PIFELTRO™ (doravirine)
Film Coated Tablet
100 mg

1. INDICATIONS AND USAGE

PIFELTRO 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 NNRTI.

2. DOSAGE AND ADMINISTRATION

2.1 General

PIFELTRO is a tablet containing 100 mg of doravirine.

2.2 Adult Patients

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

Missed Dose

If the patient misses a dose of PIFELTRO within 12 hours of the time it is usually taken, the patient should take PIFELTRO as soon as possible and resume the normal dosing schedule. If a patient misses a dose by more than 12 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not take 2 doses at one time.

2.3 Pediatric Patients

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

2.4 Elderly Patients

There are limited data available on the use of doravirine in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients *[see Use in*

Specific Populations (6.4) and Clinical Pharmacology (10.4)]. No dose adjustment of PIFELTRO is needed in elderly patients.

2.5 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 Use in Specific Populations (6.5) and Clinical Pharmacology (10.4)]*.

2.6 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 Use in Specific Populations (6.6) and Clinical Pharmacology (10.4)]*.

2.7 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 and Other Forms of Interactions (5.1) and Clinical Pharmacology (10.5)]*.

3. CONTRAINDICATIONS

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

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

4. WARNINGS AND PRECAUTIONS

4.1 Drug Interactions

Caution should be given to prescribing PIFELTRO with drugs that may reduce the exposure of doravirine *[see Contraindications (3), Drug Interactions and Other Forms of Interactions (5.1), and Clinical Pharmacology (10.5)]*.

4.2 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.

5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS

5.1 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 (3), Warnings and Precautions (4.1), and Clinical Pharmacology (10.5)]*. Co-administration of PIFELTRO and drugs that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine.

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

Table 1 shows the established and other potentially significant drug interactions with PIFELTRO but is not inclusive.

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

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
HIV-Antiviral Agents		
efavirenz* 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, 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, 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*	↓ 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 (2.7)]*.
Azole Antifungal Agents		
fluconazole itraconazole ketoconazole* posaconazole voriconazole	↑ doravirine ↔ azole antifungal agents	Concomitant use of PIFELTRO with azole antifungal agents 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 azole antifungal agents.
↑ = increase, ↓ = decrease, ↔ = no change *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. PIs=Protease Inhibitors		

5.2 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 Clinical Pharmacology (10.5)]:* 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.

5.3 Lactose

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

6. USE IN SPECIFIC POPULATIONS

6.1 Pregnancy

Risk Summary

No adequate human data are available to establish whether or not PIFELTRO poses a risk to pregnancy outcomes. Doravirine use in women during pregnancy has not been evaluated.

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

6.2 Nursing Mothers

Risk Summary

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.

Animal 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.

6.3 Pediatric Use

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

6.4 Elderly Use

There are limited data available on the use of doravirine in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients *[see Clinical Pharmacology (10.4)]*. No dose adjustment of PIFELTRO is needed in elderly patients.

6.5 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 Clinical Pharmacology (10.4)]*.

6.6 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 Clinical Pharmacology (10.4)]*.

7. ADVERSE REACTIONS

7.1 Clinical Trials Experience

Summary of the safety profile

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

Tabulated summary of adverse reactions

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

Table 2: Tabulated summary of adverse reactions associated with doravirine used in combination with other antiretrovirals

Frequency	Adverse reactions
Infections and infestations	
Rare	rash pustular
Metabolism and nutrition disorders	
Uncommon	hypophosphataemia
Rare	hypomagnesaemia
Psychiatric disorders	
Common	abnormal dreams, insomnia[1]
Uncommon	nightmare, depression[2], anxiety[3], irritability, confusional state, suicidal ideation

Rare	aggression, hallucination, adjustment disorder, mood altered, somnambulism
Nervous system disorders	
Common	headache, dizziness, somnolence
Uncommon	disturbance in attention, memory impairment, paraesthesia, hypertonia, poor quality sleep
Vascular disorders	
Uncommon	hypertension
Respiratory, thoracic and mediastinal disorders	
Rare	dyspnoea, tonsillar hypertrophy
Gastrointestinal disorders	
Common	nausea, diarrhoea, flatulence, abdominal pain[4], vomiting
Uncommon	constipation, abdominal discomfort[5], abdominal distension, dyspepsia, faeces soft[6], gastrointestinal motility disorder[7]
Rare	rectal tenesmus
Skin and subcutaneous tissue disorders	
Common	rash[8]
Uncommon	pruritus
Rare	dermatitis allergic, rosacea
Musculoskeletal and connective tissue disorders	
Uncommon	myalgia, arthralgia
Rare	musculoskeletal pain
Renal and urinary disorders	
Rare	acute kidney injury, renal disorder, calculus urinary, nephrolithiasis
General disorders and administration site conditions	
Common	fatigue
Uncommon	asthenia, malaise
Rare	chest pain, chills, pain, thirst
Investigations	
Common	alanine aminotransferase increased[9]
Uncommon	lipase increased, aspartate aminotransferase increased, amylase increased, haemoglobin

	decreased
Rare	blood creatine phosphokinase increased

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

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

[3]anxiety includes: anxiety and generalized anxiety disorder

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

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

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

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

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

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

8. 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.

9. CLINICAL STUDIES

9.1 Adult Subjects with No Antiretroviral Treatment History

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

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

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

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

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

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

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

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

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

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

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

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

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

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

¶Viral subtype was not available for two subjects.

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

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

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

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

At Week 48, the proportion of subjects with HIV-1 RNA less than 50 copies/mL was 79% (85/108) and 82% (89/108) for PIFELTRO 100 mg and EFV, respectively. At Week 96, the proportion of subjects with HIV-1 RNA less than 50 copies/mL was 76% (82/108) and 76% (82/108) for PIFELTRO 100 mg and EFV, respectively. At Week 48, mean CD4+ T-cell counts in the PIFELTRO 100 mg and EFV groups increased from baseline by 192 and 195 cells/mm^3, respectively. At Week 96, mean

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

9.2 Virologically-Suppressed Adult Subjects

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

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

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

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

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

*The 95% CI for the treatment difference was calculated using stratum-adjusted Mantel-Haenszel method.

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

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

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

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

10. CLINICAL PHARMACOLOGY

10.1 Therapeutic Class

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

10.2 Mechanism of Action

PIFELTRO is an antiviral drug *[see Clinical Pharmacology (10.3)]*.

10.3 Pharmacodynamics

Effects on Electrocardiogram

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

Microbiology

Mechanism of Action

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

Antiviral Activity in Cell Culture

Doravirine exhibited an EC_{50} value of 12.0±4.4 nM against wild-type laboratory strains of HIV-1 when tested in the presence of 100% normal human serum (NHS) using MT4-GFP reporter cells. Doravirine demonstrated antiviral activity against a broad panel of primary HIV-1 isolates (A, A1, AE, AG, B, BF, C, D, G, H) with EC_{50} values ranging from 1.2 nM to 10.0 nM.

Antiviral Activity in Combination with other HIV Antiviral Agents

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

Resistance

In Cell Culture

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

In Clinical Trials

In Adult Subjects with No Antiretroviral Treatment History

The phase 3 studies, DRIVE-FORWARD and DRIVE-AHEAD, including previously untreated patients (n=747) where the following NNRTI substitutions were part of the exclusion criteria: L100I, K101E, K101P, K103N, K103S, V106A, V106I, V106M, V108I, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, Y188C, Y188H, Y188L, G190A, G190S, H221Y, L234I, M230I, M230L, P225H, F227C, F227L, F227V.

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

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

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

In Virologically-Suppressed Adult Subjects

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

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

Treatment-emergent doravirine resistance-associated substitutions may confer cross-resistance to efavirenz, rilpivirine, nevirapine, and etravirine. Of the 8 virologic failure subjects who developed doravirine phenotypic resistance, all had phenotypic resistance to nevirapine, 6 had phenotypic resistance to efavirenz, 4 had phenotypic resistance to rilpivirine, and 4 had partial resistance to etravirine based on the Monogram Phenosense assay.

10.4 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 AUC_{0-24}, C_{max}, and C_{24}. Doravirine steady state pharmacokinetics following administration of 100 mg once daily to HIV-1-infected subjects, based on a population pharmacokinetic analysis, are provided below.

Parameter GM (%CV)	AUC_{0-24} µ M hr	C_{max} µ M	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.

Effect of Food on Oral Absorption

The administration of a single PIFELTRO tablet with a high-fat meal to healthy subjects resulted in a 16% and 36% increase in doravirine AUC and C_{24}, respectively, while C_{max} was not significantly affected.

Special Populations

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 Use in Specific Populations (6.5)]*.

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 Use in Specific Populations (6.6)]*.

Pediatric

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

Elderly

No clinically relevant differences in the pharmacokinetics of doravirine have been identified in subjects at least 65 years of age compared to subjects less than 65 years of age in a Phase 1 trial or in a population pharmacokinetic analysis *[see Use in Specific Populations (6.4)]*.

Race

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.

Gender

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

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

Table 5: Drug Interactions: Changes in Pharmacokinetic Parameter Values of Doravirine in the Presence of Co-administered Drug

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Doravirine	N	Geometric Mean Ratio (90% CI) of Doravirine Pharmacokinetics with/without Co-administered Drug (No Effect=1.00)		
				AUC*	C_{max}	C_{24}
Azole Antifungal Agents						
ketoconazole	400 mg QD	100 mg SD	10	3.06 (2.85, 3.29)	1.25 (1.05, 1.49)	2.75 (2.54, 2.98)
Antimycobacterials						
rifampin	600 mg SD	100 mg SD	11	0.91 (0.78, 1.06)	1.40 (1.21, 1.63)	0.90 (0.80, 1.01)
	600 mg QD	100 mg SD	10	0.12 (0.10, 0.15)	0.43 (0.35, 0.52)	0.03 (0.02, 0.04)
rifabutin	300 mg QD	100 mg SD	12	0.50 (0.45, 0.55)	0.99 (0.85, 1.15)	0.32 (0.28, 0.35)
HIV Antiviral Agents						
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	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)

and magnesium hydroxide oral suspension)						
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 *$AUC_{0-\infty}$ for single dose, AUC_{0-24} for once daily. † Interaction was assessed following the cessation of efavirenz therapy.						

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

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Doravirine	N	Geometric Mean Ratio [90% CI] Drug Pharmacokinetics with/without Co-administered Doravirine (No Effect=1.00)		
				AUC*	C_{max}	C_{24}
CYP3A Substrate						
midazolam	2 mg SD	120 mg QD	7	0.82 (0.70, 0.97)	1.02 (0.81, 1.28)	-
HIV Antiviral Agents						
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				1.03 (0.98, 1.09)	1.03 (0.97, 1.09)	--
Oral Contraceptives						
ethinyl	0.03 mg ethinyl	100 mg QD	19	0.98 (0.94, 1.03)	0.83 (0.80, 0.87)	--

estradiol	estradiol + 0.15 mg levonorgestrel (Nordette®-28) SD					
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.

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

11. ANIMAL TOXICOLOGY

11.1 Acute Toxicity

No acute toxicity studies were performed with doravirine.

11.2 Chronic Toxicity

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

11.3 Carcinogenesis

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

11.4 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.

11.5 Reproduction

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

11.6 Development

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

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

12. NAME OF THE DRUG

PIFELTRO (doravirine).

13. PHARMACEUTICAL FORM

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

14. PHARMACEUTICAL PARTICULARS

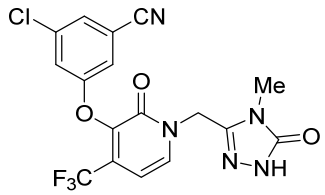
PIFELTRO is a film-coated tablet containing doravirine for oral administration.

14.1 Chemistry

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.

14.2 Composition

Active Ingredient

Each tablet contains 100 mg of doravirine.

Inactive Ingredients (List of Excipients)

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

14.3 Storage

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

Store PIFELTRO below 30°C.

Special Precautions for Storage

14.4 Shelf Life

Refer to outer carton.

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

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

Product Owner:

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USA

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MSD