SCHEDULING STATUS

S4

1 NAME OF THE MEDICINAL PRODUCT

PIFELTRO® 100 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg of doravirine.

Excipient with known effect:

Each film-coated tablet contains 222 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, oval-shaped, tablet of dimensions 19,00 mm x 9,50 mm, 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 adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a medical practioner experienced in the management of HIV infection.

Posology

The recommended dose is one 100 mg tablet taken orally once daily with or without food.

Dose adjustment

If PIFELTRO is co-administered with rifabutin, one 100 mg tablet of PIFELTRO should be taken twice daily (approximately 12 hours apart) (see section 4.5).

Co-administration of doravirine with other moderate CYP3A inducers has not been evaluated, but. decreased doravirine concentrations are expected. If co-administration with other moderate CYP3A inducers (e.g. dabrafenib, lesinurad, bosentan, thioridazine, nafcillin, modafinil, telotristat ethyl) cannot be avoided, one 100 mg tablet of PIFELTRO should be taken twice daily (approximately 12 hours apart).

Missed dose

If the patient misses a dose of PIFELTRO within 12 hours of the time it is usually taken, the patient should take 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.

Special populations

Elderly

No dose adjustment of doravirine is needed in elderly patients (see section 5.2).

Renal impairment

No dose adjustment of doravirine is required in patients with mild, moderate or severe renal impairment. Doravirine has not been studied in patients with end-stage renal disease and has not been studied in dialysis patients (see section 5.2).

Hepatic impairment

No dose adjustment of doravirine is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Doravirine has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). It is not known whether the exposure to doravirine will increase in patients with severe hepatic impairment. Therefore, caution is advised when doravirine is administered to patients with severe hepatic impairment (see section 5.2).

Paediatric population

Safety and efficacy of doravirine have not been established in patients younger than18 years of age. No data are available.

Method of administration

PIFELTRO must be taken orally, once daily with or without food and swallowed whole (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with medicinal products that are strong cytochrome P450 (CYP)3A enzyme inducers is contraindicated as significant decreases in doravirine plasma concentrations are expected to occur, which may decrease the effectiveness of PIFELTRO (see sections 4.4 and 4.5). These medicinal products include, but are not limited, to the following:

- carbamazepine, oxcarbazepine, phenobarbitone, phenytoin
- rifampicin, rifapentine
- St. John's wort (*Hypericum perforatum*)

- mitotane
- enzalutamide
- lumacaftor.

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission of HIV-1, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

NNRTI substitutions and use of doravirine

Doravirine has not been evaluated in patients with previous virologic failure to any other antiretroviral therapy. NNRTI-associated mutations detected at screening were part of exclusion criteria in the Phase 2b/3-studies. A breakpoint for a reduction in susceptibility, yielded by various NNRTI substitutions, that is associated with a reduction in clinical efficacy has not been established (see section 5.1). There is not sufficient clinical evidence to support the use of doravirine in patients infected with HIV-1 with evidence of resistance to the NNRTI class.

Use with CYP3A inducers

Caution should be given to prescribing doravirine with medicinal products that may reduce the exposure of doravirine (see sections 4.3 and 4.5).

Immune reactivation syndrome

Immune reactivation 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 [PJP] 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 reactivation; however, the time to onset is more variable and can occur many months after initiation of treatment.

Lactose

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

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicinal products on doravirine

Doravirine is primarily metabolised by CYP3A and medicinal products that induce or inhibit CYP3A are expected to affect the clearance of doravirine (see section 5.2). Doravirine should not be co-administered with medicinal products that are strong CYP3A enzyme inducers as significant decreases in doravirine plasma concentrations are expected to occur, which may decrease the effectiveness of doravirine (see sections 4.3 and 5.2).

Co-administration with the moderate CYP3A inducer rifabutin decreased doravirine concentrations (see **Table 1**). When doravirine is co-administered with rifabutin, the doravirine dose should be increased to 100 mg twice daily (the doses should be taken approximately 12 hours apart) (see section 4.2).

Co-administration of doravirine with other moderate CYP3A inducers has not been evaluated, but decreased doravirine concentrations are expected. If co-administration with other moderate CYP3A inducers (e.g. dabrafenib, lesinurad, bosentan, thioridazine, nafcillin, modafinil, telotristat ethyl) cannot be avoided, the doravirine dose should be increased to

100 mg twice daily (the doses should be taken approximately 12 hours apart) (see section 4.2).

Co-administration of doravirine and medicinal products that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine. However, no dose adjustment is needed when doravirine is co-administered with CYP3A inhibitors as the plasma levels remain within therapeutically acceptable levels.

Effects of doravirine on other medicinal products

Doravirine at a dose of 100 mg once daily is not likely to have a clinically relevant effect on the plasma concentrations of medicinal products that are dependent on transport proteins for absorption and/or elimination or that are metabolised by CYP enzymes.

However, co-administration of doravirine and the sensitive CYP3A substrate midazolam resulted in a 18 % decrease in midazolam exposure, suggesting that doravirine may be a weak CYP3A inducer. Therefore caution should be used when co-administering doravirine with medicinal products that are sensitive CYP3A substrates that also have a narrow therapeutic window (e.g. tacrolimus and sirolimus).

Interactions table

Table 1 shows the established and other potential medicinal product interactions with doravirine but is not all inclusive (increase is indicated as ↑, decrease is indicated as ↓ and no change as ↔).

Table 1: Interactions of doravirine with other medicinal products

Medicinal Product by Therapeutic Area	Effects on Medicinal Product Levels Geometric Mean Ratio (90 % CI)*	Recommendation Concerning Co-administration with doravirine

Acid-Reducing Medicines		
antacid (aluminium and magnesium hydroxide oral suspension) (20 mL SD, doravirine 100 mg SD)	↔ doravirine AUC 1,01 (0,92, 1,11) C_{max} 0,86 (0,74, 1,01) C_{24hr} 1,03 (0,94, 1,12)	No dose adjustment is required.
pantoprazole (40 mg QD, doravirine 100 mg SD)	↓ doravirine AUC 0,83 (0,76, 0,91) C_{max} 0,88 (0,76, 1,01) C_{24hr} 0,84 (0,77, 0,92)	No dose adjustment is required.
omeprazole	Interaction not studied. Expected: ↔ doravirine	No dose adjustment is required.
Angiotensin Converting Enzyme Inhibitors		
lisinopril	Interaction not studied. Expected: ↔ lisinopril	No dose adjustment is required.
Antiandrogens		
enzalutamide	Interaction not studied. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
Antibiotics		

nafcillin	Interaction not studied. Expected: ↓ doravirine (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).
Anticonvulsants		
carbamazepine oxcarbazepine phenobarbitone phenytoin	Interaction not studied. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
Antidiabetics		
metformin (1 000 mg SD, doravirine 100 mg QD)	↔ metformin AUC 0.94 (0,88, 1,00) C_{max} 0,94 (0,86, 1,03)	No dose adjustment is required.
canagliflozin liraglutide sitagliptin	Interaction not studied. Expected: ↔ canagliflozin ↔ liraglutide ↔ sitagliptin	No dose adjustment is required.
Antidiarrhoeals		

telotristat ethyl	Interaction not studied. Expected: ↓ doravirine (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 Medicines		
lesinurad	Interaction not studied. Expected: ↓ doravirine (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		
Single dose rifampicin (600 mg SD, doravirine 100 mg SD) Multiple dose rifampicin	↔ doravirine AUC 0,91 (0,78, 1,06) C_{max} 1,40 (1,21, 1,63) C_{24hr} 0,90 (0,80, 1,01) ↓ doravirine	Co-administration is contraindicated.

(600 mg QD, doravirine 100 mg SD)	AUC 0,12 (0,10, 0,15) C_{max} 0,43 (0,35, 0,52) C_{24hr} 0,03 (0,02, 0,04) (Induction of CYP3A)	
rifapentine	Interaction not studied. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
rifabutin (300 mg QD, doravirine 100 mg SD)	↓ doravirine AUC 0,50 (0,45, 0,55) C_{max} 0,99 (0,85, 1,15) C_{24hr} 0,32 (0,28, 0,35) (Induction of CYP3A)	If doravirine is co-administered with rifabutin, the doravirine dose should be increased to 100 mg twice daily (approximately 12 hours apart).
Antineoplastics		
mitotane	Interaction not studied. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
Antipsychotics		

thioridazine	Interaction not studied. Expected: ↓ doravirine (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 Medicines		
ketoconazole (400 mg QD, doravirine 100 mg SD)	↑ doravirine AUC 3,06 (2,85, 3,29) C_{max} 1,25 (1,05, 1,49) C_{24hr} 2,75 (2,54, 2,98) (Inhibition of CYP3A)	No dose adjustment is required.
fluconazole itraconazole posaconazole voriconazole	Interaction not studied. Expected: ↑ doravirine (Inhibition of CYP3A4)	No dose adjustment is required.
Calcium Channel Blockers		
diltiazem verapamil	Interaction not studied. Expected: ↑ doravirine (CYP3A inhibition)	No dose adjustment is required.
Cystic Fibrosis Treatment		

lumacaftor	Interaction not studied. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
Endothelin Receptor Antagonists		
bosentan	Interaction not studied. Expected: ↓ doravirine (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).
Hepatitis C Antiviral Medicines		

elbasvir + grazoprevir (50 mg elbasvir QD + 200 mg grazoprevir QD, doravirine 100 mg QD)	↑ doravirine AUC 1,56 (1,45, 1,68) C_{max} 1,41 (1,25, 1,58) C_{24hr} 1,61 (1,45, 1,79) (Inhibition of CYP3A) ↔ elbasvir AUC 0,96 (0,90, 1,02) C_{max} 0,96 (0,91, 1,01) C_{24hr} 0,96 (0,89, 1,04) ↔ grazoprevir AUC 1,07 (0,94, 1,23) C_{max} 1,22 (1,01, 1,47) C_{24hr} 0,90 (0,83, 0,96)	No dose adjustment is required.
ledipasvir + sofosbuvir (90 mg ledipasvir SD + 400 mg sofosbuvir SD, doravirine 100 mg SD)	↑ doravirine AUC 1,15 (1,07, 1,24) C_{max} 1,11 (0,97, 1,27) C_{24hr} 1,24 (1,13, 1,36) ↔ ledipasvir AUC 0,92 (0,80, 1,06) C_{max} 0,91 (0,80, 1,02)	No dose adjustment is required.

	↔ sofosbuvir AUC 1,04 (0,91, 1,18) C_{max} 0,89 (0,79, 1,00) ↔ GS-331007 AUC 1,03 (0,98, 1,09) C_{max} 1,03 (0,97, 1,09)	
sofosbuvir/velpatasvir	Interaction not studied. Expected: ↔ doravirine	No dose adjustment is required.
sofosbuvir	Interaction not studied. Expected: ↔ doravirine	No dose adjustment is required.
daclatasvir	Interaction not studied. Expected: ↔ doravirine	No dose adjustment is required.
ombitasvir/paritaprevir/ritonavir and dasabuvir+/-ritonavir	Interaction not studied. Expected: ↑ doravirine (Inhibition of CYP3A due to ritonavir)	No dose adjustment is required.
dasabuvir	Interaction not studied. Expected: ↔ doravirine	No dose adjustment is required.

glecaprevir, pibrentasvir	Interaction not studied. Expected: ↑ doravirine (inhibition of CYP3A)	No dose adjustment is required.
ribavirin	Interaction not studied. Expected: ↔ doravirine	No dose adjustment is required.
Herbal Supplements		
St John's wort (*Hypericum perforatum*)	Interaction not studied. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
HIV Antiviral Medicines		
Fusion and Entry Inhibitors		
enfuvirtide	Interaction not studied. Expected: ↔ doravirine ↔ enfuvirtide	No dose adjustment is required.
maraviroc	Interaction not studied. Expected: ↔ doravirine ↔ maraviroc	No dose adjustment is required.
Protease Inhibitors		

ritonavir†-boosted PIs (atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, saquinavir, tipranavir)	Interaction not studied. Expected: ↑ doravirine (Inhibition of CYP3A) ↔ boosted PIs	No dose adjustment is required.
cobicistat-boosted PIs (darunavir, atazanavir)	Interaction not studied. Expected: ↑ doravirine (Inhibition of CYP3A) ↔ boosted PIs	No dose adjustment is required.
Integrase Strand Transfer Inhibitors		
dolutegravir (50 mg QD, doravirine 200 mg QD)	↔ doravirine AUC 1,00 (0,89, 1,12) C_{max} 1,06 (0,88, 1,28) C_{24hr} 0,98 (0,88, 1,09) ↑ dolutegravir AUC 1,36 (1,15, 1,62) C_{max} 1,43 (1,20, 1,71) C_{24hr} 1,27 (1,06, 1,53) (Inhibition of BCRP)	No dose adjustment is required.
raltegravir	Interaction not studied. Expected: ↔ doravirine	No dose adjustment is required.

	↔ raltegravir	
ritonavir†-boosted elvitegravir	Interaction not studied. Expected: ↑ doravirine (CYP3A inhibition) ↔ elvitegravir	No dose adjustment is required.
cobicistat-boosted elvitegravir	Interaction not studied. Expected: ↑ doravirine (CYP3A inhibition) ↔ elvitegravir	No dose adjustment is required.
Nucleoside Reverse Transcriptase Inhibitors		
tenofovir disoproxil (245 mg QD, doravirine 100 mg SD)	↔ doravirine AUC 0,95 (0,80,1,12) C_{max} 0,80 (0,64,1,01) C_{24hr} 0,94 (0,78, 1,12)	No dose adjustment is required.
lamivudine + tenofovir disoproxil (300 mg lamivudine SD + 245 mg tenofovir disoproxil SD, doravirine 100 mg SD)	↔ doravirine AUC 0,96 (0,87, 1,06) C_{max} 0,97 (0,88, 1,07) C_{24hr} 0,94 (0,83, 1,06) ↔ lamivudine AUC 0,94 (0,88, 1,00) C_{max} 0,92 (0,81, 1,05)	No dose adjustment is required.

	↔ tenofovir AUC 1,11 (0,97, 1,28) C_{max} 1,17 (0,96, 1,42)	
abacavir	Interaction not studied. Expected: ↔ doravirine ↔ abacavir	No dose adjustment is required.
emtricitabine	Interaction not studied. Expected: ↔ doravirine ↔ emtricitabine	No dose adjustment is required.
tenofovir alafenamide	Interaction not studied. Expected: ↔ doravirine ↔ tenofovir alafenamide	No dose adjustment is required.
Immunosuppressants		
tacrolimus sirolimus	Interaction not studied. Expected: ↔ doravirine ↓ tacrolimus, sirolimus (Induction of CYP3A)	Monitor blood concentrations of tacrolimus and sirolimus as the dose of these agents may need to be adjusted.
Kinase Inhibitors		

dabrafenib	Interaction not studied. Expected: ↓ doravirine (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).
Opioid Analgesics		
methadone 20 to 200 mg QD individualised dose, doravirine 100 mg QD	↓ doravirine AUC 0,74 (0,61, 0,90) C_{max} 0,76 (0,63, 0,91) C_{24hr} 0,80 (0,63, 1,03) ↔ R-methadone AUC 0,95 (0,90, 1,01) C_{max} 0,98 (0,93, 1,03) C_{24hr} 0,95 (0,88, 1,03) ↔ S-methadone AUC 0,98 (0,90, 1,06) C_{max} 0,97 (0,91, 1,04) C_{24hr} 0,97 (0,86, 1,10)	No dose adjustment is required.

buprenorphine naloxone	Interaction not studied. Expected: ↔ buprenorphine ↔ naloxone	No dose adjustment is required.
Oral Contraceptives		
0,03 mg ethinylestradiol/0,15 mg levonorgestrel SD, doravirine 100 mg QD	↔ ethinylestradiol AUC 0,98 (0,94, 1,03) C_{max} 0,83 (0,80, 0,87) ↑ levonorgestrel AUC 1,21 (1,14, 1,28) C_{max} 0,96 (0,88, 1,05)	No dose adjustment is required.
norgestimate/ethinylestradiol	Interaction not studied. Expected: ↔ norgestimate/ethinylestradiol	No dose adjustment is required.
Pharmacokinetic Enhancers		
ritonavir (100 mg BID, doravirine 50 mg SD)	↑ doravirine AUC 3,54 (3,04, 4,11) C_{max} 1,31 (1,17, 1,46) C_{24hr} 2,91 (2,33, 3,62) (Inhibition of CYP3A)	No dose adjustment is required.
cobicistat	Interaction not studied. Expected:	No dose adjustment is required.

	↑ doravirine (Inhibition of CYP3A)	
Psychostimulants		
modafinil	Interaction not studied. Expected: ↓doravirine (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).
Sedatives/Hypnotics		
midazolam (2 mg SD, doravirine120 mg QD)	↓ midazolam AUC 0,82 (0,70, 0,97) C_{max} 1,02 (0,81, 1,28)	No dose adjustment is required.
Statins		
atorvastatin (20 mg SD, doravirine100 mg QD)	↔ atorvastatin AUC 0,98 (0,90, 1,06) C_{max} 0,67 (0,52, 0,85)	No dose adjustment is required.
rosuvastatin simvastatin	Interaction not studied. Expected: ↔ rosuvastatin ↔ simvastatin	No dose adjustment is required.
↑ = increase, ↓ = decrease, ↔ = no change		

CI = Confidence interval; SD = Single Dose; QD = Once Daily; BID = Twice Daily

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

†The interaction was evaluated with ritonavir only.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of doravirine in pregnant women.

Antiretroviral pregnancy registry

To monitor maternal-foetal outcomes in patients exposed to antiretroviral medicinal products while pregnant, an Antiretroviral Pregnancy Registry has been established. Medical Practitioner are encouraged to register patients in this registry.

Animal studies with doravirine do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of doravirine during pregnancy.

Breastfeeding

It is unknown whether doravirine is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of doravirine in milk (see section 5.3).

Because of the potential for HIV-1 transmission and the potential for serious adverse reactions in breastfeeding infants, mothers should be instructed not to breastfeed if they are receiving PIFELTRO.

Fertility

No human data on the effect of doravirine on fertility are available. Animal studies do not indicate harmful effects of doravirine on fertility at exposure levels higher than the exposure in humans at the recommended clinical dose (see section 5.3).

4.7 Effects on ability to drive and use machines

PIFELTRO may have a minor influence on the ability to drive or use machines. Patients should be informed that fatigue, dizziness and somnolence have been reported during treatment with doravirine (see section 4.8). This should be considered when assessing a patient's ability to drive or operate machinery.

4.8 Undesirable effects

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	hypophosphatemia
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 generalised 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 generalised, rash maculo-papular, rash papular and urticarial

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 to SAHPRA via the **6.04 Adverse Drug Reaction Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

There is no information on potential acute symptoms and signs of overdose with doravirine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, ATC code: J05AG06.

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 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 medicinal products

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 disoproxil 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, Y318F. Common NNRTI resistant mutations (K103N, Y181C) were not selected in the *in vitro* study. V106A (yielding a fold change of around 19) appeared

as an initial substitution in subtype B virus, and V106A or M in subtype A and C virus. Subsequently F227(L/C/V) or L234I emerged in addition to V106 substitution (double mutants yielding a fold change of > 100).

In clinical trials

Treatment Naïve adult subjects

The phase 3 studies, DRIVE-FORWARD and DRIVE-AHEAD, included previously untreated patients (n=747) where the following NNRTI substitutions were part of 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.

The following *de novo* resistance was seen in the resistance analysis subset (subjects with HIV-1 RNA > 400 copies per mL at virologic failure or early study discontinuation and having resistance data).

Table 3. Resistance development in protocol defined virologic failure population + early discontinuation population

	DRIVE-FORWARD		**DRIVE-AHEAD**	
	DOR (383) + NRTIs*	**DRV + r (383) + NRTIs***	**DOR/TDF/3TC (364)**	**EFV/TDF/FTC (364)**
Successful genotype, n	9	10	22	23
RAM DOR/control, n	1/9 (DOR)	0/10 (DRV)	6/22 (DOR)	12/23 (EFV)
NRTI mutation, n	1**/9	0/10	6/22	5/23

*NRTIs in DOR arm: FTC/TDF (333) or ABC/3TC (50); NRTIs in DRV + r arm: FTC/TDF (335) or ABC/3TC (48)

**The subject received FTC/TDF

ABC = abacavir; FTC = emtricitabine; DRV = darunavir; r = ritonavir; RAM = resistance associated mutation

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.

Virologically suppressed adult subjects

The DRIVE-SHIFT study included virologically suppressed patients (N=670) with no history of treatment failure (see section, Clinical experience). A documented absence of genotypic resistance (prior to starting first therapy) to doravirine, lamivudine and tenofovir was part of the inclusion criteria for patients who switched from a PI- or INI-based regimen. Exclusionary NNRTI substitutions were those listed above (DRIVE-FORWARD and DRIVE-AHEAD), with the exception of substitutions RT K103N, G190A and Y181C (accepted in DRIVE-SHIFT). Documentation of pre-treatment resistance genotyping was not required for patients who switched from a NNRTI-based regimen.

In the DRIVE-SHIFT clinical trial, no subjects developed genotypic or phenotypic resistance to DOR, 3TC or TDF during the initial 48 weeks (immediate switch, N=447) or 24 weeks (delayed switch, N=209) of treatment with DOR/3TC/TDF. One subject developed RT M184M/I mutation and phenotypic resistance to 3TC and FTC during treatment with their baseline regimen. None of the 24 subjects (11 in the immediate switch group, 13 in the delayed switch group) with baseline NNRTI mutations (RT K103N, G190A or Y181C) experienced virologic failure through Week 48 or at time of discontinuation.

Abacavir, lamivudine, emtricitabine or tenofovir disoproxil

In a pooled analysis of antiretroviral-naïve subjects who received doravirine and other NRTIs (abacavir, lamivudine, emtricitabine or tenofovir disoproxil), genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-1 RNA > 400 copies per mL at confirmed virologic failure, at week 48 or at time of early study drug discontinuation. Genotypic resistance developed in 8 evaluable subjects. The resistance-associated substitutions that emerged were RT M41L (n=1), K65R (n=2) and M184V/I (n=5).

Cross-resistance

Doravirine has been evaluated in a limited number of patients with NNRTI resistance (K103N n=7, G190A n=1); all patients were suppressed to < 40 copies/mL at week 48. A breakpoint for a reduction in susceptibility, yielded by various NNRTI substitutions, that is associated with a reduction in clinical efficacy has not been established.

Laboratory strains of HIV-1 harbouring the common NNRTI-associated mutations K103N, Y181C or K103N/Y181C substitutions in RT exhibit < a 3-fold decrease in susceptibility to doravirine compared to wild-type virus when evaluated in the presence of 100 % normal human serum. In *in vitro* studies, doravirine was able to suppress the following NNRTI-associated substitutions; K103N, Y181C and G190A 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 or V106 substitutions in combination with A98G, H221Y, P225H, F227C or Y318F showed a >100-fold reduced susceptibility to doravirine. Other established NNRTI substitutions yielded a fold change of 5 to 10 (G190S (5,7), K103N/P225H (7,9), V108I/Y181C (6,9), Y181V (5,1)). The clinical relevance of a 5- to 10-fold reduction in susceptibility is unknown.

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

Clinical experience

Treatment-naïve adult subjects

The efficacy of doravirine is based on the analyses of 96-week data from 2 randomised, multicentre, double-blind, active controlled Phase 3 trials, (DRIVE-FORWARD and DRIVE-AHEAD) in antiretroviral treatment-naïve, HIV-1 infected subjects (n=1 494). Refer to Resistance section for NNRTI substitutions that were part of exclusion criteria.

In DRIVE-FORWARD, 766 subjects were randomised and received at least 1 dose of either doravirine 100 mg or darunavir + ritonavir 800+100 mg once daily, each in combination with emtricitabine/tenofovir disoproxil (FTC/TDF) or abacavir/lamivudine (ABC/3TC) selected by the investigator. At baseline, the median age of subjects was 33 years (range 18 to 69 years), 86 % had CD4+ T-cell count > 200 cells per mm^3, 84 % were male, 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 > 100 000 copies per mL, 13 % received ABC/3TC and 87 % received FTC/TDF; these characteristics were similar between treatment groups.

In DRIVE-AHEAD, 728 subjects were randomised and received at least 1 dose of either doravirine/lamivudine/tenofovir disoproxil 100/300/245 mg (DOR/3TC/TDF) or efavirenz/emtricitabine/tenofovir disoproxil (EFV/FTC/TDF) once daily. At baseline, the median age of subjects was 31 years (range 18 to 70 years), 85 % were male, 52 % were non-white, 3 % had hepatitis B or C co-infection, 14 % had a history of AIDS, 21 % had HIV-

1 RNA > 100 000 copies per mL and 12 % had CD4+ T-cell count < 200 cells per mm^3; these characteristics were similar between treatment groups.

Week 48 and 96 outcomes for DRIVE-FORWARD and DRIVE-AHEAD are provided in **Table 4**. The doravirine-based regimens demonstrated consistent efficacy across demographic and baseline prognostic factors.

Table 4: Efficacy response (< 40 copies/mL, Snapshot approach) in the pivotal studies

	DRIVE-FORWARD		**DRIVE-AHEAD**	
	DOR + 2 NRTIs (383)	**DRV+ r + 2 NRTIs (383)**	**DOR/3TC/TDF (364)**	**EFV/FTC/TDF (364)**
Week 48	83 %	79 %	84 %	80 %
Difference (95 % CI)	4,2 % (-1,4 %, 9,7 %)		4,1 % (-1,5 %, 9,7 %)	
Week 96*	72 % (N=379)	64 % (N=376)	76 % (N=364)	73 % (N=364)
Difference (95 % CI)	7,6 % (1,0 %, 14,2 %)		3,3 % (-3,1 %, 9,6 %)	
Week 48 outcome (< 40 copies/mL) by baseline factors				
HIV-1 RNA copies/mL				
≤ 100 000	256/285 (90 %)	248/282 (88 %)	251/277 (91 %)	234/258 (91 %)
> 100 000	63/79 (80 %)	54/72 (75 %)	54/69 (78 %)	56/73 (77 %)
CD4 count, cells/µL				
≤ 200	34/41 (83 %)	43/61 (70 %)	27/42 (64 %)	35/43 (81 %)
> 200	285/323 (88 %)	260/294 (88 %)	278/304 (91 %)	255/288 (89 %)
NRTI background therapy				

TDF/FTC	276/316 (87 %)	267/312 (86 %)	NA	
ABC/3TC	43/48 (90 %)	36/43 (84 %)		
Viral subtype				
B	222/254 (87 %)	219/255 (86 %)	194/222 (87 %)	199/226 (88 %)
non-B	97/110 (88 %)	84/100 (84 %)	109/122 (89 %)	91/105 (87 %)
Mean CD4 change from baseline				
Week 48	193	186	198	188
Week 96	224	207	238	223

*For Week 96, certain subjects with missing HIV-1 RNA were excluded from the analysis.

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

Table 5: Efficacy response at week 24 (FDA Snapshot approach)

	Doravirine 25 mg (N=40) n (%)	**Doravirine 50 mg (N=43) n (%)**	**Doravirine 100 mg (N=42) n (%)**	**Doravirine 200 mg (N=41) n (%)**	**Efavirenz 600 mg (N=42) n (%)**
HIV-1 RNA < 40 copies/mL	32 (80)	32 (74)	30 (71)	33 (80)	27 (64)

Treatment differences[†] (95 % CI)[††]	16 (-4, 34)	10 (-10, 29)	6,6 (-13, 26)	16 (-3, 34)	
Mean CD4 change from baseline (cells/mm^3)[**]	154	113	134	141	121

[†]A positive value favours doravirine over efavirenz.

[††]The 95 % CIs were calculated using Miettinen and Nurminen's method with weights proportional to the size of each stratum (screening HBV-1 RNA > 100 000 copies/mL or ≤ 100 000 copies/mL.

[**]Approach to handle missing data: Observed Failure (OF) approach. Baseline CD4 cell count was carried forward for subjects who discontinued assigned therapy due to lack of efficacy.

Note: Both doravirine and efavirenz were administered with emtricitabine/tenofovir disoproxil (FTC/TDF).

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 DOR/3TC/TDF was evaluated in a randomised, open-label trial (DRIVE-SHIFT), in virologically-suppressed HIV-1 infected adults. Subjects must have been virologically suppressed (HIV-1 RNA < 40 copies/mL) on their baseline regimen for at least 6 months prior to trial entry, with no history of virologic failure, and a documented absence of RT substitutions of relevance for doravirine, lamivudine and tenofovir (see

Resistance section). Subjects were randomised to either switch to DOR/3TC/TDF at baseline [N=447, Immediate Switch Group (ISG)] or stay on their baseline regimen until Week 24, at which point they switched to DOR/3TC/TDF [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 DOR/3TC/TDF 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 < 40 copies/mL. Treatment results are shown in **Table 6**. Consistent results were seen for the comparison at Study Week 24 in each treatment group.

Table 6: Efficacy response (FDA Snapshot approach) in the DRIVE-SHIFT study

Outcome	DOR/3TC/TDF Once Daily ISG Week 48 N=447	Baseline Regimen DSG Week 24 N=223
HIV-1 RNA < 40 copies/mL	90 %	93 %
ISG-DSG, Difference (95 % CI)*	-3.6 % (-8.0 %, 0.9 %)	
Proportion (%) of Subjects With HIV-1 RNA < 40 copies/mL by Baseline Regimen Received		
Ritonavir- or Cobicistat-boosted PI	280/316 (89 %)	145/156 (93 %)
Cobicistat-boosted elvitegravir	23/25 (92 %)	11/12 (92 %)
NNRTI	98/106 (92 %)	52/55 (95 %)
Proportion (%) of Subjects With HIV-1 RNA < 40 copies/mL by Baseline CD4+ T-cell Count (cells/mm^3)		

< 200 cells/mm^3	10/13 (77 %)	3/4 (75 %)
≥ 200 cells/mm^3	384/426 (90 %)	202/216 (94 %)
HIV-1 RNA ≥ 40 copies/mL[†]	3 %	4 %
No Virologic Data Within the Time Window	8 %	3 %
Discontinued study due to AE or Death[‡]	3 %	0
Discontinued study for Other Reasons[§]	4 %	3 %
On study but missing data in window	0	0

[*]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 ≥ 40 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.

Discontinuation due to adverse events

In a pooled analysis combining data from two treatment-naïve trials (P007 and DRIVE-AHEAD), a 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 group (6,1 %) (treatment difference -3,4 %, p-value 0,012).

Paediatric population

The efficacy of PIFELTRO has not been established in patients younger than 18 years of age.

5.2 Pharmacokinetic properties

Absorption

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 was generally achieved by Day 2 of once daily dosing, with accumulation ratios of 1,2 to 1,4 for $AUC_{0\text{-}24hr}$, C_{max} and C_{24hr}. Doravirine steady-state pharmacokinetics following administration of 100 mg once daily to HIV-1 infected subjects, based on a population pharmacokinetics analysis, are provided below.

Parameter GM (% CV)	$AUC_{0\text{-}24hr}$ µM hr	C_{max} µM	C_{24hr} nM
Doravirine 100 mg once daily	37,8 (29)	2,26 (19)	930 (63)
GM: geometric mean, % CV: Geometric coefficient of variation			

Following oral dosing, peak plasma concentrations are achieved 2 hours after dosing. Doravirine has an estimated absolute bioavailability of approximately 64 % for the 100 mg tablet.

Effect of food on oral absorption

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

Distribution

Based on administration of an IV micro-dose, the volume of distribution of doravirine is 60,5 L. Doravirine is approximately 76 % bound to plasma proteins.

Biotransformation

Based on *in vitro* data, doravirine is primarily metabolised by CYP3A.

Elimination

Doravirine has a terminal half-life ($t_{1/2}$) of approximately 15 hours. Doravirine is primarily eliminated via oxidative metabolism mediated by CYP3A4. Biliary excretion of unchanged medicinal product may contribute to the elimination of doravirine, but this elimination route is not expected to be significant. Excretion of unchanged medicinal product via urinary excretion is minor.

Special populations

Renal impairment

Renal excretion of doravirine is minor. In a study comparing 8 subjects with severe renal impairment to 8 subjects without renal impairment, the single dose exposure of doravirine was 31 % higher in subjects with severe renal impairment. In a population pharmacokinetic analysis, which included subjects with CrCl between 17 and 317 mL/min, 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 section 4.2).

Hepatic impairment

Doravirine is primarily metabolised 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 (classified as Child-Pugh score B primarily due to increased encephalopathy and ascites scores) 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 4.2).

Elderly

Although a limited number of subjects aged 65 years and over has been included (n=36), 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. No dose adjustment is required.

Gender

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

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.

5.3 Preclinical safety data

Reproductive toxicity

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 recommended human dose (RHD) with no effects on embryo-foetal (rats and rabbits) or pre/postnatal (rats) development. 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.

Doravirine was excreted into the milk of lactating rats following oral administration, with milk concentrations approximately 1,5 times that of maternal plasma concentrations.

Carcinogenesis

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

Mutagenesis

Doravirine was not genotoxic in a battery of *in vitro* or *in vivo* assays.

Impairment of fertility

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: croscarmellose sodium (E468); hypromellose acetate succinate; lactose monohydrate; magnesium stearate (E470b); microcrystalline cellulose (E460); silica and colloidal anhydrous (E551).

Film-coating: carnauba wax (E903); hypromellose (E464); lactose monohydrate; titanium dioxide (E171) and triacetin (E1518).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C. Store in the original bottle and keep the bottle tightly closed in order to protect from moisture. Do not remove the desiccant.

6.5 Nature and contents of container

Each carton contains a white, high density polyethylene (HDPE) bottle with a white polypropylene child-resistant closure with silica gel desiccant.

The following pack size is available: 1 bottle with 30 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

MSD (Pty) Ltd, 117 16th Road, Halfway House 1685, South Africa

8 MARKETING AUTHORISATION NUMBER

To be advised

9 DATE OF FIRST AUTHORISATION

Date of first authorisation: 25 January 2022

10 DATE OF REVISION OF THE TEXT