▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

PIFELTRO®

(doravirine)
Tablets

1 NAME OF THE MEDICINE

doravirine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Active Ingredient

Each tablet contains 100 mg of doravirine.

Inactive Ingredients (List of Excipients)

List of excipients with known effect:

- lactose (as monohydrate).

For the full list of excipients, see section 6.1 List of excipients.

Doravirine is practically insoluble in water.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PIFELTRO is indicated, in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infection in adults who are antiretroviral therapy (ART) naïve with no known substitutions associated with resistance to doravirine.

4.2 DOSE AND METHOD OF ADMINISTRATION

PIFELTRO is a tablet containing 100 mg of doravirine.

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, the patient should take PIFELTRO as soon as possible unless it is almost time for the next dose. The patient should not take 2 doses at one time and instead take the next dose at the regularly scheduled time.

Paediatric Patients

Safety and efficacy of PIFELTRO have not been established in patients younger than 18 years of age (see section 5.2, *Special populations*).

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 sections 4.4 and 5.2, *Special populations*). No dose adjustment of PIFELTRO is needed in elderly patients.

Renal Impairment

No dose adjustment of PIFELTRO is required in patients with mild, moderate or severe (eGFR 15-<30 mL/min/1.73 m^2) renal impairment. PIFELTRO has not been adequately studied in patients with end-stage renal disease and has not been studied in dialysis patients (see section 4.4 and 5.2, *Special populations*).

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 section 4.4 and 5.2, *Special populations*).

Co-administration with Moderate CYP3A Inducers

If PIFELTRO is co-administered with rifabutin, one tablet of PIFELTRO should be taken twice daily (approximately 12 hours apart) (see section 4.5 and 5.2, *Drug interaction studies*).

Co-administration of doravirine with other moderate CYP3A inducers has not been evaluated. If co-administration with other moderate CYP3A inducers (e.g. dabrafenib, lesinurad, bosentan, thioridazine, nafcillin, modafinil, telotristat ethyl) cannot be avoided, an additional 100 mg dose of doravirine should be administered 12 hours following the initial dose of doravirine (see section 4.5).

4.3 CONTRAINDICATIONS

PIFELTRO should not be 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 section 5.2). These drugs include, but are not limited to, the following:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifampicin
- St. John's wort (*Hypericum perforatum*)
- mitotane
- enzalutamide
- lumacaftor

PIFELTRO is contraindicated in patients who are hypersensitive to any component of this medicine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Drug Interactions

Caution should be given to prescribing PIFELTRO with drugs that may reduce the exposure of doravirine (see section 4.3, 4.5 and 5.2, *Special populations*).

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

Use in 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 section 5.2, *Special populations)*.

Use in renal impairment

No dose adjustment of PIFELTRO is required in patients with mild, moderate or severe (eGFR 15-<30 mL/min/1.73 m^2) renal impairment. PIFELTRO has not been adequately studied in patients with end-stage renal disease and has not been studied in dialysis patients (see section 5.2, *Special populations*).

Use in the elderly

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 section 5.2, *Special populations*). No dose adjustment of PIFELTRO is needed in elderly patients.

Paediatric use

Safety and efficacy of PIFELTRO have not been established in patients younger than 18 years of age (see section 5.2, *Special populations*).

Effects on laboratory tests

See Section 4.8, *Laboratory abnormalities*.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 section 4.3, 4.4 and 5.2, *Drug Interaction Studies*). Co-administration of TRADEMARK with strong inducers of CYP3A is contraindicated (see section 4.3). 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		

Antiobiotics		
nafcillin	Interaction not studied. Expected: (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, one tablet of doravirine should be taken twice daily (approximately 12 hours apart).
Antidiarrheal		
Telotristat ethyl	Interaction not studied. Expected: (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, one tablet of doravirine should be taken twice daily (approximately 12 hours apart).
Antigout and Uricosuric Agents		
lesinurad	Interaction not studied. Expected: (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, one tablet of doravirine should be taken twice daily (approximately 12 hours apart).
Antimycobacterials		
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 section 4.2).
Antipsychotics		
thioridazine	Interaction not studied. Expected: (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, one tablet of doravirine should be taken twice daily (approximately 12 hours apart).
Azole Antifungal Agents		
fluconazole itraconazole ketoconazole* posaconazole voriconazole	antifungal agents	Concomitant use of PIFELTRO with azole antifungal agents may cause an increase in the plasma concentrations of PIFELTRO (inhibition of CYP3A enzymes). No doravirine dose adjustment is required when PIFELTRO is co-administered with azole antifungal agents.

Endothelin Receptor Antagonists		
bosentan	Interaction not studied. Expected: (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, one tablet of doravirine should be taken twice daily (approximately 12 hours apart).
Kinase Inhibitors		
dabrafenib	Interaction not studied. Expected: (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, one tablet of doravirine should be taken twice daily (approximately 12 hours apart).
Pscychostimulants		
modafinil	Interaction not studied. Expected: (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, one tablet of doravirine should be taken twice daily (approximately 12 hours apart).

*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

Drugs with No Observed or Predicted Interactions with PIFELTRO

Drug-drug interactions with PIFELTRO and the following drugs were evaluated in clinical studies and no dose adjustment is needed for either drug (see section 5.2, Drug *Interaction Studies*): aluminium hydroxide/magnesium hydroxide/simethicone-containing antacid, pantoprazole, atorvastatin, an oral contraceptive containing ethinylestradiol 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There were no effects on fertility, mating performance or early embryonic development when doravirine was administered to rats up to the highest dose tested (450 mg/kg/day). Systemic exposures (AUC) to doravirine were 5-7 times the exposure in humans at the recommended human dose (RHD).

Use in pregnancy (Category B1)

Antiretroviral Pregnancy Registry

To monitor maternal-foetal outcomes of pregnant patients exposed to PIFELTRO, an International Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients via email at SM_APR@INCResearch.com or via facsimile at +1-910-256-0637.

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 with orally administered doravirine have been performed in rats and rabbits at exposures approximately 8 times the exposure in humans at the RHD with no effects on embryo-foetal (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 foetus through the placenta, with foetal plasma concentrations of up to 40% (rabbits) and 52% (rats) that of maternal concentrations observed on gestation day 20.

Use in lactation

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.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of PIFELTRO on the ability to drive or operate machinery have been performed. Patients should be informed that dizziness has been reported during treatment with PIFELTRO. This should be considered when assessing a patient's ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials Experience

Treatment-Emergent Adverse Drug Reactions

The safety assessment of PIFELTRO in antiretroviral treatment-naïve, HIV-1 infected subjects, is based on the analyses of data through 48 weeks from two Phase 3, randomized, international, multicentre, 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 DF (FTC/TDF) or abacavir/lamivudine (ABC/3TC). By Week 48, 1.6% in the PIFELTRO group and 3.1% in the DRV+r group had adverse events leading to discontinuation of study medication.

In DRIVE-AHEAD, 728 adult subjects received either DELSTRIGO®-(doravirine/lamivudine/tenofovir DF (DOR/3TC/TDF) (n=364) or efavirenz/emtricitabine/tenofovir DF (EFV/FTC/TDF) once daily (n=364). By Week 48, 3.0% in the DELSTRIGO-DOR/3TC/TDF group and 6.6% in the EFV/FTC/TDF group had adverse events leading to discontinuation of study medication.

In DRIVE FORWARD and DRIVE AHEAD, the frequency of serious adverse reactions was less than 1% in PIFELTRO and DELSTRIGO -treated subjects versus less than 1% DRV+r and 1% in EFV/FTC/TDF -treated subjects.

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

Table 2: Adverse Reactions [†] of Subjects in Any Treatment Group in Adults with No Antiretroviral Treatment History in DRIVE-FORWARD and DRIVE-AHEAD (Week 48)

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

Frequencies of adverse reactions are based on all adverse events attributed to trial drugs by the investigator.

[†]No adverse

NRTIs = nucleoside reverse transcriptase inhibitors

NRTIs = FTC/TDF or ABC/3TC.

Laboratory Abnormalities

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

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

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

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

Change in Lipids from Baseline

For DRIVE-FORWARD and DRIVE-AHEAD, changes from baseline at Week 48 in LDL-cholesterol, non-HDL-cholesterol, total cholesterol, triglycerides, and HDL-cholesterol are shown in Table 4.

For LDL- and non-HDL-cholesterol, total cholesterol, and triglycerides, the differences in the mean change from baseline at Week 48 (PIFELTRO – DRV+r and DELSTRIGO-DOR/3TC/TDF – EFV/FTC/TDF) favoured the doravirine treatment groups. The LDL and non-HDL comparisons were pre-specified and the differences were statistically significant, showing superiority for doravirine for both parameters.

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

Laboratory Parameter Preferred Term	DRIVE-FORWARD		DRIVE-AHEAD	
	PIFELTRO +2 NRTIs Once Daily	DRV+r +2 NRTIs Once Daily	DELSTRIGO-DOR/3TC/TDF Once Daily	EFV/FTC/TDF Once Daily
	N=320	N=311	N=320	N=307
LDL-Cholesterol (mg/dL)*	-4.6	9.5	-2.1	8.3
Non-HDL Cholesterol (mg/dL)*	-5.4	13.7	-4.1	12.7
Total Cholesterol (mg/dL)	-1.4	18.0	-2.2	21.1
Triglycerides (mg/dL)	-3.1	24.5	-12.0	21.6
HDL-Cholesterol (mg/dL)	4.0	4.3	1.8	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-DOR/3TC/TDF n=15 and EFV/FTC/TDF n=10). Subjects initiating a lipid-lowering agent post-baseline had their last fasted on-treatment value (prior to starting the agent) carried forward (in DRIVE-FORWARD: PIFELTRO n=6 and DRV+r n=4; in DRIVE-AHEAD: DELSTRIGO-DOR/3TC/TDF =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.
Note: NRTIs = FTC/TDF or ABC/3TC.

Neuropsychiatric Adverse Events

For DRIVE-AHEAD, the analysis of subjects with neuropsychiatric adverse events by Week 48 is presented in Table 5. A statistically significantly lower proportion of DELSTRIGO-DOR/3TC/TDF-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 5: DRIVE-AHEAD - Analysis of Subjects with Neuropsychiatric Adverse Events (Week 48)

	DELSTRIGO-DOR/3TC/TDF Once Daily	EFV/FTC/TDF Once Daily	Treatment Difference (DELSTRIGO-DOR/3TC/TDF - EFV/FTC/TDF) Estimate (95% CI)*	2-Sided P-value
	N=364	N=364		
Subjects with one or more neuropsychiatric adverse events	24%	57%	-33.2 (-39.8, -26.4)	
Dizziness	9%	37%	-28.3 (-34.0, -22.5)	<0.001
Sleep disorders and disturbances	12%	26%	-13.5 (-19.1, -7.9)	<0.001
Altered sensorium	4%	8%	-3.8 (-7.6, -0.3)	0.033
Depression and suicide/self-injury	4%	7%	-2.5 (-5.9, 0.8)	nps†
Psychosis and psychotic disorders	<1%	1%	-0.8 (-2.5, 0.5)	nps†

*The 95% CIs were calculated using Miettinen and Nurminen's method.
†Not pre-specified for statistical testing.

Discontinuation due to Adverse Events

In a pooled analysis combining data from two treatment-naïve trials (P007 and DRIVE-AHEAD), a statistically significantly lower proportion of subjects who discontinued due to an adverse event by Week 48 was seen for the combined doravirine (100 mg) treatment groups (2.8%) compared with the combined EFV treatment groups (6.1%) [treatment difference -3.4%, p-value 0.012].

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no known specific treatment for overdose with PIFELTRO. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

PIFELTRO is an antiviral drug.

Doravirine is a pyridinone non-nucleoside reverse transcriptase inhibitor of HIV-1 and inhibits HIV-1 replication by allosteric inhibition of HIV-1 reverse transcriptase (RT). Doravirine does not inhibit the human cell

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

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 0.6 nM to 10.0 nM.

Antiviral Activity in Combination with other HIV Antiviral Agents

The antiviral activity of doravirine was not antagonistic when combined with the NNRTIs delavirdine, efavirenz, etravirine, nevirapine, or rilpivirine; the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir DF, zalcitabine 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, V106M, V106I, V108I, F227L, F227C, F227V, H221Y, M230I, L234I, P236L, and Y318F.

In Clinical Trials

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

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

Cross-Resistance

Laboratory strains of HIV-1 harbouring 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% foetal bovine serum. Clinical isolates containing the Y188L substitution alone of Y188L or V106A substitutions in combination with E138K, F227L, G190A, K103N and/or M230L showed a greater than 100-fold reduced susceptibility to doravirine.

Treatment emergent doravirine resistance associated substitutions may confer cross resistance to efavirenz, rilpivirine, nevirapine, and etravirine. Of the 7 subjects who developed doravirine resistance, 6 had phenotypic resistance to EFV and nevirapine, 3 had phenotypic resistance to rilpivirine, and 2 had partial resistance to etravirine based on the Monogram Phenosense assay.

Clinical trials

Treatment-Naïve Adult Subjects

The efficacy of PIFELTRO is based on the analyses of 48-week data from two randomized, multicentre, 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-DOR/3TC/TDF 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 48 outcomes for DRIVE-FORWARD and DRIVE-AHEAD are provided in Table 6. 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- -cell count, and viral subtypes. Mean CD4+ T-cell counts in the PIFELTRO and DRV+r groups increased from baseline by 193 and 186 cells/mm^3, respectively.

In DRIVE-AHEAD, DELSTRIGO-DOR/3TC/TDF 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-DOR/3TC/TDF and EFV/FTC/TDF groups increased from baseline by 198 and 188 cells/mm^3, respectively.

Table 6: Virologic Outcome at Week 48 (FDA Snapshot Approach)

Outcome	DRIVE-FORWARD		DRIVE-AHEAD	
	PIFELTRO + 2 NRTIs Once Daily	**DRV+r + 2 NRTIs Once Daily**	**DELSTRIGO-DOR/3TC/TDF Once Daily**	**EFV/FTC/TDF Once Daily**
	N=383	**N=383**	**N=364**	**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- [†]	11%	13%	11%	10%
No Virologic Data at Week 48 Window	5%	7%	5%	9%
Reasons				
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%	82%	84%	80%
Female	81%	67%	85%	83%
Race				
White	87%	83%	84%	81%
Non-White	75%	73%	84%	80%
Ethnicity				
Hispanic or Latino	88%	81%	83%	84%
Not Hispanic or Latino	82%	79%	85%	79%
NRTI Background Therapy				
FTC/TDF	83%	81%	-	-
ABC/3TC	86%	75%	-	-
Baseline HIV-1 RNA (copies/mL)				
copies/mL	86%	81%	86%	83%
>100,000 copies/mL	77%	74%	77%	72%

CD4+ T-cell Count (cells/mm^3)				
^{3}	81%	66%	66%	78%
>200 cells/mm^3	84%	83%	87%	81%
Viral Subtype				
Subtype B	84%	82%	84%	80%
Subtype Non-B	83%	76%	85%	83%

*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.

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 (FDA Snapshot Approach). 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.

5.2 PHARMACOKINETIC PROPERTIES

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}**	**C_{max}**	**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.

Excretion

Doravirine has a terminal half-life (t1/2) of approximately 15 hours. Doravirine is primarily eliminated via oxidative metabolism. Excretion of unchanged drug via urinary excretion is minor. Biliary excretion of unchanged drug is not expected to be significant.

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 (eGFR 15-<30 mL/min/1.73 m^2) 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 (eGFR 15-<30 mL/min/1.73 m^2) renal impairment. Doravirine has not been studied in patients with end-stage renal disease or in patients undergoing dialysis (see section 4.4).

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 section 4.4).

Paediatric

The pharmacokinetics and dosing recommendations of PIFELTRO in patients younger than 18 years of age have not been established (see section 4.4).

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 section 4.4). The pharmacokinetics of doravirine have been studied in a limited number of subjects (n=4) over 75 years of age (see section 4.4).

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.

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 Cmax, AUC, and C_{24} values of doravirine are summarized in Table 7. The effects of co-administration of doravirine on the C_{max} and AUC values of other drugs are summarized in Table 8 (see section 4.5).

Table 7: 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 (aluminium and magnesium hydroxide oral suspension)	20 mL SD	100 mg SD	14	1.01 (0.92, 1.11)	0.86 (0.74, 1.01)	1.03 (0.94, 1.12)
pantoprazole	40 mg QD	100 mg SD	13	0.83 (0.76, 0.91)	0.88 (0.76, 1.01)	0.84 (0.77, 0.92)
Opioid Analgesics						

methadone	20-200 mg QD individualized dose	100 mg QD	14	0.74 (0.61, 0.90)	0.76 (0.63, 0.91)	0.80 (0.63, 1.03)

CI = Confidence interval; SD = Single Dose; QD = Once Daily; BID = Twice Daily
*$AUC_{0-\infty}$ for single-dose, AUC_{0-24} for once daily.
†Interaction was assessed following the cessation of efavirenz therapy.

Table 8: 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						
ethinylestradiol	0.03 mg ethinylestradiol + 0.15 mg levonorgestrel (Nordette®-28) SD	100 mg QD	19	0.98 (0.94, 1.03)	0.83 (0.80, 0.87)	--
levonorgestrel				1.21 (1.14, 1.28)	0.96 (0.88, 1.05)	--
Statins						
atorvastatin	20 mg SD	100 mg QD	14	0.98 (0.90, 1.06)	0.67 (0.52, 0.85)	-
Antidiabetics						
metformin	1000 mg SD	100 mg QD	14	0.94 (0.88, 1.00)	0.94 (0.86, 1.03)	-
Opioid Analgesics						
methadone (R-methadone)	20-200 mg QD individualized dose	100 mg QD	14	0.95 (0.90, 1.01)	0.98 (0.93, 1.03)	0.95 (0.88, 1.03)
methadone (S-methadone)				0.98 (0.90, 1.06)	0.97 (0.91, 1.04)	0.97 (0.86, 1.10)

CI = Confidence interval; SD = Single Dose; QD = Once Daily.
*$AUC_{0-\infty}$ for single-dose, AUC_{0-24} for once daily.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Doravirine was not genotoxic in a battery of *in vitro* or *in vivo* assays, including microbial mutagenesis, chromosomal aberration in Chinese Hamster Ovary cells, and in *in vivo* rat micronucleus assays.

Carcinogenicity

Long-term oral carcinogenicity studies of doravirine in mice and rats showed no evidence of carcinogenic potential at exposures up to 5 times (mice) and 7 times (rats) the human exposures at the RHD.

Animal Toxicology

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).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet includes the following inactive ingredients: colloidal anhydrous silica, 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.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR 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.

6.5 NATURE AND CONTENTS OF CONTAINER

PIFELTRO (doravirine) is available in HDPE (high density polyethylene) bottles of 30 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

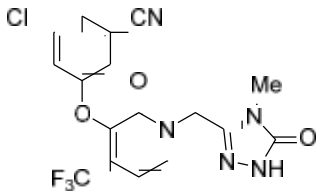
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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.

Chemical structure



CAS number

1338225-97-0.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4).

8 SPONSOR

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9 DATE OF FIRST APPROVAL

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