ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 (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, and adolescents aged 12 years and older weighing at least 35 kg infected with human immunodeficiency virus type 1 (HIV-1) without past or present evidence of resistance to the non-nucleoside reverse transcriptase inhibitors (NNRTI) class (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician 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 required 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 Pifeltro in children aged less than 12 years or weighing less than 35 kg have not been established. 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 CYP3A 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, phenobarbital, phenytoin
- rifampicin, rifapentine
- St. John's wort (*Hypericum perforatum*)
- mitotane
- enzalutamide
- lumacaftor

4.4 Special warnings and precautions for use

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.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), have been reported during the postmarketing experience with doravirine-containing regimens (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of

these reactions appear, doravirine-containing regimens should be withdrawn immediately and an alternative treatment considered (as appropriate). Clinical status should be closely monitored, and appropriate therapy should be initiated. If the patient has developed a serious reaction such as TEN, with the use of doravirine-containing regimens, treatment with doravirine-containing regimens must not be restarted in this patient at any time.

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 [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 medicinal product.

4.5 Interaction with other medicinal products 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.

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 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) C_{24} 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_{24} 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).

Medicinal product by therapeutic area	Effects on medicinal product levels geometric mean ratio (90 % CI)*	Recommendation concerning co-administration with doravirine
Anticonvulsants		
carbamazepine oxcarbazepine phenobarbital 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 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) Multiple dose rifampicin (600 mg QD, 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) ↓ 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)	Co-administration is contraindicated.
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).

Medicinal product by therapeutic area	Effects on medicinal product levels geometric mean ratio (90 % CI)*	Recommendation concerning co-administration with doravirine
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) C_{max} 1.25 (1.05, 1.49) C_{24} 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).

Medicinal product by therapeutic area	Effects on medicinal product levels geometric mean ratio (90 % CI)*	Recommendation concerning co-administration with doravirine
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.

Medicinal product by therapeutic area	Effects on medicinal product levels geometric mean ratio (90 % CI)*	Recommendation concerning co-administration with doravirine
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.

Medicinal product by therapeutic area	Effects on medicinal product levels geometric mean ratio (90 % CI)*	Recommendation concerning co-administration with doravirine
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.
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 (NRTI)		
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_{24} 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_{24} 0.94 (0.83, 1.06) ↔ lamivudine AUC 0.94 (0.88, 1.00) C_{max} 0.92 (0.81, 1.05) ↔ tenofovir AUC 1.11 (0.97, 1.28) C_{max} 1.17 (0.96, 1.42)	No dose adjustment is required.
abacavir	Interaction not studied. Expected: ↔ doravirine ↔ abacavir	No dose adjustment is required.

Medicinal product by therapeutic area	Effects on medicinal product levels geometric mean ratio (90 % CI)*	Recommendation concerning co-administration with doravirine
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.

Medicinal product by therapeutic area	Effects on medicinal product levels geometric mean ratio (90 % CI)*	Recommendation concerning co-administration with doravirine
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) C_{max} 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 *$AUC_{0-\infty}$ for single dose, AUC_{0-24} 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. Physicians 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.

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 (see section 5.3).

It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

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 has a minor influence on the ability to drive and 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

In phase 3 clinical trials with doravirine plus 2 nucleoside reverse transcriptase inhibitors (NRTIs), the most frequently reported adverse reactions were nausea (4 %) and headache (3 %).

Tabulated summary of adverse reactions

The adverse reactions with doravirine plus 2 NRTIs from Phase 3 clinical trials (DRIVE FORWARD, DRIVE SHIFT and DRIVE AHEAD) and postmarketing experience 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), rare (≥ 1/10 000 to < 1/1 000), or not known (cannot be estimated from the available data).

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	

Frequency	Adverse reactions
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
Not known	toxic epidermal necrolysis
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

Description of selected adverse reactions

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 (see section 4.4).

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs), such as toxic epidermal necrolysis (TEN), have been reported in association with doravirine-containing treatment regimens (see section 4.4).

Paediatric population

The safety of doravirine as a component of doravirine/lamivudine/tenofovir disoproxil was evaluated in 45 HIV-1 infected virologically suppressed or treatment-naïve paediatric patients 12 to less than 18 years of age through Week 48 in an open-label trial (IMPAACT 2014 (Protocol 027)). The safety profile in paediatric subjects was similar to that in adults.

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 via the national reporting system listed in Appendix V.

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, F227I, F227V, H221Y, M230I, L234I, P236L, and Y318F. The V106A, V106M, V108I, H221Y, F227C, M230I, P236L, and Y318F

substitutions conferred 3.4-fold to 70-fold reductions in susceptibility to doravirine. Y318F in combination with V106A, V106M, V108I, or F227C conferred greater decreases in susceptibility to doravirine than Y318F alone, which conferred a 10-fold reduction in susceptibility to doravirine. 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 substitutions (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 at 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.

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.

Paediatric subjects
In the IMPAACT 2014 (Protocol 027) clinical trial, no subject who was virologically suppressed at baseline met the criteria for resistance analysis. One treatment-naïve subject who met the protocol-defined virologic failure criteria (defined as 2 consecutive plasma HIV-1 RNA test results ≥200 copies/mL at or after Week 24) was evaluated for the development of resistance; no emergence of genotypic or phenotypic resistance to doravirine was detected.

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 8 subjects who developed high level doravirine resistance in the pivotal studies, 6 had phenotypic resistance to EFV and nevirapine, 3 to rilpivirine, and 3 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 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 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 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 18-70 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 (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 conferring resistance to doravirine, lamivudine and tenofovir (see section, Resistance). 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 (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 treatment 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 treatment, 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 doravirine was evaluated in combination with lamivudine and tenofovir disoproxil (DOR/3TC/TDF) in an open-label, single-arm trial in HIV-1 infected paediatric patients 12 to less than 18 years of age (IMPAACT 2014 (Protocol 027)).

At baseline, the median age of subjects was 15 years (range: 12 to 17), 58% were female, 78% were Asian and 22% were Black, and the median CD4+ T-cell count was 713 cells per mm^3 (range: 84 to 1,397). After switching to DOR/3TC/TDF, 95% (41/43) of virologically suppressed subjects remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 24 and 93% (40/43) remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48.

The European Medicines Agency has deferred the obligation to submit the results of studies with doravirine in one or more subsets of the paediatric population in treatment of human immunodeficiency virus-1 (HIV-1) infection. See section 4.2 for information on paediatric use.

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

Parameter GM (% CV)	AUC_{0-24} µg•h/mL	C_{max} µg/mL	C_{24} µg/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 $C_{24,}$ respectively, while C_{max} was not significantly affected.

Distribution

Based on administration of an intravenous 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 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.

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).

Paediatric population

Mean doravirine exposures were similar in 54 paediatric patients aged 12 to less than 18 years and weighing at least 35 kg who received doravirine or doravirine/lamivudine/tenofovir disoproxil in IMPAACT 2014 (Protocol 027) relative to adults following administration of doravirine or doravirine/lamivudine/tenofovir disoproxil (Table 7).

Table 7: Steady state pharmacokinetics for doravirine following administration of doravirine or doravirine/lamivudine/tenofovir disoproxil in HIV infected paediatric patients aged 12 to less than 18 years and weighing at least 35 kg

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

*Presented as geometric mean (%CV: geometric coefficient of variation)
†From population PK analysis (n=54)
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.

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, colloidal anhydrous (E551)

Film-coating

Carnauba wax (E903)
Hypromellose (E464)
Lactose monohydrate
Titanium dioxide (E171)
Triacetin (E1518)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months
After first opening of the bottle use within 35 days.

6.4 Special precautions for storage

Store in the original bottle and keep the bottle tightly closed in order to protect from moisture. Do not remove the desiccant. This medicinal product does not require any special temperature storage conditions. For storage conditions after first opening of the bottle see section 6.3.

6.5 Nature and contents of container

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

The following pack sizes are available:
- 1 bottle with 30 film-coated tablets.
- 90 film-coated tablets (3 bottles of 30 film-coated tablets).

Not all pack sizes may be marketed.

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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1332/001
EU/1/18/1332/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2018
Date of latest renewal: 07 July 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release
Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
NETHERLANDS

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Pifeltro 100 mg film-coated tablets
doravirine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg of doravirine.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets
90 (3 bottles of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use. Swallow whole.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1332/001
EU/1/18/1332/002 90 (3 x 30) tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pifeltro

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle label

1. NAME OF THE MEDICINAL PRODUCT

Pifeltro 100 mg film-coated tablets
doravirine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg of doravirine.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Swallow whole.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1332/001
EU/1/18/1332/002 90 (3 x 30) tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Pifeltro 100 mg film-coated tablets
doravirine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pifeltro is and what it is used for

What Pifeltro is
Pifeltro is used to treat HIV ('human immunodeficiency virus') infection. It belongs to a group of medicines called 'antiretroviral medicines'.

Pifeltro contains the active substance doravirine - a non-nucleoside reverse transcriptase inhibitor (NNRTI).

What Pifeltro is used for
Pifeltro is used to treat HIV infection in adults, and adolescents aged 12 years and older weighing at least 35 kg. HIV is the virus that causes AIDS ('acquired immune deficiency syndrome'). You should not take Pifeltro if your doctor has told you that the virus causing your infection is resistant to doravirine.

Pifeltro must be used in combination with other medicines for HIV.

How Pifeltro works
When used with other medicines, Pifeltro works by preventing HIV from making more viruses in your body. This will help by:
- reducing the amount of HIV in your blood (this is called your 'viral load')
- increasing the number of white blood cells called '$CD4^+$ T'. This can make your immune system stronger. This may reduce your risk of early death or catching infections because your immune system is weak.

2. What you need to know before you take Pifeltro

Do not take Pifeltro
- if you are allergic to doravirine or any of the other ingredients of this medicine listed in section 6.
- if you are taking the following medicines:
  - carbamazepine, oxcarbazepine, phenobarbital, phenytoin (medicines for seizures)
  - rifampicin, rifapentine (medicines for tuberculosis)
  - St. John's wort (*Hypericum perforatum*, a herbal remedy used for depression and anxiety) or products that contain it
  - mitotane (a medicine to treat cancer)
  - enzalutamide (a medicine to treat prostate cancer)
  - lumacaftor (a medicine to treat cystic fibrosis)

Do not take Pifeltro if the above applies to you. If you are not sure, talk to your doctor, pharmacist, or nurse before taking Pifeltro. See also "Other Medicines and Pifeltro" section.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before taking Pifeltro.

Severe skin reactions
Severe skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis, have been reported in association with Pifeltro treatment. Stop using Pifeltro and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

Immune reactivation syndrome
This can happen when you start taking any HIV medicine, including this medicine. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your doctor right away if you start having any new symptoms after starting your HIV medicine.

Autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Children and adolescents
Do not give this medicine to children aged less than 12 years or weighing less than 35 kg. The use of Pifeltro in children aged less than 12 years or weighing less than 35 kg has not yet been studied.

Other medicines and Pifeltro
Tell your doctor, pharmacist, or nurse if you are taking, have recently taken or might take any other medicines. This is because other medicines may affect how Pifeltro works, and Pifeltro might affect the way some other medicines work.

There are some medicines you must not take with Pifeltro. See list under "Do not take Pifeltro" section.

Talk to your doctor before taking the following medicines with Pifeltro, as your doctor may need to change the dose of your medicines:
- bosentan (a medicine to treat lung disease)
- dabrafenib (a medicine to treat skin cancer)
- lesinurad (a medicine to treat gout)

- modafinil (a medicine to treat excessive sleepiness)
- nafcillin (a medicine to treat some bacterial infections)
- rifabutin (a medicine to treat some bacterial infections such as tuberculosis)
- telotristat ethyl (a medicine to treat diarrhoea in people with carcinoid syndrome)
- thioridazine (a medicine to treat psychiatric conditions such as schizophrenia)

If your doctor decides you should take these medicines with Pifeltro, one tablet of doravirine should be taken twice daily (approximately 12 hours apart).

Your doctor may check your blood levels or monitor for side effects if you take the following medicines with Pifeltro:
- sirolimus (a medicine used to control your body's immune response after a transplant)
- tacrolimus (a medicine used to control your body's immune response after a transplant)

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, talk to your doctor about the risks and benefits of taking Pifeltro. It is preferable to avoid the use of this medicine during pregnancy. This is because it has not been studied in pregnancy and it is not known if it will harm your baby while you are pregnant.

Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk.

If you are breast-feeding, or thinking about breast-feeding, you should discuss it with your doctor as soon as possible.

Driving and using machines
Use caution when driving, riding a bicycle, or operating machines if you feel tired, dizzy, or sleepy after taking this medicine.

Pifeltro tablets contain lactose
If you have been told by your doctor that you have an intolerance to lactose, talk to your doctor before taking this medicine.

3. How to take Pifeltro

Always take this medicine exactly as your doctor, pharmacist, or nurse has told you. Check with your doctor, pharmacist, or nurse if you are not sure. This medicine must be used in combination with other medicines for HIV.

How much to take
The recommended dose is 1 tablet once a day. If you take certain medicines, your doctor may need to change the amount of doravirine you take. See "Other medicines and Pifeltro" section for a list of medicines.

Taking this medicine
- Swallow the tablet whole (do not crush or chew).
- This medicine can be taken with food or between meals.

If you take more Pifeltro than you should
Do not take more than the recommended dose. If you accidentally take more, contact your doctor.

If you forget to take Pifeltro
- It is important that you do not miss or skip doses of this medicine.

- If you forget to take a dose, take it as soon as you remember. But if your next dose is due within 12 hours, skip the dose you missed and take the next one at the usual time. Then continue your treatment as before.
- Do not take a double dose to make up for a missed dose.
- If you are not sure what to do, call your doctor or pharmacist.

If you stop taking Pifeltro
Do not run out of this medicine. Refill your prescription or talk to your doctor before it is all gone.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Do not stop taking this medicine without first talking to your doctor.

Stop using Pifeltro and seek medical attention immediately if you notice any of the following symptoms: reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome/toxic epidermal necrolysis). The frequency of these reactions cannot be estimated from the available data.

Other side effects that may occur

Common: may affect up to 1 in 10 people:
- abnormal dreams, difficulty in sleeping (insomnia)
- headache, dizziness, sleepiness
- feeling sick (nausea), diarrhoea, stomach pain, vomiting, wind (flatulence)
- rash
- feeling tired

Blood tests may also show:
- increased levels of liver enzymes (ALT)

Uncommon: may affect up to 1 in 100 people:
- nightmares, depression, anxiety, irritability, confusion, suicidal thoughts
- trouble concentrating, memory problems, tingling of hands and feet, stiff muscles, poor quality sleep
- high blood pressure
- constipation, stomach discomfort, swollen or bloated stomach (abdominal distension), indigestion, soft stools, stomach spasms
- itchiness
- muscle pain, joint pain
- feeling weak, general feeling of being unwell

Blood tests may also show:
- decreased levels of phosphate
- increased levels of liver enzymes (AST)
- increased levels of lipase
- increased levels of amylase
- decreased levels of haemoglobin

Rare: may affect up to 1 in 1 000 people:
- aggression, hallucinations, difficulty adjusting to changes, mood changes, sleep walking
- difficulty breathing, enlarged tonsils

- feeling of incomplete defecation
- inflammation of the skin due to allergy, redness on the cheeks, nose, chin or forehead, bumps or pimples on the face
- kidney damage, kidney problems, kidney stones
- pain in the chest, feeling cold, pain, thirst

Blood tests may also show:
- decreased levels of magnesium
- increased levels of creatine phosphokinase

Reporting of side effects
If you get any side effects, talk to your doctor,pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Pifeltro

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the bottle after EXP. This medicine should be used within 35 days after first opening of the bottle.
- The bottle contains a desiccant protecting the tablets from moisture. Keep the desiccant inside the bottle and do not throw away until you have finished taking all of the medicine.
- Keep the bottle tightly closed in order to protect from moisture.
- This medicinal product does not require any special temperature storage conditions.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pifeltro contains
- The active substance is doravirine 100 mg.
- The other ingredients are croscarmellose sodium E468; hypromellose acetate succinate; lactose monohydrate; magnesium stearate E470b; microcrystalline cellulose E460; and silica, colloidal anhydrous E551. The tablets are film-coated with a coating material containing the following ingredients: carnauba wax E903; hypromellose E464; lactose monohydrate; titanium dioxide E171; and triacetin E1518.

What Pifeltro looks like and contents of the pack
Pifeltro is available as a white, oval-shaped, film-coated tablet, and is debossed with the corporate logo and 700 on one side and plain on the other side.

The following pack sizes are available:
- 1 bottle with 30 film-coated tablets
- 90 film-coated tablets (3 bottles of 30 film-coated tablets)

Not all pack sizes may be available in your country.

Marketing Authorisation Holder and Manufacturer
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.