HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PIFELTRO™ (doravirine) tablets, for oral use
Initial U.S. Approval: 2018

RECENT MAJOR CHANGES

Indications and Usage (1)	09/2019
Warnings and Precautions, Immune Reconstitution Syndrome (5.2)	09/2019

INDICATIONS AND USAGE

PIFELTRO, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients:

- with no prior antiretroviral treatment history, **OR**
- to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to doravirine. (1)

DOSAGE AND ADMINISTRATION

- Recommended dosage: One tablet taken orally once daily with or without food in adult patients. (2.1)
- Dosage adjustment with rifabutin: One tablet taken twice daily (approximately 12 hours apart). (2.2)

DOSAGE FORMS AND STRENGTHS

- Tablets: 100 mg doravirine. (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Monitor for Immune Reconstitution Syndrome. (5.2)

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

Consult the full prescribing information prior to and during treatment for important potential drug-drug interactions. (4, 5.1, 7)

USE IN SPECIFIC POPULATIONS

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

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

Revised: 09/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PIFELTRO™ is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients:

- with no prior antiretroviral treatment history; **OR**
- to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to doravirine *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage regimen of PIFELTRO in adults is one 100 mg tablet taken orally once daily with or without food *[see Clinical Pharmacology (12.3)]*.

2.2 Dosage Adjustment with Rifabutin

If PIFELTRO is co-administered with rifabutin, increase PIFELTRO dosage to one tablet twice daily (approximately 12 hours apart) for the duration of rifabutin co-administration *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].*

3 DOSAGE FORMS AND STRENGTHS

PIFELTRO film-coated tablets are white, oval-shaped tablets, debossed with the corporate logo and 700 on one side and plain on the other side. Each tablet contains 100 mg doravirine.

4 CONTRAINDICATIONS

PIFELTRO is contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of PIFELTRO *[see Warnings and Precautions (5.1), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*. These drugs include, but are not limited to, the following:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the androgen receptor inhibitor enzalutamide
- the antimycobacterials rifampin, rifapentine
- the cytotoxic agent mitotane
- St. John's wort (*Hypericum perforatum)*

5 WARNINGS AND PRECAUTIONS

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

The concomitant use of PIFELTRO and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of PIFELTRO and possible development of resistance *[see Dosage and Administration (2.2), Contraindications (4) and Drug Interactions (7.1)].*

See Table 6 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during PIFELTRO therapy, review concomitant medications during PIFELTRO therapy, and monitor for adverse reactions.

5.2 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as

Mycobacterium avium infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

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

6 ADVERSE REACTIONS

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

- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Adults with No Antiretroviral Treatment History
The safety assessment of PIFELTRO used in combination with other antiretroviral agents is based on Week 48 data from two Phase 3, randomized, international, multicenter, double-blind, active-controlled trials (DRIVE-FORWARD (Protocol 018) and DRIVE-AHEAD (Protocol 021)).

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, each in combination with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or abacavir/lamivudine (ABC/3TC). By Week 48, 2% in the PIFELTRO group and 3% in the DRV+r group had adverse events leading to discontinuation of study medication.

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

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

Table 1: Adverse Reactions* (All Grades) Reported in ≥5%† 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 N=383	DRV+r +2 NRTIs‡ Once Daily N=383	DELSTRIGO Once Daily N=364	EFV/FTC/TDF Once Daily N=364
Nausea	7%	8%	5%	7%
Headache	6%	3%	4%	4%
Fatigue	6%	3%	4%	4%
Diarrhea	5%	13%	3%	5%
Abdominal Pain	5%	2%	1%	2%
Dizziness	3%	2%	7%	32%
Rash	2%	3%	2%	12%

Abnormal Dreams	1%	<1%	5%	9%
Insomnia	1%	2%	4%	5%
Somnolence	0%	<1%	3%	7%

*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.
‡NRTI = nucleoside reverse transcriptase inhibitor.
NRTIs = FTC/TDF or ABC/3TC.
Fatigue: includes fatigue, asthenia, malaise
Abdominal Pain: includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort
Rash: includes rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular

The majority (72%) of adverse reactions associated with doravirine occurred at severity Grade 1 (mild).

Neuropsychiatric Adverse Events

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

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

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

	DELSTRIGO Once Daily N=364	**EFV/FTC/TDF Once Daily N=364**	**Treatment Difference DELSTRIGO - EFV/FTC/TDF Estimate (95% CI)†**
Sleep disorders and disturbances‡	12%	26%	-13.5 (-19.1, -7.9)
Dizziness	9%	37%	-28.3 (-34.0, -22.5)
Altered sensorium§	4%	8%	-3.8 (-7.6, -0.3)

*All causality and all grade events were included in the analysis.
†The 95% CIs were calculated using Miettinen and Nurminen's method. Categories pre-specified for statistical testing were dizziness (p <0.001), sleep disorders and disturbances (p <0.001), and altered sensorium (p=0.033).
‡Predefined using MedDRA preferred terms, including: abnormal dreams, hyposomnia, initial insomnia, insomnia, nightmare, sleep disorder, somnambulism.
§Predefined using MedDRA preferred terms, including: altered state of consciousness, lethargy, somnolence, syncope.

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

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

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

Laboratory Abnormalities

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

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

	DRIVE-FORWARD		DRIVE-AHEAD	
Laboratory Parameter Preferred Term (Unit)/Limit	**PIFELTRO +2 NRTIs Once Daily N=383**	**DRV+r +2 NRTIs Once Daily N=383**	**DELSTRIGO Once Daily N=364**	**EFV/FTC/TDF Once Daily N=364**
Blood Chemistry				
Total bilirubin				
1.1 - < 1.6 x ULN	5%	1%	4%	0%
1.6 - <2.6 x ULN	2%	<1%	2%	0%
≥2.6 x ULN	0%	0%	<1%	<1%
Creatinine (mg/dL)				
>1.3 - 1.8 x ULN or Increase of >0.3 mg/dL above baseline	3%	4%	2%	1%
>1.8 x ULN or Increase of ≥1.5 x above baseline	2%	3%	2%	1%
Aspartate aminotransferase (IU/L)				
2.5 - <5.0 x ULN	4%	3%	2%	2%
≥5.0 x ULN	<1%	2%	<1%	2%
Alanine aminotransferase (IU/L)				
2.5 - <5.0 x ULN	3%	2%	3%	4%
≥5.0 x ULN	1%	2%	<1%	2%
Alkaline phosphatase (IU/L)				
2.5 - <5.0 x ULN	<1%	<1%	0%	<1%
≥5.0 x ULN	0%	0%	0%	<1%
Lipase				
1.5 - <3.0 x ULN	4%	5%	5%	4%
≥3.0 x ULN	3%	2%	1%	2%
Creatine kinase (IU/L)				
6.0 - <10.0 x ULN	2%	3%	2%	2%
≥10.0 x ULN	3%	4%	2%	3%
Cholesterol, fasted (mg/dL)				
≥300 mg/dL	0%	<1%	<1%	<1%
LDL cholesterol, fasted (mg/dL)				
≥190 mg/dL	<1%	3%	<1%	2%
Triglycerides, fasted (mg/dL)				
>500 mg/dL	<1%	1%	<1%	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.

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

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

DRIVE-FORWARD

	PIFELTRO +2 NRTIs Once Daily N=320		DRV+r +2 NRTIs Once Daily N=311		
Laboratory Parameter Preferred Term	**Baseline**	**Change**	**Baseline**	**Change**	**Difference Estimates (95% CI)**
LDL-Cholesterol (mg/dL)*	91.4	-4.6	92.3	9.5	-14.4 (-18.0, -10.8)
Non-HDL Cholesterol (mg/dL)*	113.6	-5.4	114.5	13.7	-19.4 (-23.4, -15.4)
Total Cholesterol (mg/dL)†	157.2	-1.4	157.8	18.0	-
Triglycerides (mg/dL)†	111.0	-3.1	113.7	24.5	-
HDL-Cholesterol (mg/dL)†	43.6	4.0	43.3	4.3	-
DRIVE-AHEAD					
	DELSTRIGO Once Daily N=320		**EFV/FTC/TDF Once Daily N=307**		
Laboratory Parameter Preferred Term	**Baseline**	**Change**	**Baseline**	**Change**	**Difference Estimates (95% CI)**
LDL-Cholesterol (mg/dL)*	91.7	-2.1	91.3	8.3	-10.2 (-13.8, -6.7)
Non-HDL Cholesterol (mg/dL)*	114.7	-4.1	115.3	12.7	-16.9 (-20.8, -13.0)
Total Cholesterol (mg/dL)†	156.8	-2.2	156.8	21.1	-
Triglycerides (mg/dL)†	118.7	-12.0	122.6	21.6	-
HDL-Cholesterol (mg/dL)†	42.1	1.8	41.6	8.4	-

Subjects on lipid-lowering agents at baseline were excluded from these analyses (in DRIVE-FORWARD: PIFELTRO n=12 and DRV+r n=14; in DRIVE-AHEAD: DELSTRIGO n=15 and EFV/FTC/TDF n=10). Subjects initiating a lipid-lowering agent post-baseline had their last fasted on-treatment value (prior to starting the agent) carried forward (in DRIVE-FORWARD: PIFELTRO n=6 and DRV+r n=4; in DRIVE-AHEAD: DELSTRIGO n=3 and EFV/FTC/TDF n=8).
*p-values for the pre-specified hypothesis testing for treatment difference were <0.0001 in both DRIVE-FORWARD and DRIVE-AHEAD.
†Not pre-specified for hypothesis testing.

Adverse Reactions in Virologically-Suppressed Adults

The safety of DELSTRIGO in virologically-suppressed adults was based on Week 48 data from 670 subjects in the DRIVE-SHIFT trial (Protocol 024), a randomized, international, multicenter, open-label trial in which virologically-suppressed subjects were switched from a baseline regimen consisting of two NRTIs in combination with a protease inhibitor (PI) plus either ritonavir or cobicistat, or elvitegravir plus cobicistat, or a non-nucleoside reverse transcriptase inhibitor (NNRTI) to DELSTRIGO. Overall, the safety profile in virologically-suppressed adult subjects was similar to that in subjects with no antiretroviral treatment history.

Laboratory Abnormalities

Serum ALT and AST Elevations: In the DRIVE-SHIFT trial, 22% and 16% of subjects in the immediate switch group experienced ALT and AST elevations greater than 1.25 X ULN, respectively, through 48 weeks on DELSTRIGO. For these ALT and AST elevations, no apparent patterns with regard to time to onset relative to switch were observed. One percent of subjects had ALT or AST elevations greater than 5 X ULN through 48 weeks on DELSTRIGO. The ALT and AST elevations were generally asymptomatic and not associated with bilirubin elevations. In comparison, 4% and 4% of subjects in the delayed switch group experienced ALT and AST elevations of greater than 1.25 X ULN through 24 weeks on their baseline regimen.

Change in Lipids from Baseline

Changes from baseline at Week 24 in LDL-cholesterol, non-HDL-cholesterol, total cholesterol, triglycerides, and HDL-cholesterol in subjects on a PI plus ritonavir-based regimen at baseline are shown in Table 5. The LDL and non-HDL comparisons were pre-specified, and the differences were statistically significant, showing superiority for an immediate switch to DELSTRIGO for both parameters. The clinical benefit of these findings has not been demonstrated.

Table 5: Mean Change from Baseline in Fasting Lipids in Adult Virologically-Suppressed Subjects on a PI plus Ritonavir-based Regimen at Baseline in DRIVE-SHIFT (Week 24)

Laboratory Parameter Preferred Term	DELSTRIGO (Week 0-24) Once Daily N=244		PI+ritonavir (Week 0-24) Once Daily N=124		Difference Estimates
	Baseline	Change	Baseline	Change	Difference (95% CI)
LDL-Cholesterol (mg/dL)*	108.7	-16.3	110.5	-2.6	-14.5 (-18.9, -10.1)
Non-HDL Cholesterol (mg/dL)*	138.6	-24.8	138.8	-2.1	-22.8 (-27.9, -17.7)
Total Cholesterol (mg/dL)†	188.5	-26.1	187.4	-0.2	-
Triglycerides (mg/dL)†	153.1	-44.4	151.4	-0.4	-
HDL-Cholesterol (mg/dL)†	50.0	-1.3	48.5	1.9	-

Subjects on lipid-lowering agents at baseline were excluded from these analyses (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 (DELSTRIGO n=4 and PI+ritonavir n=2).
*P-value for the pre-specified hypothesis testing for treatment difference was <0.0001.
†Not pre-specified for hypothesis testing.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on PIFELTRO

Co-administration of PIFELTRO with a CYP3A inducer decreases doravirine plasma concentrations, which may reduce PIFELTRO efficacy *[see Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*. Co-administration of PIFELTRO and drugs that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine.

Table 6 shows significant drug interactions with PIFELTRO.

Table 6: Drug Interactions with PIFELTRO*

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Androgen Receptors		
enzalutamide	↓ doravirine	Co-administration is contraindicated with enzalutamide. At least a 4-week cessation period is recommended prior to initiation of PIFELTRO.
Anticonvulsants		
carbamazepine oxcarbazepine phenobarbital phenytoin	↓ doravirine	Co-administration is contraindicated with these anticonvulsants. At least a 4-week cessation period is recommended prior to initiation of PIFELTRO.
Antimycobacterials		
rifampin† rifapentine	↓ doravirine	Co-administration is contraindicated with rifampin or rifapentine. At least a 4-week cessation period is recommended prior to initiation of PIFELTRO.
rifabutin†	↓ doravirine	Increase PIFELTRO dosage to one tablet twice daily when co-administered with rifabutin *[see Dosage and Administration (2.2)]*.
Cytotoxic Agents		

mitotane	↓ doravirine	Co-administration is contraindicated with mitotane. At least a 4-week cessation period is recommended prior to initiation of PIFELTRO.
HIV Antiviral Agents		
efavirenz[†] etravirine nevirapine	↓ doravirine	Use with efavirenz, etravirine, or nevirapine is not recommended.
Herbal Products		
St. John's wort	↓ doravirine	Co-administration is contraindicated with St. John's wort. At least a 4-week cessation period is recommended prior to initiation of PIFELTRO.
↑ = increase, ↓ = decrease *This table is not all inclusive. [†]The interaction between PIFELTRO and the concomitant drug was evaluated in a clinical study. All other drug-drug interactions shown are anticipated based on the known metabolic and elimination pathways.		

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

7.2 Effect of PIFELTRO on Other Drugs

No clinically significant changes in concentration were observed for the following agents when co-administered with doravirine: dolutegravir, lamivudine, TDF, elbasvir and grazoprevir, ledipasvir and sofosbuvir, atorvastatin, an oral contraceptive containing ethinyl estradiol and levonorgestrel, metformin, methadone, and midazolam *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to PIFELTRO during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

No adequate human data are available to establish whether or not PIFELTRO poses a risk to pregnancy outcomes. In animal reproduction studies, no adverse developmental effects were observed when doravirine was administered at exposures ≥8 times the exposure in humans at the recommended human dose (RHD) of PIFELTRO (*see Data*).

The background rate of major birth defects is 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15-20%. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates individuals and infants from the limited geographic area, and does not include outcomes for births that occurred at less than 20 weeks gestation.

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

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

Data

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical trials of PIFELTRO did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of PIFELTRO in elderly patients, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

No dosage 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 Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage 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 Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

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

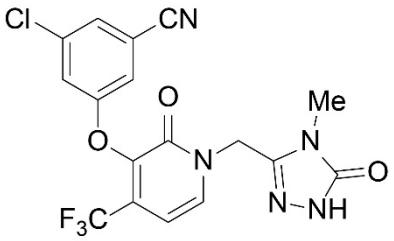
Doravirine is an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI).

Each tablet contains 100 mg of doravirine as the active ingredient. The tablets include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film coated with a coating material containing the following inactive ingredients: hypromellose, lactose monohydrate, titanium dioxide, and triacetin. The coated tablets are polished with carnauba wax.

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

It has a molecular formula of $C_{17}H_{11}ClF_3N_5O_3$ and a molecular weight of 425.75.

It has the following structural formula:



Doravirine is practically insoluble in water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Doravirine is an antiretroviral drug *[see Microbiology (12.4)].*

12.2 Pharmacodynamics

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

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

Doravirine pharmacokinetics are similar in healthy subjects and HIV-1-infected subjects. Doravirine pharmacokinetics are provided in Table 7.

Table 7: Pharmacokinetic Properties of Doravirine

Parameter	Doravirine
General	
Steady State Exposure[*,†]	
AUC_{0-24} (mcg•h/mL)	16.1 (29)
C_{max} (mcg/mL)	0.962 (19)
C_{24} (mcg/mL)	0.396 (63)
Time to Steady State (Days)	2

Accumulation Ratio	1.2 to 1.4
Absorption	
Absolute Bioavailability	64%
T_{max} (h)	2
Effect of Food[‡]	
AUC Ratio	1.16 (1.06, 1.26)
C_{max} Ratio	1.03 (0.89, 1.19)
C_{24} Ratio	1.36 (1.19, 1.55)
Distribution	
V_{dss} (L)[§]	60.5
Plasma Protein Binding	76%
Elimination	
$t_{1/2}$ (h)	15
CL/F (mL/min)[†]	106 (35.2)
CL_{renal} (mL/min)[†]	9.3 (18.6)
Metabolism	
Primary Pathway(s)	CYP3A
Excretion	
Major Route of Elimination	Metabolism
Urine (unchanged)	6%
Biliary/Fecal (unchanged)	Minor

*Doravirine 100 mg once daily to HIV-1 infected subjects
[†]Presented as geometric mean (%CV: geometric coefficient of variation)
[‡]Geometric mean ratio [high-fat meal/fasting] and (90% confidence interval) for PK parameters. High fat meal is approximately 1,000 kcal, 50% fat. The effect of food is not clinically relevant.
[§]Based on IV dose

Abbreviations: AUC=area under the time concentration curve; C_{max}=maximum concentration; C_{24}=concentration at 24 hours; T_{max} time to C_{max}; V_{dss}= volume of distribution at steady state, $t_{1/2}$=elimination half-life; CL/F=apparent clearance; CL_{renal}=apparent renal clearance

Specific Populations

No clinically significant difference on the pharmacokinetics of doravirine were observed based on age (18 to 78 years of age), sex, and race/ethnicity, mild to severe renal impairment (creatinine clearance (CLcr) >15 mL/min, estimated by Cockcroft-Gault), or moderate hepatic impairment (Child-Pugh B). The pharmacokinetics of doravirine in patients with end-stage renal disease or undergoing dialysis, severe hepatic impairment (Child-Pugh C), or <18 years of age is unknown.

Patients with Renal Impairment

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. Doravirine has not been studied in patients with end-stage renal disease or in patients undergoing dialysis *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

No clinically significant difference in the pharmacokinetics of doravirine was observed in subjects with moderate hepatic impairment (Child-Pugh score B) compared to subjects without hepatic impairment. Doravirine has not been studied in subjects with severe hepatic impairment (Child-Pugh score C) *[see Use in Specific Populations (8.7)]*.

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. Doravirine did not inhibit major drug metabolizing enzymes *in vitro*, including CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, and UGT1A1 and is not likely to be an inducer of CYP1A2, 2B6, or 3A4. Based on *in vitro* assays, doravirine is not likely to be an inhibitor of OATP1B1, OATP1B3, P-glycoprotein, BSEP, OAT1, OAT3, OCT2, MATE1, and MATE2K. Drug interaction studies were performed with doravirine and other drugs likely to be co-administered or commonly used as probes for pharmacokinetic interactions. The effects of co-administration with other drugs on the exposure (C_{max}, AUC, and C_{24}) of doravirine are summarized in Table 8. A single doravirine 100 mg dose was administered in these studies unless otherwise noted.

Table 8: Drug Interactions: Changes in Pharmacokinetic Parameter Values of Doravirine in the Presence of Co-administered Drug

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

CI = confidence interval; QD = once daily; BID = twice daily
*$AUC_{0-\infty}$ for single-dose, AUC_{0-24} for once daily.
†Changes in doravirine pharmacokinetic values are not clinically relevant.
‡A single doravirine 50 mg dose (0.5 times the recommended approved dose) was administered.
§The first day following the cessation of efavirenz therapy and initiation of doravirine 100 mg QD.
¶14 days following the cessation of efavirenz therapy and initiation of doravirine 100 mg QD.

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

12.4 Microbiology

Mechanism of Action

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

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 in cell culture 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; the gp41 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, H221Y, F227C, F227I, F227L, F227V, M230I, L234I, P236L, and Y318F.

In Clinical Trials

Clinical Trial Results in Adults with No Antiretroviral Treatment History

In the doravirine treatment arms of the DRIVE-FORWARD and DRIVE-AHEAD trials (n=747) at Week 48, 11 subjects showed the emergence of doravirine-associated resistance substitutions in their HIV among 28 (39%) subjects in the resistance analysis subset (subjects with HIV-1 RNA greater than 400 copies per mL at virologic failure or early study discontinuation and having resistance data). Emergent doravirine resistance-associated substitutions in RT included one or more of the following: A98G, V106I, V106A, V106M/T, V108I, E138G/K, Y188L, H221Y, P225H, F227C, F227C/R, and Y318Y/F. Seven of 11 (64%) subjects with emergent doravirine-associated resistance substitutions showed doravirine phenotypic resistance and all of them had at least a 100-fold reduction in doravirine susceptibility (range >97- to >211–fold reduction in doravirine susceptibility). The other 4 virologic failures who had only amino acid mixtures of NNRTI resistance substitutions showed doravirine phenotypic fold-changes of less than 2-fold. Of the 28 subjects in the resistance analysis subset, 8 subjects (29%) developed genotypic and/or phenotypic resistance to the other drugs (abacavir, lamivudine, emtricitabine, or TDF) in the regimens of the DRIVE-FORWARD and DRIVE-AHEAD trials. The resistance-associated substitutions that emerged were RT M41L (n=1), A62V (n=1), K65R (n=2), T69T/A (n=1), and M184V (n=5).

In the DRV+r treatment arm of the DRIVE-FORWARD trial (n=383) at Week 48, no subjects showed the emergence of darunavir-associated resistance substitutions among 9 subjects with resistance data and none of the subjects had emergent resistance to lamivudine or TDF. In the EFV/FTC/TDF treatment arm of the DRIVE-AHEAD trial (n=364), 12 subjects showed the emergence of efavirenz-associated resistance substitutions among 20 (60%) subjects in the resistance analysis subset and genotypic resistance to emtricitabine or tenofovir developed in 5 evaluable subjects; emergent resistance-associated substitutions were RT K65R (n=1), D67G/K70E (n=1), L74V/V75M/V118I (n=1), and M184V/I (n=5).

Clinical Trial Results in Virologically-Suppressed Adults

In the DRIVE-SHIFT clinical trial *[see Clinical Studies 14.2]*, there were 6 subjects in the immediate switch group (n=447) and 2 subjects in the delayed switch group (n=209) who met the protocol-defined virologic failure criteria (confirmed HIV-1 RNA ≥ 50 copies/mL). Two of the 6 virologic failure subjects in the immediate switch group had available resistance data and neither developed detectable genotypic or phenotypic resistance to doravirine, lamivudine, or tenofovir during treatment with DELSTRIGO. One of the two virologic failure subjects in the delayed switch group who had available resistance data developed the RT M184M/I substitution and phenotypic resistance to emtricitabine and lamivudine during treatment with their baseline regimen.

Cross-Resistance

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

Cross-resistance has been observed among NNRTIs. Treatment-emergent doravirine resistance-associated substitutions can confer cross resistance to efavirenz, etravirine, nevirapine, and rilpivirine. Of the 7 virologic failures who developed doravirine phenotypic resistance, all had phenotypic resistance to nevirapine, 6 had phenotypic resistance to efavirenz, 4 had phenotypic resistance to rilpivirine, and 3 had partial resistance to etravirine based on the Monogram PhenoSense assay.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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.

Impairment of fertility

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

14 CLINICAL STUDIES

14.1 Clinical Trial Results in Adults with No Antiretroviral Treatment History

The efficacy of PIFELTRO is based on the analyses of 48-week data from two randomized, multicenter, double-blind, active controlled Phase 3 trials (DRIVE-FORWARD, NCT02275780 and DRIVE-AHEAD, NCT02403674) in HIV-1 infected subjects with no antiretroviral treatment history (n=1494).

In DRIVE-FORWARD, 766 subjects were randomized and received at least 1 dose of either PIFELTRO once daily or darunavir 800 mg + ritonavir 100 mg (DRV+r) once daily each in combination with emtricitabine/tenofovir DF (FTC/TDF) or abacavir/lamivudine (ABC/3TC) selected by the investigator. At baseline, the median age of subjects was 33 years, 16% were female, 27% were non-white, 4% had hepatitis B and/or C virus co-infection, 10% had a history of AIDS, 20% had HIV-1 RNA greater than 100,000 copies/mL, 86% had CD4+ T-cell count greater than 200 cells/mm^3, 13% received ABC/3TC, and 87% received FTC/TDF; these characteristics were similar between treatment groups.

In DRIVE-AHEAD, 728 subjects were randomized and received at least 1 dose of either DELSTRIGO (DOR/3TC/TDF) or EFV 600 mg/FTC 200 mg/TDF 300 mg once daily. At baseline, the median age of subjects was 31 years, 15% were female, 52% were non-white, 3% had hepatitis B or C co-infection, 14% had a history of AIDS, 21% had HIV-1 RNA greater than 100,000 copies/mL, and 88% had CD4+ T-cell count greater than 200 cells/mm^3; these characteristics were similar between treatment groups.

Week 48 outcomes for DRIVE-FORWARD and DRIVE-AHEAD are provided in Table 9. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

In DRIVE-FORWARD, the mean CD4+ T-cell counts in the PIFELTRO and DRV+r groups increased from baseline by 193 and 186 cells/mm^3, respectively.

In DRIVE-AHEAD, the mean CD4+ T-cell counts in the DELSTRIGO and EFV/FTC/TDF groups increased from baseline by 198 and 188 cells/mm^3, respectively.

Table 9: Virologic Outcomes in DRIVE-FORWARD and DRIVE-AHEAD at Week 48 in HIV-1 Adults with No Antiretroviral Treatment History

	DRIVE-FORWARD		DRIVE-AHEAD	
Outcome	**PIFELTRO + 2 NRTIs Once Daily N=383**	**DRV+r + 2 NRTIs Once Daily N=383**	**DELSTRIGO Once Daily N=364**	**EFV/FTC/TDF Once Daily N=364**
HIV-1 RNA <50 copies/mL	84%	80%	84%	81%
Treatment Differences (95% CI) *	3.9% (-1.6%, 9.4%)		3.5% (-2.0%, 9.0%)	
HIV-1 RNA ≥ 50 copies/mL†	11%	13%	11%	10%
No Virologic Data at Week 48 Window	5%	7%	5%	9%
Discontinued study due to AE or Death‡	1%	3%	2%	7%
Discontinued study for Other Reasons§	3%	4%	2%	2%
On study but missing data in window	<1%	<1%	0	<1%
Proportion (%) of Subjects With HIV-1 RNA <50 copies/mL at Week 48 by Baseline and Demographic Category				
Gender				
Male	84% (N = 319)	82% (N = 326)	84% (N = 305)	80% (N = 311)
Female	81% (N = 64)	67% (N = 57)	85% (N = 59)	83% (N = 53)
Race				
White	87% (N = 280)	83% (N = 280)	84% (N = 177)	81% (N = 170)
Non-White	75% (N = 103)	73% (N = 103)	84% (N = 187)	80% (N = 194)
Ethnicity				
Hispanic or Latino	88% (N = 93)	81% (N = 86)	83% (N = 126)	84% (N = 120)
Not Hispanic or Latino	82% (N = 284)	79% (N = 290)	85% (N = 236)	79% (N = 238)
NRTI Background Therapy				
FTC/TDF	83% (N = 333)	81% (N = 335)	-	-
ABC/3TC	86% (N = 50)	75% (N = 48)	-	-
Baseline HIV-1 RNA (copies/mL)				
≤100,000 copies/mL	86% (N = 300)	81% (N = 308)	86% (N = 291)	83% (N = 282)
>100,000 copies/mL	77% (N = 83)	74% (N = 74)	77% (N = 73)	72% (N = 82)
CD4+ T-cell Count (cells/mm^3)				
≤200 cells/mm^3	81% (N = 42)	66% (N = 67)	66% (N = 44)	78% (N = 46)
>200 cells/mm^3	84% (N = 341)	83% (N = 316)	87% (N = 320)	81% (N = 318)
Viral Subtype¶				
Subtype B	84% (N = 266)	82% (N = 272)	84% (N = 232)	80% (N = 253)
Subtype Non-B	83% (N = 117)	76% (N = 111)	85% (N = 130)	83% (N = 111)

¶Viral subtype was not available for two subjects in DRIVE-AHEAD.

*The 95% CIs for the treatment differences were calculated using stratum-adjusted Mantel-Haenszel method.
†Includes subjects who discontinued study drug or study before Week 48 for lack or loss of efficacy and subjects with HIV-1 RNA equal to or above 50 copies/mL in the Week 48 window (relative day 295-378).
‡Includes subjects who discontinued because of adverse event (AE) or death if this resulted in no virologic data in the Week 48 window.
§Other Reasons include: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, protocol deviation, screen failure, withdrawal by subject.
Note: NRTIs = FTC/3TC or ABC/3TC.

14.2 Clinical Trial Results in Virologically-Suppressed Adults

The efficacy of switching from a baseline regimen consisting of two NRTIs in combination with a PI plus either ritonavir or cobicistat, or elvitegravir plus cobicistat, or an NNRTI to DELSTRIGO was evaluated in a randomized, open-label trial (DRIVE-SHIFT, NCT02397096), in virologically-suppressed HIV-1 infected adults. Subjects must have been virologically suppressed (HIV-1 RNA < 50 copies/mL) on their baseline regimen for at least 6 months prior to trial entry, with no history of virologic failure. Subjects were randomized to either switch to DELSTRIGO at baseline (n = 447, Immediate Switch Group (ISG)), or stay on their baseline regimen until Week 24, at which point they switched to DELSTRIGO (n = 223, Delayed Switch Group (DSG)).

At baseline, the median age of subjects was 43 years, 16% were female, and 24% were Non-White, 21% were of Hispanic or Latino ethnicity, 3% had hepatitis B and/or C virus co-infection, 17% had a history of AIDS, 96% had CD4+ T-cell count greater than or equal to 200 cells/mm^3, 70% were on a regimen containing a PI plus ritonavir, 24% were on a regimen containing an NNRTI, 6% were on a regimen containing elvitegravir plus cobicistat, and 1% were on a regimen containing a PI plus cobicistat; these characteristics were similar between treatment groups.

Virologic outcome results are shown in Table 10.

Table 10: Virologic Outcomes in DRIVE-SHIFT in HIV-1 Virologically-Suppressed Subjects Who Switched to DELSTRIGO

Outcome	DELSTRIGO Once Daily ISG Week 48 N=447	Baseline Regimen DSG Week 24 N=223
HIV-1 RNA ≥ 50 copies/mL*	2%	1%
ISG-DSG, Difference (95% CI) †‡	0.7% (-1.3%, 2.6%)	
HIV-1 RNA <50 copies/mL	91%	95%
No Virologic Data Within the Time Window	8%	4%
Discontinued study due to AE or Death§	3%	<1%
Discontinued study for Other Reasons¶	4%	4%
On study but missing data in window	0	0
Proportion (%) of Subjects With HIV-1 RNA <50 copies/mL by Baseline and Demographic Category		
Age (years)		
< 50	90% (N = 320)	95% (N = 157)
≥ 50	94% (N = 127)	94% (N = 66)
Gender		
Male	91% (N = 372)	94% (N = 194)
Female	91% (N = 75)	100% (N = 29)
Race		
White	90% (N = 344)	95% (N = 168)

Non-White	93% (N = 103)	93% (N = 55)
Ethnicity		
Hispanic or Latino	88% (N = 99)	91% (N = 45)
Not Hispanic or Latino	91% (N = 341)	95% (N = 175)
CD4+ T-cell Count (cells/mm^3)		
<200 cells/mm^3	85% (N = 13)	75% (N = 4)
≥200 cells/mm^3	91% (N = 426)	95% (N = 216)
Baseline Regimen[#]		
PI plus either ritonavir or cobicistat	90% (N=316)	94% (N=156)
elvitegravir plus cobicistat or NNRTI	93% (N=131)	96% (N=67)

*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.
[†]The 95% CI for the treatment difference was calculated using stratum-adjusted Mantel-Haenszel method.
[‡]Assessed using a non-inferiority margin of 4%.
[§]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 = PI plus either ritonavir or cobicistat (specifically atazanavir, darunavir, or lopinavir), or elvitegravir plus cobicistat, or NNRTI (specifically efavirenz, nevirapine, or rilpivirine), each administered with two NRTIs.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each PIFELTRO tablet contains 100 mg of doravirine, is white, oval-shaped and film-coated, and is debossed with the corporate logo and 700 on one side and plain on the other side. Each bottle contains 30 tablets (NDC 0006-3069-01) with silica gel desiccant and is closed with a child-resistant closure.

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

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

17 PATIENT COUNSELING INFORMATION

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

Drug Interactions

Inform patients that PIFELTRO may interact with certain other drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort *[see Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7.1)]*

For patients concomitantly receiving rifabutin, take one tablet of PIFELTRO twice daily (approximately 12 hours apart) *[see Dosage and Administration (2.2)]*.

Immune Reconstitution Syndrome

Inform patients that in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight

infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection *[see Warnings and Precautions (5.2)].*

Dosing Instructions

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

Pregnancy Registry

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

Lactation

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

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

uspi-mk1439-t-XXXXrXXX

Patient Information
PIFELTRO™ (pih-FEL-tro)
(doravirine)
tablets

What is PIFELTRO?

PIFELTRO is a prescription medicine that is used together with other HIV-1 medicines to treat Human Immunodeficiency Virus-1 (HIV-1) infection in adults:

- who have not received HIV-1 medicines in the past, or
- to replace their current HIV-1 medicines for people whose healthcare provider determines that they meet certain requirements.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

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

Who should not take PIFELTRO?

Do not take PIFELTRO if you take any of the following medicines:

- carbamazepine
- oxcarbazepine
- phenobarbital
- phenytoin
- enzalutamide
- rifampin
- rifapentine
- mitotane
- St. John's wort

Ask your doctor or pharmacist if you are not sure if your medicine is one that is listed above. If you have taken any of the medicines in the past 4 weeks, talk to your doctor or pharmacist before starting treatment with PIFELTRO.

What should I tell my doctor before treatment with PIFELTRO?

Before treatment with PIFELTRO, tell your doctor about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if PIFELTRO can harm your unborn baby. Tell your doctor if you become pregnant during treatment with PIFELTRO.
  Pregnancy Registry: There is a pregnancy registry for people who take PIFELTRO during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your doctor about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. Do not breastfeed if you take PIFELTRO.
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - It is not known if PIFELTRO can pass into your breast milk.
  - Talk with your doctor about the best way to feed your baby.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

- **Some medicines interact with PIFELTRO**. **Keep a list of your medicines to show your doctor and pharmacist.**
- Tell your doctor if you have taken rifabutin in the past 4 weeks.
- You can ask your doctor or pharmacist for a list of medicines that interact with PIFELTRO.
- **Do not start taking a new medicine without telling your doctor**. Your doctor can tell you if it is safe to take PIFELTRO with other medicines.

How do I take PIFELTRO?

- Take PIFELTRO every day exactly as your doctor tells you to take it.

- Take PIFELTRO **1** time each day, at about the same time every day.
- If you take the medicine rifabutin during treatment with PIFELTRO, take PIFELTRO **2** times each day, about 12 hours apart, as prescribed by your doctor. You may not have enough doravirine in your blood if you take rifabutin during treatment with PIFELTRO.
- Take PIFELTRO with or without food.
- Do not change your dose or stop taking PIFELTRO without talking to your doctor. Stay under a doctor's care when taking PIFELTRO.
- It is important that you do not miss or skip doses of PIFELTRO.
- If you miss a dose of PIFELTRO, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the next dose at your regular time. Do not take 2 doses of PIFELTRO at the same time.
- If you have any questions, call your doctor or pharmacist.
- When your PIFELTRO supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to PIFELTRO and become harder to treat.

What are the possible side effects of PIFELTRO?

PIFELTRO can cause serious side effects, including:

- **Changes in your immune system (Immune Reconstitution Syndrome)** 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. Tell your doctor right away if you start having any new symptoms after starting your HIV-1 medicine.

The most common side effects of PIFELTRO include:

- nausea
- dizziness
- headache
- tiredness
- diarrhea
- stomach (abdominal) pain
- abnormal dreams

These are not all the possible side effects of PIFELTRO.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PIFELTRO?

- Store PIFELTRO tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep PIFELTRO in the original bottle.
- Do not take the tablets out of the bottle to store in another container, such as a pill box.
- Keep the bottle tightly closed to protect PIFELTRO from moisture.
- The PIFELTRO bottle contains a desiccant to help keep your medicine dry (protect it from moisture). Keep the desiccant in the bottle. **Do not eat the desiccant.**

Keep PIFELTRO and all medicines out of the reach of children.

General information about the safe and effective use of PIFELTRO.

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use PIFELTRO for a condition for which it was not prescribed. Do not give PIFELTRO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about PIFELTRO that is written for healthcare professionals.

What are the ingredients in PIFELTRO?

Active ingredient: doravirine.

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablet film coating contains hypromellose, lactose monohydrate, titanium dioxide and triacetin. The coated tablets are polished with carnauba wax.

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For patent information: www.merck.com/product/patent/home.html

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For more information, go to www.PIFELTRO.com or call 1-877-888-4231.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 09/2019