE-FORWARD, 766 subjects were randomized and received at least 1 dose of either PIFELTRO® once daily or DRV+r 800/100 mg once daily each in combination with emtricitabine/tenofovir DF (FTC/TDF) or abacavir/lamivudine (ABC/3TC) selected by the investigator. At baseline, the demographic characteristics were similar between treatment groups.

In DRIVE-AHEAD, 728 subjects were randomized and received at least 1 dose of either DELSTRIGO® or EFV/FTC/TDF once daily. At baseline, the demographic characteristics were similar between treatment groups.

The demographic and baseline characteristics of patients in DRIVE-FORWARD and DRIVE-AHEAD and are summarized in Table 10.

Table 10– Demographic and Baseline Characteristics in DRIVE-FORWARD and DRIVE-AHEAD at Week 48 in HIV-1 Adult Subjects with No Antiretroviral Treatment History

	DRIVE-FORWARD P018		DRIVE-AHEAD P021	
	PIFELTRO® + 2 NRTIs Once Daily (N = 383)	**Comparator Once Daily (N = 383)**	**DELSTRIGO® Once Daily (N = 364)**	**Comparator Once Daily (N = 364)**
Gender n (%)				
Male	319 (83.3)	326 (85.1)	305 (83.8)	311 (85.4)
Female	64 (16.7)	57 (14.9)	59 (16.2)	53 (14.6)
Race n (%)				
American Indian or Alaska Native	3 (0.8)	3 (0.8)	10 (2.7)	6 (1.6)
Asian	7 (1.8)	7 (1.8)	59 (16.2)	65 (17.9)
Black or African American	86 (22.5)	88 (23.0)	67 (18.4)	68 (18.7)
Multiple	6 (1.6)	2 (0.5)	51 (14.0)	55 (15.1)
Native Hawaiian or Other Pacific Islander	1 (0.3)	2 (0.5)	-	-
White	280 (73.1)	280 (73.1)	177 (48.6)	170 (46.7)
Missing	0 (0.0)	1 (0.3)	-	-
Ethnicity n (%)				
Hispanic or Latino	93 (24.3)	86 (22.5)	126 (34.6)	120 (33.0)
Not Hispanic or Latino	284 (74.2)	290 (75.7)	236 (64.8)	238 (65.4)
Unknown	6 (1.6)	7 (1.8)	2 (0.5)	6 (1.6)
Region n (%)				
Africa	23 (6.0)	22 (5.7)	37 (10.2)	27 (7.4)
Asia / Pacific	12 (3.1)	3 (0.8)	59 (16.2)	62 (17.0)
Europe	170 (44.4)	179 (46.7)	88 (24.2)	94 (25.8)
Latin America	38 (9.9)	33 (8.6)	89 (24.5)	87 (23.9)
North America	140 (36.6)	146 (38.1)	91 (25.0)	94 (25.8)
Age (years)				
18 to 64	381 (99.5)	379 (99.0)	362 (99.5)	362 (99.5)
≥ 65	2 (0.5)	4 (1.0)	2 (0.5)	2 (0.5)
Mean (SD)	34.8 (10.5)	35.7 (10.7)	33.6 (10.5)	32.7 (9.9)
Median (min, max)	33.0 (18, 68)	34.0 (18, 69)	32.0 (18, 70)	30.0 (18, 69)
Baseline CD4+ T-Cell Count (cells/mm^3)				
N$^+$	383	383	364	364
Mean (SD)	432.6 (208.4)	411.9 (229.6)	434.9 (217.9)	415.5 (210.6)
Median (min, max)	410.0 (19, 1822)	393.0 (19, 1303)	413.5 (19, 1399)	388.0 (19, 1452)
Baseline CD4+ T-Cell Count n (%)				

	DRIVE-FORWARD P018		DRIVE-AHEAD P021	
	PIFELTRO® + 2 NRTIs Once Daily (N = 383)	**Comparator Once Daily (N = 383)**	**DELSTRIGO® Once Daily (N = 364)**	**Comparator Once Daily (N = 364)**
≤ 50 cells/mm ^{3}	6 (1.6)	19 (5.0)	9 (2.5)	10 (2.7)
> 50 cells/mm ^{3} and ≤ 200 cells/mm^3	36 (9.4)	48 (12.5)	35 (9.6)	35 (9.9)
> 200 cells/mm ^{3}	41 (89.0)	316 (82.5)	320 (87.9)	318 (87.4)
Baseline Plasma HIV-1 RNA (log_{10} copies/mL)				
N†	383	382	364	364
Mean (SD)	4.4 (0.7)	4.4 (0.7)	4.4 (0.7)	4.4 (0.7)
Median (min, max)	4.4 (2.0, 6.4)	4.4 (2.4, 6.5)	4.4 (2.4, 6.1)	4.5 (2.6, 6.4)
Baseline Plasma HIV-1 RNA (copies/mL)				
N†	383	382	364	364
Geometric Mean	26917.6	26630.5	23760.4	29087.1
Median (min, max)	27073.0 (105, 2776658)	27357.0 (235, 3272236)	22438.5 (259, 1268560)	25467.5 (403, 2692740)
Baseline Plasma HIV-1 RNA n (%)				
≤ 100,000 copies/mL	300 (78.3)	308 (80.4)	291(79.9)	282 (77.5)
> 100,000 copies/mL	83 (21.7)	74 (19.3)	73 (20.1)	82 (22.5)
Missing	0 (0.0)	1 (0.3)	-	-
History of AIDS n (%)				
Yes	36 (9.4)	37 (9.7)	46 (12.6)	53 (14.6)
No	347 (90.6)	346 (90.3)	318 (87.4)	311 (85.4)
Stratum n (%)				
Screening HIV RNA ≤ 100,000	290 (75.7)	289 (75.5)	275 (75.5)	274 (75.3)
Screening HIV RNA > 100,000	93 (24.3)	94 (24.5)	89 (24.5)	90 (24.7)
Truvada*	333 (86.9)	335 (87.5)	-	-
Kivexa*	50 (13.1)	48 (12.5)	-	-
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 (2.9)	18 (4.7)	11 (3.0)	9 (2.5)
Hepatitis B Positive Only	4 (1.0)	12 (3.1)	9 (2.5)	8 (2.2)
Hepatitis C Positive Only	7 (1.8)	6 (1.6)	2 (0.5)	1 (0.3)

	DRIVE-FORWARD P018		DRIVE-AHEAD P021	
	PIFELTRO® + 2 NRTIs Once Daily (N = 383)	**Comparator Once Daily (N = 383)**	**DELSTRIGO® Once Daily (N = 364)**	**Comparator Once Daily (N = 364)**
Viral Subtype n (%)				
Subtype B	266 (69.5)	272 (71.0)	232 (63.7)	253 (69.5)
Non-Subtype B	117 (30.5)	111 (29.0)	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.

P018
Note: Doravirine 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with Truvada* or Kivexa*.

P021
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.

Week 48 outcomes for DRIVE-FORWARD and DRIVE-AHEAD are provided in Table 11. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

In DRIVE-FORWARD, PIFELTRO® demonstrated consistent efficacy at 48-Weeks across demographic and baseline prognostic factors, including gender, race, ethnicity, NRTI background therapy, baseline HIV-1 RNA (≤100,000 or >100,000 copies/mL), CD4+ T-cell count, and viral subtypes. Mean CD4+ T-cell counts in the PIFELTRO® and DRV+r groups increased from baseline by 193 and 186 cells/mm^3, respectively. At Week 96, efficacy in the DOR treatment group was higher than in the DRV+r treatment group, using the FDA snapshot approach: 73.1% [277/379] and 66.0% [248/376] of participants in the DOR and DRV+r treatment groups, respectively, achieved HIV-1 RNA <50 copies/mL, with an estimated treatment difference of 7.1% (95% CI: 0.5, 13.7). These results support the non-inferiority of PIFELTRO® to DRV+r previously established at Week 48.

In DRIVE-AHEAD, DELSTRIGO® demonstrated consistent efficacy at 48-Weeks 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. 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% [282/364] and 73.6% [268/364] 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).

Table 11 – Virologic Outcomes at Week 48 in HIV-1 Adult Subjects with No Antiretroviral Treatment History

Outcome	DRIVE-FORWARD		DRIVE-AHEAD	
	PIFELTRO® + 2 NRTIs Once Daily	Comparator Once Daily	DELSTRIGO® Once Daily	Comparator Once Daily
	N=383	N=383	N=364	N=364
	n (%)	n (%)	n (%)	n (%)
HIV-1 RNA <50 copies/mL	321 (84%)	306 (80%)	307 (84%)	294 (81%)
Treatment Differences (95% CI)[Þ]	3.9% (-1.6%, 9.4%)		3.5% (-2.0%, 9.0%)	
HIV-1 RNA ≥ 50 copies/mL[†]	43 (11%)	50 (13%)	39 (11%)	37 (10%)
No Virologic Data at Week 48 Window	19 (5%)	27 (7%)	18 (5%)	33 (9%)
Reasons				
Discontinued study due to AE or Death[‡]	5 (1%)	11 (3%)	9 (2%)	24 (7%)
Discontinued study for Other Reasons[§]	11 (3%)	15 (4%)	9 (2%)	8 (2%)
On study but missing data in window	3 (<1%)	1 (<1%)	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 (%)**	**n / N (%)**	**n / N (%)**
Gender				
Male	269/319 (84%)	268/326 (82%)	257/305 (84%)	250/311 (80%)
Female	52/64 (81%)	38/57 (67%)	50/59 (85%)	44/53 (83%)
Race				
White	244/280 (87%)	232/280 (83%)	149/177 (84%)	138/170 (81%)
Non-White	77/103 (75%)	74/103 (73%)	158/187 (84%)	156/194 (80%)
Ethnicity				
Hispanic or Latino	82/93 (88%)	70/86 (81%)	105/126 (83%)	101/120 (84%)
Not Hispanic or Latino	233/284 (82%)	230/290 (79%)	200/236 (85%)	189/238 (79%)
NRTI Background Therapy				
FTC/TDF	278/333 (83%)	270/335 (81%)	-	-
ABC/3TC	43/50 (86%)	36/48 (75%)	-	-
Baseline HIV-1 RNA (copies/mL)				
≤ 100,000 copies/mL	257/300 (86%)	250/308 (81%)	251/291 (86%)	235/282 (83%)
> 100,000 copies/mL	64/83 (77%)	55/74 (74%)	56/73 (77%)	59/82 (72%)
CD4+ T-cell Count (cells/mm^3)				
≤ 200 cells/mm^3	34/42 (81%)	44/67 (66%)	29/44 (66%)	36/46 (78%)
>200 cells/mm^3	287/341 (84%)	262/316 (83%)	278/320 (87%)	258/318 (81%)
Viral Subtype[¶]				
Subtype B	224/266 (84%)	222/272 (82%)	195/232 (84%)	202/253 (80%)
Subtype Non-B	97/117 (83%)	84/111 (76%)	110/130 (85%)	92/111 (83%)

[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).
[¶] Viral subtype was not available for two subjects.
[‡] 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.
Note: NRTIs = FTC/TDF or ABC/3TC.

Virologically-Suppressed Adult Subjects

The demographic and baseline characteristics of patients in DRIVE-SHIFT are summarized in Table 12.

Table 12 – 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)

	DELSTRIGO® ISG Once Daily (N = 447)	Baseline Regimen DSG (N = 223)
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)
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,

	DELSTRIGO® ISG Once Daily (N = 447)	Baseline Regimen DSG (N = 223)
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.		

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 13.

Table 13 - 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.

Pediatric Subjects

Table 14 - Summary of Subject Demographics for Clinical Trials in HIV-I-Infected Pediatric Patients 12 Years of Age and Older and Weighing at Least 35 kg

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
P027 (IMPAACT 2014)	Phase 1/2 multicenter, open label 2 cohort study of the PK, safety, and tolerability of DOR and DOR/3TC/TDF in HIV-1 infected children and adolescents (age 12 to <18 years, who weigh at least 35 kg) Cohort 1: Single dose of DOR (100 mg) added to	Cohort 1: PIFELTRO® 100 mg Oral, single dose Cohort 2: DELSTRIGO® (DOR 100 mg/3TC 300mg / TDF 300 mg) Oral, once daily for 24 weeks (study is ongoing).	Cohort 1 : 9 Cohort 2: 45 (virologically suppressed (N=43) and antiretroviral treatment-naïve (N=2))	Cohort 1: 14.3 years (12 to 16 years) Cohort 2: 15.0 years (12 to 17 years)	Cohort 1: Male: 7 Female: 2 Cohort 2: Male: 19 Female: 26

	current regimen of dolutegravir or raltegravirand 2 NRTIs in virologically suppressed participants. Intensive PK evaluation completed on Day 1 to confirm the dose for Cohort 2 and safety follow-up through 2 weeks post-dose. Cohort 2: DOR/3TC/TDF once daily in virologically suppressed and antiretroviral treatment-naïve participants. PK using intensive (tenofovir [TFV] and 3TC) and semi-intensive (DOR) PK sampling at Week 1. Safety and tolerability assessed through 24 weeks.				

The efficacy of DELSTRIGO® (DOR/3TC/TDF) was evaluated in cohort 2 of an open-label, single-arm 2-cohort trial in HIV-1-infected pediatric patients 12 to less than 18 years of age (IMPAACT 2014 (Protocol 027)). In cohort 1, virologically-suppressed subjects (n=9) received a single 100 mg dose of PIFELTRO® followed by intensive PK sampling. In cohort 2, virologically-suppressed subjects (n=43) were switched to DELSTRIGO® and treatment-naïve subjects (n=2) were started on DELSTRIGO®.

In cohort 2, at baseline the median age of subjects was 15 years (range: 12 to 17), the median weight was 52 kg (range: 45 to 80), 58% were female, 78% were Asian and 22% were Black, and the median CD4+ T-cell count was 713 cells per mm^3 (range 84 to 1397). After switching to DELSTRIGO®, 95% (41/43) of virologically-suppressed subjects remained suppressed (HIV-1 RNA <50 copies/mL) at Week 24. One of the two treatment-naïve subjects achieved HIV-1 RNA <50 copies/mL at Week 24. The other treatment-naïve subject met the protocol-defined virologic failure criteria (defined as 2 consecutive plasma HIV-1 RNA test results $\geq$ 200 copies/mL at or after Week 24) and was evaluated for the development of resistance; no emergence of genotypic or phenotypic resistance to doravirine, lamivudine, or tenofovir was detected (see 15 MICROBIOLOGY).

Table 15 - Virologic Outcomes in IMPAACT 2014 at Week 24 in HIV-1 Pediatric Subjects (Cohort 2)

Outcome	Treatment Naïve N=2 n (%)	Virologically-Suppressed N=43 n (%)
HIV-1 RNA <50 copies/mL	1 (50.0)	41 (95.3)
HIV-1 RNA ≥50 copies/mL[a]	1 (50.0)	0 (0)
No Virologic Data	0 (0)	2 (4.7)
Discontinued study due to AE or Death	0 (0)	0 (0)
Discontinued for other reasons while below threshold	0 (0)	1 (2.3)
Missing data during window but on study	0 (0)	1 (2.3)
Proportion (%) of Subjects With HIV-1 RNA <50 copies/mL by Baseline and Demographic Category		
	n/N (%)	n/N (%)
Gender		
Male	1/1 (100%)	18/18 (100%)
Female	0/1 (0)	23/25 (92%)
Race		
Black or African American	0/0 (NA)	8/10 (80%)
Asian	1/2 (50%)	33/33 (100%)
Region		
South African	0/0 (NA)	7/9 (78%)
Thailand	1/2 (50%)	33/33 (100%)
United States of America	0/0 (NA)	1/1 (100%)
Ethnicity		
Hispanic or Latino	0/0 (NA)	1/1 (100%)
Not Hispanic	1/2 (50%)	40/42 (95%)
CD4+ T-cell Count (cells/mm^3)		
≤ 200 cells/mm^3	1/2 (50%)	0/0 (NA)
>200 cells/mm^3	0/0 (NA)	41/43 (95%)

[a] Includes subjects who discontinued study drug or study before Week 24 for lack or loss of efficacy and subjects with HIV-1 RNA equal to or above 50 copies/mL in the Week 24 window (relative day 141-210).

NA = Not Applicable

15 MICROBIOLOGY

Mechanism of Action

Doravirine is a pyridinone NNRTI of HIV-1 and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT). The inhibitory concentration at 50% (IC_{50}) of doravirine for RNA-dependent DNA polymerization of recombinant wild-type HIV-1 RT in a biochemical assay was 12.2±2.0 nM (n=3). Doravirine does not inhibit the human cellular DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity in Cell Culture

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.

Antiviral Activity in Combination with other HIV Antiviral Agents

The antiviral activity of doravirine was not antagonistic when combined with the NNRTIs delavirdine, efavirenz, etravirine, nevirapine, or rilpivirine; the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir DF, or zidovudine; the PIs darunavir or indinavir[1]; the fusion inhibitor enfuvirtide; the CCR5 co-receptor antagonist maraviroc; or the integrase strand transfer inhibitor raltegravir.

Resistance

In Cell Culture

Doravirine-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes, as well as NNRTI-resistant HIV-1. Observed emergent amino acid substitutions in RT included: V106A, V106I, V106M, V108I, H221Y, F227C, F227I, F227L, F227V, M230I, L234I, P236L, and Y318F. The V106A, V106M, V108I, H221Y, F227C, M230I, P236L, and Y318F substitutions conferred 3.4-fold to 70-fold reductions in susceptibility to doravirine. Y318F in combination with V106A, V106M, V108I, and F227C conferred greater decreases in susceptibility to doravirine than Y318F alone, which conferred a 10-fold reduction in susceptibility to doravirine.

[1] Not marketed in Canada

In Clinical Trials

In Adult Subjects with No Antiretroviral Treatment History

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

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

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

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.

In Pediatric Subjects

In the IMPAACT 2014 (Protocol 027) clinical trial, no subject who was virologically-suppressed at baseline met the criteria for resistance analysis. One treatment-naïve subject who met the protocol-defined virologic failure criteria (defined as 2 consecutive plasma HIV-1 RNA test results ≥200 copies/mL at or after Week 24) was evaluated for the development of resistance; no emergence of genotypic or phenotypic resistance to doravirine was detected (see **Pediatric Subjects**).

Cross-Resistance

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

A panel of 96 diverse clinical isolates containing NNRTI-associated 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 8 virologic failure subjects who developed doravirine phenotypic resistance, all had phenotypic resistance to nevirapine, 6 had phenotypic resistance to efavirenz, 4 had phenotypic resistance to rilpivirine, and 4 had partial resistance to etravirine based on the Monogram Phenosense assay.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity: 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.

Genotoxicity: 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.

Reproductive and Developmental Toxicology:

Reproduction

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PIFELTRO®

doravirine tablets

Read this carefully before you start taking **PIFELTRO® (doravirine)** 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 **PIFELTRO®**.

What is PIFELTRO® used for?

- PIFELTRO® is used to treat Human Immunodeficiency Virus-1 (HIV-1) infection in adults and children 12 years of age or older who weigh at least 35 kilograms (77 pounds). HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).
- PIFELTRO® is used along with other medicines to treat HIV infection.
- PIFELTRO® is for people who do not have HIV virus that is resistant to doravirine.

How does PIFELTRO® work?

- PIFELTRO® is a type of medicine called an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI).
- PIFELTRO® blocks an enzyme that HIV needs in order to make more virus.
- PIFELTRO® 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.
- PIFELTRO® does not cure HIV or AIDS. It is important to keep taking PIFELTRO® to control your HIV infection.

What are the ingredients in PIFELTRO®?

Medicinal ingredient: doravirine.
Non-medicinal ingredients: Carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose.

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

PIFELTRO® comes in the following dosage forms:

As 100 mg tablets.

Do not use PIFELTRO® if you:

- are allergic to doravirine.
- are allergic to any of the other ingredients in PIFELTRO® 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

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

- are pregnant or planning to become pregnant
- are breastfeeding or planning to breastfeed
- develop a rash while taking PIFELTRO®

Other warnings you should know about:

Pregnancy:

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

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 PIFELTRO®, talk to your doctor about taking part in this registry.

Breastfeeding:

You should not breastfeed if you are taking PIFELTRO®. 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.

Driving and using machines:

PIFELTRO® 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.

The following may interact with PIFELTRO®:

- The medicine rifabutin used to treat some bacterial infections such as tuberculosis. If you also take the medicine rifabutin, take PIFELTRO® twice a day, about 12 hours apart, 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.

How to take PIFELTRO®:

- Take PIFELTRO® exactly as your doctor tells you.
- Your treatment with PIFELTRO® 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 PIFELTRO®.

Usual dose:

- Take 1 tablet once a day by mouth at about the same time every day with or without food.

Overdose:

If you think you, or a person you are caring for, have taken too much PIFELTRO®, contact a 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 PIFELTRO®.
- 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 PIFELTRO® at the same time.
- If you are not sure what to do, call your doctor or pharmacist.

What are possible side effects from using PIFELTRO®?

These are not all the possible side effects you may have when taking PIFELTRO®. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects include:

- abnormal dreams, difficulty in sleeping (insomnia), nightmares, sleep problems
- headache
- dizziness, sleepiness
- feeling sick (nausea), diarrhea, stomach pain, vomiting
- feeling tired

Other side effects include:

- feeling weak
- depression

Serious side effects may include:

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**	
VERY RARE			
Allergic reactions: Severe allergic reactions causing a swollen face, lips, mouth, tongue or throat, which may lead to difficulty swallowing or breathing			✓
UNKNOWN			

Severe skin reactions (including toxic epidermal necrolysis [TEN]):
• rash
• painful rash with any of the following symptoms:
  ○ fever
  ○ blisters or sores in the mouth
  ○ blisters or peeling of the skin
  ○ redness or swelling of the eyes (conjunctivitis)
		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) 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 PIFELTRO® in the original bottle. Keep the bottle tightly closed to protect from moisture. Do not remove the desiccant.

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

Keep out of reach and sight of children.

If you want more information about PIFELTRO®:
- 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: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.merck.ca, or by calling 1-800-567-2594.

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