

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

 **PIFELTRO™**

doravirine tablets

Tablets, 100 mg, oral

Antiviral Agent

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RECENT MAJOR LABEL CHANGES

Not applicable

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PIFELTRO™ (doravirine) is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV-1 without past or present evidence of viral resistance to doravirine.

1.1 Pediatrics (< 18 years of age)

Safety and efficacy of PIFELTRO™ 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 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 **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

PIFELTRO™ 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 PIFELTRO™ (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, rifapentine¹
- the cytotoxic agent mitotane
- St. John's wort (*Hypericum perforatum*).

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

PIFELTRO™ is a tablet containing 100 mg of doravirine.

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

3.2 Recommended Dose and Dosage Adjustment

Recommended Dosage

Adults

The recommended dosage regimen of PIFELTRO™ is one 100 mg tablet taken orally once daily with or without food.

Pediatrics (< 18 years of age)

Safety and efficacy of PIFELTRO™ 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 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](#)). 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 [WARNINGS AND PRECAUTIONS, Special Populations, Renal Impairment and ACTION AND CLINICAL PHARMACOLOGY, 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 [WARNINGS AND PRECAUTIONS, Special Populations, Hepatic Impairment and ACTION AND CLINICAL PHARMACOLOGY, 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 [DRUG INTERACTIONS, Drug-Drug Interactions](#)).

3.3 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.

4 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.

5 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.

6 WARNINGS AND PRECAUTIONS

Driving and Operating Machinery

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

Caution should be given to prescribing PIFELTRO™ with drugs that may reduce the exposure of doravirine (see [CONTRAINDICATIONS, DRUG INTERACTIONS, 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 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, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

Sexual Health

Reproduction

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:

<http://www.apregistry.com/>

Telephone: 1-800-258-4263

Fax: 1-800-800-1052

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-FORWARD and DRIVE-AHEAD, respectively. Discontinue PIFELTRO™ immediately if signs or symptoms of severe skin or hypersensitivity reactions develop.

6.1 Special Populations

6.1.1 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.

6.1.2 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™.

6.1.3 Pediatrics (< 18 years of age)

Safety and efficacy of PIFELTRO™ have not been established in patients younger than 18 years of age (see [ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics](#)).

6.1.4 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 [ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics](#)). No dose adjustment of

PIFELTRO™ is needed in elderly patients.

6.1.5 Renal impairment

PIFELTRO™ has not been adequately studied in patients with end-stage renal disease and has not been studied in dialysis patients (see [ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics](#)) to recommend dosage adjustment in these patients. No dose adjustment of PIFELTRO™ is required in patients with mild, moderate or severe renal impairment.

6.1.6 Hepatic impairment

PIFELTRO™ has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see [ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics](#)). No dose adjustment of PIFELTRO™ is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

7 ADVERSE REACTIONS

7.1 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 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%.

7.2 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.

Treatment-Emergent Adverse Drug Reactions

In DRIVE-FORWARD, 766 adult subjects received either PIFELTRO™ 100 mg (n=383) or darunavir 800 mg + ritonavir 100 mg (DVR+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 PIFELTRO™/lamivudine/tenofovir DF (DOR/3TC/TDF) (n=364) or efavirenz/emtricitabine/tenofovir DF (EFV/FTC/TDF) once daily (n=364). By Week 48, 3.0% in the PIFELTRO™/3TC/TDF 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^p (All Grades) Reported in $\geq 2\%$ [†] 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	PIFELTRO™/ 3TC/TDF 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%
<p>^p Frequencies of adverse reactions are based on all adverse events attributed to trial drugs by the investigator.</p> <p>[†] No adverse reactions of Grade 2 or higher (moderate or severe) occurred in $\geq 2\%$ of subjects treated with doravirine.</p> <p>NRTIs = nucleoside reverse transcriptase inhibitors NRTIs = FTC/TDF or ABC/3TC.</p>				

7.3 Less Common Clinical Trial Adverse Reactions

Other adverse reactions reported in <2% of patients in the DRIVE-FORWARD and DRIVE-AHEAD trials are listed below.

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

Cardiac Disorders: palpitations.

Ear and Labyrinth Disorders: motion sickness.

Gastrointestinal Disorders: abdominal discomfort, abdominal distension, abdominal pain, abnormal feces, constipation, dyspepsia, dysphagia, epigastric discomfort, feces soft,

flatulence, frequent bowel movements, gastrointestinal motility disorder, gastroesophageal reflux disease, rectal tenesmus.

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

Infections and Infestations: conjunctivitis, folliculitis, gastroenteritis, nasopharyngitis, rash pustular.

Investigations: alanine aminotransferase increased, amylase increased, aspartate aminotransferase increased, blood creatinine phosphokinase increased, hemoglobin decreased, lipase increased, weight decreased, weight increased.

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

Musculoskeletal and Connective Tissue Disorders: arthralgia, myalgia.

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

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

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

Respiratory, Thoracic and Mediastinal Disorders: cough, dyspnea, tonsillar hypertrophy.

Skin and Subcutaneous Tissue Disorders: acne, alopecia, dermatitis allergic, pruritus, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rosacea, seborrheic dermatitis, skin lesion, urticaria.

Vascular Disorders: hypertension

7.4 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 PIFELTRO™/3TC/TDF 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)

Laboratory Parameter Preferred Term (Unit)	Limit	DRIVE-FORWARD		DRIVE-AHEAD	
		PIFELTRO™ +2 NRTIs Once Daily	DRV+r +2 NRTIs Once Daily	PIFELTRO™/3TC/TDF Once Daily	EFV/FTC/TDF Once Daily
		N=383	N=383	N=364	N=364
Blood Chemistry					
Total bilirubin					
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.

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.

Table 4 - Mean Change from Baseline in Fasting Lipids in DRIVE-FORWARD and DRIVE-AHEAD (Week 48)

Laboratory Parameter Preferred Term	DRIVE-FORWARD		DRIVE-AHEAD	
	PIFELTRO™ +2 NRTIs Once Daily	DRV+r +2 NRTIs Once Daily	PIFELTRO™/3TC/TDF Once Daily	EFV/FTC/TDF Once Daily
	N=320	N=311	N=320	N=307
LDL-Cholesterol (mmol/L) ^P	-0.12	0.25	-0.05	0.21
Non-HDL Cholesterol (mmol/L) ^P	-0.14	0.36	-0.11	0.33
Total Cholesterol (mmol/L)	-0.04	0.47	-0.06	0.55
Triglycerides (mmol/L)	-0.03	0.28	-0.14	0.24
HDL-Cholesterol (mmol/L)	0.10	0.11	0.05	0.22

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: PIFELTRO™/3TC/TDF n=15 and EFV/FTC/TDF n=10). Subjects initiating a lipid-lowering agent post-baseline had their last fasted on-treatment value (prior to starting the agent) carried forward (in DRIVE-FORWARD: PIFELTRO™ n=6 and DRV+r n=4; in DRIVE-AHEAD: PIFELTRO™/3TC/TDF n=3 and EFV/FTC/TDF n=8).
^P P-values for the pre-specified hypothesis testing for treatment difference were <0.0001 in both DRIVE-FORWARD and DRIVE-AHEAD.
 Note: NRTIs = FTC/TDF or ABC/3TC.

7.5 Clinical Trial Adverse Reactions (Pediatrics)

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

7.6 Post-Market Adverse Reactions

Not applicable.

8 DRUG INTERACTIONS

8.1 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 **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Drug-Drug Interactions** and **section below Drug Interactions Studies**). Co-administration of PIFELTRO™ and drugs that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine.

8.2 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 ^P 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) ritonavir-boosted elvitegravir	↑ doravirine ↔ boosted PIs ↔ elvitegravir	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). No dose adjustment is required when PIFELTRO™ is co-administered with ritonavir-boosted PIs or ritonavir-boosted elvitegravir.
cobicistat-boosted PIs (darunavir, atazanavir) cobicistat-boosted elvitegravir	↑ doravirine ↔ boosted PIs ↔ elvitegravir	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). 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 ↔ unboosted PIs	Concomitant use of PIFELTRO™ with unboosted PIs may cause an increase in the plasma concentrations of doravirine (inhibition of CYP3A enzymes). No dose adjustment is required when PIFELTRO™ is co-administered with unboosted PIs.
Antimycobacterials		
rifabutin ^P	↓ doravirine ↔ rifabutin	Concomitant use of PIFELTRO™ with rifabutin may cause a decrease in the plasma concentrations of doravirine (induction of CYP3A enzymes). If PIFELTRO™ is co-administered with rifabutin, one tablet of PIFELTRO™ should be taken twice daily (approximately 12 hours apart) (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment)
Azole Antifungal Agents		
fluconazole itraconazole ketoconazole ^P posaconazole voriconazole	↑ doravirine ↔ azole antifungal agents	Concomitant use of PIFELTRO™ with azole antifungal agents may cause an increase in the plasma concentrations of PIFELTRO™ (inhibition of CYP3A enzymes). No doravirine dose adjustment is required when PIFELTRO™ is co-administered with azole antifungal agents.
<p>↑ = increase, ↓ = decrease, ↔ = no change, PIs = Protease Inhibitors ^P 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.</p>		

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 (see **DRUG INTERACTIONS section below**).

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 ^p	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)

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 ^P	C _{max}	C ₂₄
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 + 300 mg tenofovir DF SD	100 mg SD	15	0.96 (0.87, 1.06)	0.97 (0.88, 1.07)	0.94 (0.83, 1.06)
Hepatitis C Antiviral Agents						
elbasvir + grazoprevir	50 mg elbasvir QD + 200 mg grazoprevir QD	100 mg QD	12	1.56 (1.45, 1.68)	1.41 (1.25, 1.58)	1.61 (1.45, 1.79)
ledipasvir + sofosbuvir	90 mg ledipasvir SD + 400 mg sofosbuvir SD	100 mg SD	14	1.15 (1.07, 1.24)	1.11 (0.97, 1.27)	1.24 (1.13, 1.36)
Acid-Reducing Agents						
antacid (aluminum and magnesium hydroxide oral suspension)	20 mL SD	100 mg SD	14	1.01 (0.92, 1.11)	0.86 (0.74, 1.01)	1.03 (0.94, 1.12)
pantoprazole	40 mg QD	100 mg SD	13	0.83 (0.76, 0.91)	0.88 (0.76, 1.01)	0.84 (0.77, 0.92)
Opioid Analgesics						
methadone	20-200 mg QD 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 ^P AUC _{0-∞} 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 ^p	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.
^p AUC_{0-∞} for single-dose, AUC₀₋₂₄ for once daily.
²The predominant circulating nucleoside metabolite of sofosbuvir.

8.3 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 C₂₄, respectively, and C_{max} was not significantly affected (3% increase), in comparison to fasting.

PIFELTRO™ can be taken with or without food.

8.4 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 PIFELTRO™ with St. John's wort is contraindicated.

8.5 Drug-Laboratory Test Interactions

Interactions with clinical laboratory tests have not been established.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

PIFELTRO™ contains the antiviral drug doravirine, which is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1 (see [MICROBIOLOGY, Mechanism of Action](#)).

9.2 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.

9.3 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, C_{max}, 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 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.

Special Populations and Conditions***Pediatrics:***

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

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 Impairment:

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**).

Renal Impairment:

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**).

10 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).

¹ Not marketed in Canada

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

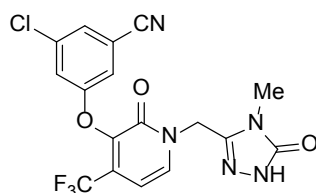
Drug Substance

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: C₁₇H₁₁ClF₃N₅O₃, 425.75

Structural formula:



Physicochemical properties: Doravirine is practically insoluble in water

12 CLINICAL TRIALS

12.1 Trial Design and Study Demographics

Table 8 - Summary of subject demographics for clinical trials in treatment-naïve HIV-infected subjects

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)	PIFELTRO™ 100 mg or DVR+r 800mg/100mg each in combination with FTC/TDF or ABC/3TC Oral, once daily 48 weeks	766	35.2 years (18 to 69 years)	Male: 645 Female: 121
P021 (DRIVE-AHEAD)	Randomized, international, multicenter, double-blind, active-controlled trial	PIFELTRO™/3TC/TDF or EFV/FTC/TDF Oral, once daily 48 weeks	728	33.1 years (18 to 70 years)	Male: 616 Female: 112

Treatment-Naïve Adult Subjects

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 PIFELTRO™/3TC/TDF or EFV/FTC/TDF once daily. At baseline, the demographic characteristics were similar between treatment groups.

Table 9 – Demographic and Baseline Characteristics

	DRIVE-FORWARD P018		DRIVE-AHEAD P021	
	PIFELTRO™ + 2 NRTIs Once Daily (N = 383)	Comparator Once Daily (N = 383)	PIFELTRO™/ 3TC/TDF 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 Cell Count (cells/mm³)				
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 Cell Count n (%)				
≤ 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 (log₁₀ 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)

	DRIVE-FORWARD P018		DRIVE-AHEAD P021	
	PIFELTRO™ + 2 NRTIs Once Daily (N = 383)	Comparator Once Daily (N = 383)	PIFELTRO™/ 3TC/TDF Once Daily (N = 364)	Comparator Once Daily (N = 364)
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)
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.				

12.2 Study Results

Week 48 outcomes for DRIVE-FORWARD and DRIVE-AHEAD are provided in Table 10. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

In DRIVE-FORWARD, PIFELTRO™ demonstrated consistent efficacy across demographic and baseline prognostic factors, including gender, race, ethnicity, NRTI background therapy, baseline HIV-1 RNA ($\leq 100,000$ 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/mm³, respectively.

In DRIVE-AHEAD, PIFELTRO™/3TC/TDF demonstrated consistent efficacy across demographic and baseline prognostic factors, including gender, race, ethnicity, baseline HIV-1 RNA ($\leq 100,000$ or $> 100,000$ copies/mL), CD4+ T-cell count, and viral subtypes. Mean CD4+ T-cell counts in the PIFELTRO™/3TC/TDF and EFV/FTC/TDF groups increased from baseline by 198 and 188 cells/mm³, respectively.

Table 10 - Virologic Outcome at Week 48 (FDA Snapshot Approach)

Outcome	DRIVE-FORWARD		DRIVE-AHEAD	
	PIFELTRO™ + 2 NRTIs Once Daily	Comparator Once Daily	PIFELTRO™/ 3TC/TDF 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) ^p	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/mm³)				
≤ 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%)
<p>^p The 95% CIs for the treatment differences were calculated using stratum-adjusted Mantel-Haenszel method.</p> <p>[†] 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).</p> <p>[‡] Includes subjects who discontinued because of adverse event (AE) or death if this resulted in no virologic data in the Week 48 window.</p> <p>[§] Other Reasons include: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, protocol deviation, screen failure, withdrawal by subject.</p> <p>Note: NRTIs = FTC/3TC or ABC/3TC.</p>				

13 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). Doravirine does not inhibit the human cellular DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity in Cell Culture

Doravirine exhibited an EC₅₀ 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 EC₅₀ values ranging from 0.6 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, zalcitabine¹ or zidovudine; the PIs darunavir or indinavir¹; 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, V106M, V106I, V108I, F227L, F227C, F227V, H221Y, M230I, L234I, P236L, and Y318F.

In Clinical Trials

In the doravirine treatment arms of the treatment-naïve trials DRIVE-FORWARD and DRIVE-AHEAD (n=747), emergent doravirine-associated resistance 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-associated resistance 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-associated resistance substitutions were observed in 12 out of 24 subjects in the resistance analysis subset.

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.

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 7 subjects who developed doravirine resistance, 6 had phenotypic resistance to EFV and nevirapine, 3 had phenotypic resistance to rilpivirine, and 2 had partial resistance to etravirine based on the Monogram Phenosense assay.

14 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.

Fertility

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.

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

** 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. 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™?

Each tablet has the following medicine: doravirine

Each tablet has the following ingredients that are not medicines: 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 form:

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.

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

There is very little information on the use of doravirine 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 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.

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.

HIV Transmission:

PIFELTRO™ 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:

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 are removed from the body by a system called CYP3A. If you are not sure whether a medicine you take uses 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 adult 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 have taken too much PIFELTRO™, 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 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 feel when taking PIFELTRO™. If you experience any side effects not listed here, contact 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

Immune Reconstitution Inflammatory Syndrome:

Changes in your immune system can happen when you start taking any HIV medicine. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling or fatigue, or any new symptoms, contact your doctor right away.

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	
<p><u>VERY RARE</u> Allergic reactions:</p> <ul style="list-style-type: none"> Severe allergic reactions causing a swollen face, lips, mouth, tongue or throat, which may lead to difficulty swallowing or breathing 			✓
<p><u>VERY RARE</u> Severe skin rash:</p> <ul style="list-style-type: none"> Mouth sores or blisters on your body 			✓

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.

<p>Reporting Side Effects</p> <p>You can report any suspected side effects associated with the use of health products to Health Canada by:</p> <ul style="list-style-type: none"> Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mpps/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. <p><i>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.</i></p>
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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 (<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 PIFELTRO™, please contact 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

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