200 mm

440 mm

To be sold by retail on the prescription of a Registered Medical Practitioner only.

Doravirine Tablets 100 mg

HOFIX® होफिक्स

1. Generic Name
Doravirine Tablets 100 mg

2. Qualitative and quantitative composition
Each film coated tablet contains:
Doravirine 100 mg
Excipients q.s.
Colour: Titanium Dioxide IP

3. Dosage form and strength
Film coated tablet
Each film coated tablet contains Doravirine 100 mg

4. Clinical particulars

4.1 Therapeutic indication
Doravirine is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg with no prior antiretroviral treatment history only (treatment naive).

4.2 Posology and method of administration
Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology
The recommended dosage regimen of Doravirine in adults and pediatric patients (12 to 18 years) weighing at least 35 kg is one 100 mg tablet taken orally once daily with or without food.

Dose adjustment
If Doravirine is co-administered with rifabutin, one 100 mg tablet of Doravirine should be taken twice daily (approximately 12 hours apart).

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 Doravirine should be taken twice daily (approximately 12 hours apart).

Missed dose
If the patient misses a dose of Doravirine 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.

Method of administration
For oral use.
Doravirine must be taken orally, once daily with or without food and swallowed whole.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

Co-administration with medicinal products that are strong cytochrome P450 CYP3A enzyme inducers is contraindicated as significant decreases in Doravirine plasma concentrations are expected to occur, which may decrease the effectiveness of Doravirine. These medicinal products include, but are not limited, to the following:
- carbamazepine, oxcarbazepine, phenobarbital, 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 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. 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.

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 [PCP], or tuberculosis), which may necessitate further evaluation and treatment.
Autoimmune disorders (such as Graves' disease, autoimmune hepatitis, 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 this medicine.

4.5 Drugs interactions
Effects of other medicinal products on doravirine
Doravirine is primarily metabolised by CYP3A, and medicinal products that induce or inhibit CYP3A are expected to af ect the clearance of doravirine. 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.
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).
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).
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.

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 metabolized 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 Agents		
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) C24 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) C24 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 phenobarbital phenytoin	Interaction not studied. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
Antidiabetics		
metformin (1000 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 Agents		
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)	↔ doravirine AUC 0.91 (0.78, 1.06) C_{max} 1.40 (1.21, 1.63) C_{24} 0.90 (0.80, 1.01)	Co-administration is contraindicated.
Multiple dose rifampicin (600 mg QD, doravirine 100 mg SD)	↓ doravirine AUC 0.12 (0.10, 0.15) C_{max} 0.43 (0.35, 0.52) C_{24} 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_{24} 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 Agents		
ketoconazole (400 mg QD, doravirine 100 mg SD)	↑ doravirine AUC 3.06 (2.85, 3.29) Cmax 1.25 (1.05, 1.49) C24 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 Agents		
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_{24} 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_{24} 0.96 (0.89, 1.04) ↔ grazoprevir AUC 1.07 (0.94, 1.23) C_{max} 1.22 (1.01, 1.47) C_{24} 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_{24} 1.24 (1.13, 1.36) ↔ ledipasvir AUC 0.92 (0.80, 1.06) C_{max} 0.91 (0.80, 1.02) ↔ 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)	No dose adjustment is required.
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 Agents		
Fusion and Entry Inhibitors		
enfuvirtide	Interaction not studied. Expected: ↔ doravirine ↔ enfuviritide	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_{24} 0.98 (0.88, 1.09) ↑ dolutegravir AUC 1.36 (1.15, 1.62) C_{max} 1.43 (1.20, 1.71) C_{24} 1.27 (1.06, 1.53) (Inhibition of BCRP)	No dose adjustment is required. No dose adjustment is required.
raltegravir	Interaction not studied. Expected: ↔ doravirine ↔ raltegravir	No dose adjustment is required.
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) Cmax 0.80 (0.64, 1.01) C24 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) Cmax 0.97 (0.88, 1.07) C24 0.94 (0.83, 1.06) ↔ lamivudine AUC 0.94 (0.88, 1.00) Cmax 0.92 (0.81, 1.05) ↔ tenofovir AUC 1.11 (0.97, 1.28) Cmax 1.17 (0.96, 1.42)	No dose adjustment is required.
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 20-200 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_{24} 0.80 (0.63, 1.03) ↔ R-methadone AUC 0.95 (0.90, 1.01) C_{max} 0.98 (0.93, 1.03) C_{24} 0.95 (0.88, 1.03) ↔ S-methadone AUC 0.98 (0.90, 1.06) C_{max} 0.97 (0.91, 1.04) C_{24} 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 ethinyl oestradiol/ 0.15 mg levonorgestrel SD, doravirine 100 mg QD	↔ ethinyl oestradiol 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/ethinyl oestradiol	Interaction not studied. Expected: ↔ norgestimate/ethinyl oestradiol	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_{24} 2.91 (2.33, 3.62) (Inhibition of CYP3A)	No dose adjustment is required.
cobicistat	Interaction not studied. Expected: ↑ doravirine (Inhibition of CYP3A)	No dose adjustment is required.
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, doravirine 120 mg QD)	↓ midazolam AUC 0.82 (0.70, 0.97) Cmax 1.02 (0.81, 1.28)	No dose adjustment is required.
Statins		
atorvastatin (20 mg SD, doravirine 100 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
*AUC0-∞ for single dose, AUC0-24 for once daily.
†The interaction was evaluated with ritonavir only.

YUVI 2525

Front

Generic Name Font Size : 24 pt.
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Product	Hofix	**New / Revised A/W**	New A/W	**FDA Lic. Availability**	Awaited
Dosage form	Tablet	**Colour Scheme**	Black	**Proof 1**	23.12.2024
Therapeutic Category	ARV	**Pantone Shades**	N.A.	**Corrections of Proof 1**	Editorial changes
Item	Pack Insert A/W	**Total No. of Colours**	1	**Proof 2**	26.12.2024
Dimension	L. 200 x H. 440 mm (Folded 74 x 50 mm)	**Special Effect (if any)**	N.A.	**Corrections of Proof 2**	Editorial changes
Substrate	Bible paper	**Item Code**	514445714IN01	**Proof 3**	02.01.2025
Specification	40 GSM	**Marketing Division**	Nucron	**Corrections of Proof 3**	Editorial changes
Printing Area	B/B	**Design / Colour Approved on**	At the time of launching	**Final**	02.05.2025
Item Style	N.A.	**Country**	Domestic	**A/W Checked by**	PMD Cell
A/W Proportion	Same Size			**A/W Verified by**	Production / QC
Product Status	Emcure own Jammu Unit			**A/W Approved by**	Unit Head
Remark (If any) : New artwork for Emcure to be launched at Jammu unit					

Proof 4	04.02.2025
Proof 5	07.04.2025
Proof 6	08.04.2025
Proof 7	14.04.2025
Proof 8	17.04.2025

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4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

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

Animal studies with doravirine do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of doravirine during pregnancy.

Breast-feeding

It is unknown whether doravirine is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of doravirine in milk. Because of the potential for HIV-1 transmission and the potential for serious adverse reactions in breast-feeding infants, mothers should be instructed not to breast-feed if they are receiving Doravirine.

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.

Elderly

No dose adjustment of Doravirine is needed in elderly patients.

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.

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.

Paediatric population

The safety and efficacy of Doravirine for the treatment of HIV-1 infection have been established in pediatric patients (12 to 18 years) weighing at least 35 kg.

Use of Doravirine in this group is supported by evidence from adequate and well controlled trials in adults and an open-label trial in virologically-suppressed or treatment naïve pediatric subjects 12 to less than 18 years of age. The safety, efficacy, and exposure of doravirine in these pediatric subjects were similar to that in adults.

Safety and efficacy of Doravirine in pediatric patients weighing less than 35 kg have notbeen established.

4.7 Effects on ability to drive and use machines

Doravirine 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. This should be considered when assessing a patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of safety profile

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

Tabulated list 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 ef ects 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 pain4, 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 Disorder 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

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Adverse Reactions in Pediatric Participants

The safety of doravirine as a component of FDC of Doravirine/lamivudine/tenofovir disoproxil fumarate was evaluated in 45 virologically-suppressed or treatment-naïve pediatric participants 12 to less than 18 years of age living with HIV through 48 weeks in an open-label trial (IMPAACT 2014 (Protocol 027)). The safety profile in pediatric participants was similar to that in adults.

Postmarketing Experience

The following adverse reactions have been identified during postmarketing experience in patients receiving doravirine-containing regimens. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN).

4.9 Overdose

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

5. Pharmacological properties

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

5.1 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.

5.2 Pharmacodynamic properties

Antiviral activity in cell culture

Doravirine exhibited an EC50 value of 12.0±4.4 nM against wild-type laboratory strains of HIV-1 when tested in the presence of 100 % normal human serum using MT4-GFP reporter cells. Doravirine demonstrated antiviral activity against a broad panel of primary HIV-1 isolates (A, A1, AE, AG, B, BF, C, D, G, H) with EC50 values ranging from 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, and 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 greater than 400 copies per mL at virologic failure or early study discontinuation and having resistance data).

Table 3 Resistance development up to week 96 in protocol defined virologic failure population + early discontinuation population

	DRIVE-FORWARD		DRIVE-AHEAD	
	DOR + NRTIs* (383)	DRV + r + NRTIs* (383)	DOR/TDF/3TC (364)	EFV/TDF/FTC (364)
Successful genotype, n	15	18	32	33
Genotypic resistance to				
DOR or control (DRV or EFV)	2 (DOR)	0 (DRV)	8 (DOR)	14 (EFV)
NRTI backbone	2**	0	6	5
M184I/V only	2	0	4	4
K65R only	0	0	1	0
K65R + M184I/V	0	0	1	1

*NRTIs in DOR arm: FTC/TDF (333) or ABC/3TC (50); NRTIs in DRV+r arm: FTC/TDF (335) or ABC/3TC (48)
**Subjects received FTC/TDF
ABC=abacavir; FTC=emtricitabine; DRV=darunavir; r=ritonavir

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

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 less than 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 greater than 100-fold reduced susceptibility to doravirine. Other established NNRTI substitutions yielded a fold change of 5-10 (G190S (5.7), K103N/P225H (7.9), V108I/Y181C (6.9), Y181V (5.1)). The clinical relevance of a 5-10 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 two randomised, multicentre, double-blind, active controlled Phase 3 trials, (DRIVE-FORWARD and DRIVE-AHEAD) in antiretroviral treatment-naïve, HIV-1 infected subjects (n = 1494). 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 greater than 200 cells per mm3, 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 greater than 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 randomized 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 18-70 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 mm3; 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 randomized to receive one of 4 doses of doravirine or EFV, each in combination with FTC/TDF. After week 24, all subjects randomized to receive doravirine were switched to (or maintained on) doravirine 100 mg. Additional subjects were randomized 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 (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 dif erences † (95 % CI) ††	16 (-4, 34)	10 (-10, 29)	6.6 (-13, 26)	16 (-3, 34)	
Mean CD4 change from baseline (cells/mm³) **	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 ofeach 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).

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 dif erence -3.4 %, p-value 0.012).

5.3 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 AUC0-24, Cmax, and C24. 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)	$AUC_{0\text{-}24}$ (mcg•h/mL)	C_{max} (mcg/mL)	C_{24} (mcg/mL)
Doravirine 100 mg once daily	16.1 (29)	0.962 (19)	0.396 (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 C24, respectively, while Cmax was not significantly affected.

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.

Biotransformation

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

Elimination

Doravirine has a terminal half-life (t1/2) 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.

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.

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 (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).

Paediatric population

Mean doravirine exposures were similar in 54 pediatric participants aged 12 to less than 18 years and weighing at least 35 kg who received doravirine or FDC of Doravirine/lamivudine/tenofovir disoproxil fumarate in IMPAACT 2014 (Protocol 027) relative to adults following administration of doravirine or FDC of Doravirine/lamivudine/tenofovir disoproxil fumarate (Below Table). For pediatric participants weighing ≥ 35 kg and < 45 kg who received doravirine 100 mg or FDC of Doravirine/lamivudine/tenofovir disoproxil fumarate, the population pharmacokinetic model-predicted mean C24 of doravirine was comparable to that achieved in adults, whereas mean AUC0-24 and Cmax of doravirine were 25% and 36% higher than adult values, respectively. However, the predicted AUC0-24 and Cmax increases are not considered clinically significant.

Table: Steady State Pharmacokinetics for Doravirine Following Administration of Doravirine or FDC of Doravirine/lamivudine/tenofovir disoproxil fumarate in Pediatric Participants Living with HIV Aged 12 to Less than 18 Years and Weighing at Least 35 kg

Parameter*	**Doravirine†**
$AUC_{0\text{-}24}$ (mcg•h/mL)	16.4 (24)
C_{max} (mcg/mL)	1.03 (16)
C_{24} (mcg/mL)	0.379 (42)

*Presented as geometric mean (%CV: geometric coefficient of variation)
† From population PK analysis (n=53 weighing ≥45 kg, n=1 weighing ≥35 kg to <45 kg)
Abbreviations: AUC=area under the time concentration curve; C_{max}=maximum concentration; C_{24}=concentration at 24 hours

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.

6. Nonclinical properties

6.1 General Toxicity

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.

6.2 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.

6.3 Mutagenesis

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

6.4 Impairment of Fertility

There were no effect 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.

7. Description

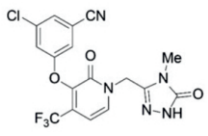
Doravirine is a film-coated tablet containing doravirine for oral administration. Doravirine is an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI). Each tablet contains 100 mg of doravirine as the active ingredient. The tablets include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film coated with a coating material containing the following inactive ingredients: HPMC 2910/hypromellose, titanium dioxide, and macrogol/PEG.

Doravirine is practically insoluble in water.

The chemical name for doravirine is 3-chloro-5-[[1-[(4,5-dihydro-4-methyl-5-oxo-1H1,2,4-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:



8. Pharmaceutical particulars

8.1 Incompatibilities

No any incompatibilities reported.

8.2 Shelf-life

Refer on the pack

8.3 Packaging information

HDPE bottle

8.4 Storage and handing instructions

Store protected from moisture, at a temperature not exceeding 30°C.

Keep out of reach of children.

9. Patient Counseling Information

Drug Interactions

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

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

Immune Reconstitution Syndrome

Inform patients that in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection [see Special Warnings and Precautions for Use].

Dosing Instructions

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

Lactation

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

10. Details of manufacturer

Emcure Pharmaceuticals Ltd.
Lane No. 3, Phase-II, SIDCO, Bari-Brahmana, Jammu - 181 133, India.

11. Details of permission or licence number with date

JK/01/08-09/155, 02/04/2025

12. Date of revision

NA

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Date of issue : May 2025
514445714IN01

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