Applicant: MSD (Pty) Ltd
APPROVED PROFESSIONAL INFORMATION
DELSTRIGO 100 mg/300 mg/245 mg Film-coated Tablets

SCHEDULING STATUS

S4

1 NAME OF THE PRODUCT

DELSTRIGO® 100 mg/300 mg/245 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg of doravirine, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil.

Excipient with known effect:

Each film-coated tablet contains 8,6 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, oval-shaped, tablet of dimensions 21,59 mm x 11,30 mm, debossed with the corporate logo and 776 on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DELSTRIGO is indicated for the treatment of adults, and adolescents aged 12 years and older weighing at least 35 kg infected with HIV-1 without past or present evidence of resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, lamivudine or tenofovir (see sections 4.4 and 5.1).

4.2 Posology and method of administration

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

Posology

The recommended dose of DELSTRIGO is one 100/300/245 mg tablet taken orally once daily with or without food.

Dose adjustment

If DELSTRIGO is co-administered with rifabutin, the doravirine dose should be increased to 100 mg twice daily. This is achieved by adding one 100 mg tablet of doravirine (as a single agent), to be taken approximately 12 hours apart from the dose of DELSTRIGO (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 doravirine should be taken daily, approximately 12 hours after the dose of DELSTRIGO (see section 4.5).

Missed dose

If the patient misses a dose of DELSTRIGO within 12 hours of the time it is usually taken, the patient should take DELSTRIGO as soon as possible and resume the normal dosing schedule. If a patient misses a dose of DELSTRIGO 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

There are limited data available on the use of doravirine, lamivudine and tenofovir disoproxil in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2). Special care is advised in this age group due to age associated changes such as decreases in renal function (see section 4.4).

Renal impairment

No dose adjustment of DELSTRIGO is required in adults with estimated creatinine clearance (CrCl) ≥ 50 mL/min.

DELSTRIGO should not be initiated in patients with estimated CrCl < 50 mL/min (see sections 4.4 and 5.2). DELSTRIGO should be discontinued if estimated CrCl declines below 50 mL per minute (see section 4.4). Patients with moderate or severe renal impairment require a dose interval adjustment of lamivudine and tenofovir disoproxil that cannot be achieved with the combination tablet (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment of doravirine/lamivudine/tenofovir disoproxil 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/lamivudine/tenofovir disoproxil is administered to patients with severe hepatic impairment (see section 5.2).

Paediatric population

Safety and efficacy of DELSTRIGO in children aged < 12 years or weighing < 35 kg have not been established.

Method of administration

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

4.3 Contraindications

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

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

- carbamazepine, oxcarbazepine, phenobarbitone, phenytoin
- rifampicin, rifapentine and any other tuberculosis medicines which are strong CYP3A enzyme inducers.
- St. John's wort (*Hypericum perforatum*)
- mitotane
- enzalutamide
- lumacaftor
- moderate and severe renal impairment (CrCL < 50 mL/minute).

4.4 Special warnings and precautions for use

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

Patients with HIV and hepatitis B or C virus co-infection

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines.

Patients co-infected with HIV and HBV who discontinue DELSTRIGO should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Discontinuation of DELSTRIGO therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Liver disease

Use of nucleoside/nucleotide analogues can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of DELSTRIGO has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant package inserts for these medicines.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial

dysfunction in HIV negative infants exposed in utero and/or postnatally to nucleoside analogues. Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed in utero to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Lactic acidosis/hyperlactataemia

Cases of lactic acidosis have been reported with tenofovir disoproxil alone or in combination with other antiretrovirals.

Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/ℓ) and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/ℓ with minimum symptoms: switch to agents that are less likely to cause lactic acidosis.

- Lactate 5-10 mmol/ℓ with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.
- Lactate> 10 mmol/ℓ: STOP all therapy (80 % mortality).

The above lactate values may not be applicable to paediatric patients.

Caution should be exercised when administering DELSTRIGO to patients with known risk factors for liver disease. Patients with predisposing factors such as patients with decompensated liver disease, or patients receiving concomitant medications known to induce lactic acidosis are at increased risk of experiencing severe lactic acidosis during tenofovir disoproxil treatment, including fatal outcomes.

Treatment with DELSTRIGO should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Pancreatitis

Pancreatitis has been observed in some patients receiving nucleoside/nucleotide analogues. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of DELSTRIGO until diagnosis of pancreatitis is excluded.

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.

New onset or worsening renal impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir disoproxil, a component of DELSTRIGO.

DELSTRIGO should be avoided with concurrent or recent use of nephrotoxic medicinal products (e.g. high-dose or multiple nonsteroidal anti-inflammatory medicinal products [NSAIDs]) (see section 4.5). Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir disoproxil. Some patients required hospitalisation and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures, and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at risk patients.

It is recommended that estimated CrCl be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with DELSTRIGO. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil, it is recommended that estimated CrCl, serum phosphorus, urine glucose and urine protein be assessed prior to initiation of DELSTRIGO and more frequent renal function monitoring should be assessed as appropriate per the patient's medical condition during DELSTRIGO therapy.

Lamivudine and tenofovir disoproxil are primarily excreted by the kidney. DELSTRIGO should be discontinued if estimated CrCl declines below 50 mL per minute as dose interval

adjustment required for lamivudine and tenofovir disoproxil cannot be achieved with the fixed dose combination tablet (see section 4.2).

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis.

Appropriate treatment of the opportunistic disease should be instituted or continued, and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (e.g Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Opportunistic infections

Patients receiving antiretroviral therapy should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Bone loss and mineralisation defects

Bone mineral density

In clinical trials in HIV-1 infected adults, tenofovir disoproxil was associated with small decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving tenofovir disoproxil. In other studies (prospective and cross-sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor.

Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy.

The effects of tenofovir disoproxil associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for HIV-1 infected adult patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial in all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained.

Mineralisation defects

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of tenofovir disoproxil. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving medicines containing tenofovir disoproxil (see section 4.4).

Co-administration with other antiviral medicines

Doravirine/lamivudine/tenofovir disoproxil must not be co-administered with other medicinal products containing lamivudine, or with medicinal products containing tenofovir disoproxil, or tenofovir alafenamide or with adefovir dipivoxil (see section 4.5).

Doravirine/lamivudine/tenofovir disoproxil should not be administered with doravirine unless needed for dose adjustment (e.g. with rifabutin) (see sections 4.2 and 4.5).

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).

Lactose

DELSTRIGO contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance e.g. galactosemia, total lactase deficiency or glucose-galactose malabsorption should not take DELSTRIGO.

4.5 Interaction with other medicines and other forms of interaction

DELSTRIGO is a complete regimen for the treatment of HIV-1 infection; therefore, DELSTRIGO should not be administered with other antiretroviral medicinal products.

Information regarding potential medicinal product interactions with other antiretroviral medicines is not provided. Interaction studies have only been performed in adults.

DELSTRIGO contains doravirine, lamivudine and tenofovir disoproxil, therefore any interactions identified for these individually are relevant to DELSTRIGO and are presented in Table 1.

Effects of other medicinal products on doravirine, lamivudine and tenofovir disoproxil

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/lamivudine/tenofovir disoproxil 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/lamivudine/tenofovir disoproxil (see sections 4.3 and 5.2).

Co-administration with the moderate CYP3A inducer rifabutin decreased doravirine concentrations (see Table 1). When DELSTRIGO is co-administered with rifabutin, a 100 mg dose of doravirine should be given daily, approximately 12 hours after doravirine/lamivudine/tenofovir disoproxil dose (see section 4.2).

Co-administration of doravirine/lamivudine/tenofovir disoproxil 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, a 100 mg dose of doravirine should be administered daily, approximately 12 hours after the administration of doravirine/lamivudine/tenofovir disoproxil dose (see section 4.2).

Co-administration of doravirine/lamivudine/tenofovir disoproxil 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.

Lamivudine

Because lamivudine is primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion (see section 5.2), co-administration of doravirine/lamivudine/tenofovir disoproxil with medicinal products that reduce renal function or compete for active tubular secretion may increase serum concentrations of lamivudine.

Tenofovir disoproxil

Because tenofovir is primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion (see section 5.2), co-administration of doravirine/lamivudine/tenofovir disoproxil with medicinal products that reduce renal function or compete for active tubular secretion via OAT1, OAT3 or MRP4 may increase serum concentrations of tenofovir.

Due to the tenofovir disoproxil component of doravirine/lamivudine/tenofovir disoproxil, use of the product should be avoided with concurrent or recent use of nephrotoxic medicinal products. Some examples include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g. gentamicin) and high-dose or multiple NSAIDs (see section 4.4).

Effects of doravirine, lamivudine and tenofovir disoproxil on other medicinal products

Doravirine

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).

Lamivudine

Lamivudine does not inhibit or induce CYP enzymes

Tenofovir

Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP-mediated interactions involving tenofovir with other medicinal products is low.

Interaction table

Table 1 shows the established and other potential medicinal product interactions with the individual components of DELSTRIGO but is not all inclusive (increase is indicated as ↑, decrease is indicated as ↓ and no change as ↔). For potential medicine product interactions with tenofovir disoproxil or lamivudine, see (sections 4.4 and 5.2).

Table 1: Interactions between the individual components of DELSTRIGO and other medicinal products

Medicinal Product by Therapeutic Area	**Effects on Medicinal Product Levels Geometric Mean Ratio (90 % CI)***	**Recommendation Concerning Co-administration with doravirine/lamivudine/tenofovir disoproxil**
Acid-Reducing Medicines		
antacid (aluminium and magnesium hydroxide oral suspension) (20 mL SD, doravirine 100 mg SD)	↔ doravirine AUC 1,01 (0,92, 1,11) C_{max} 0,86 (0,74, 1,01) C_{24hr} 1,03 (0,94, 1,12)	No dose adjustment is required.
pantoprazole (40 mg QD, doravirine 100 mg SD)	↓ doravirine AUC 0,83 (0,76, 0,91) C_{max} 0,88 (0,76, 1,01) C_{24hr} 0,84 (0,77, 0,92)	No dose adjustment is required.
omeprazole	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ doravirine	No dose adjustment is required.
Angiotensin Converting Enzyme Inhibitors		
lisinopril	Interaction not studied with doravirine or	No dose adjustment is required.

	doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ lisinopril	
Antiandrogens		
enzalutamide	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
Antibiotics		
nafcillin	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, a 100 mg dose of doravirine should be taken daily, approximately12 hours after the dose of doravirine/lamivudine/tenofovir disoproxil.
Anticonvulsants		

carbamazepine oxcarbazepine phenobarbitone phenytoin	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. 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 with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ canagliflozin ↔ liraglutide ↔ sitagliptin	No dose adjustment is required.
Antidiarrhoeals		
telotristat ethyl	Interaction not studied with doravirine or	Co-administration should be avoided. If co-administration cannot

	doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	be avoided, a 100 mg dose of doravirine should be taken daily, 12 hours after the dose of doravirine/lamivudine/tenofovir disoproxil.
Antigout and Uricosuric Medicines		
lesinurad	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, a 100 mg dose of doravirine should be taken daily, approximately 12 hours after the dose of doravirine/lamivudine/tenofovir disoproxil.
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_{24hr} 0,90 (0,80, 1,01) ↓ doravirine AUC 0,12 (0,10, 0,15) C_{max} 0,43 (0,35, 0,52) C_{24hr} 0,03 (0,02, 0,04)	Co-administration is contraindicated.

	(Induction of CYP3A)	
rifapentine	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
rifabutin (300 mg QD, doravirine 100 mg SD)	↓ doravirine AUC 0,50 (0,45, 0,55) C_{max} 0,99 (0,85, 1,15) C_{24hr} 0,32 (0,28, 0,35) (Induction of CYP3A)	If doravirine/lamivudine/tenofovir disoproxil is co-administered with rifabutin, a 100 mg dose of doravirine should be taken daily, approximately 12 hours after dose of doravirine/lamivudine/tenofovir disoproxil.
Antineoplastics		
mitotane	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine	Co-administration is contraindicated.

	(Induction of CYP3A)	
Antipsychotics		
thioridazine	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, a 100 mg dose of doravirine should be taken daily, approximately 12 hours after the dose of doravirine/lamivudine/tenofovir disoproxil.
Azole Antifungal Medicines		
ketoconazole (400 mg QD, doravirine 100 mg SD)	↑ doravirine AUC 3,06 (2,85, 3,29) C_{max} 1,25 (1,05, 1,49) C_{24hr} 2,75 (2,54, 2,98) (Inhibition of CYP3A)	No dose adjustment is required.
fluconazole itraconazole posaconazole voriconazole	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↑ doravirine (Inhibition of CYP3A)	No dose adjustment is required.

Calcium Channel Blockers		
diltiazem verapamil	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↑ doravirine (Inhibition of CYP3A)	No dose adjustment is required.
Cystic Fibrosis Treatment		
lumacaftor	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
Endothelin Receptor Antagonists		
bosentan	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil.	Co-administration should be avoided. If co-administration cannot be avoided, a 100 mg dose of doravirine should be taken daily, approximately12 hours after the

	Expected: ↓ doravirine (Induction of CYP3A)	dose of doravirine/lamivudine/tenofovir disoproxil.
Hepatitis C Antiviral Medicines		
elbasvir + grazoprevir (50 mg elbasvir QD + 200 mg grazoprevir QD, doravirine 100 mg QD)	↑ doravirine AUC 1,56 (1,45, 1,68) C_{max} 1,41 (1,25, 1,58) C_{24hr} 1,61 (1,45, 1,79) (Inhibition of CYP3A) ↔ elbasvir AUC 0,96 (0,90, 1,02) C_{max} 0,96 (0,91, 1,01) C_{24hr} 0,96 (0,89, 1,04) ↔ grazoprevir AUC 1,07 (0,94, 1,23) C_{max} 1,22 (1,01, 1,47) C_{24hr} 0,90 (0,83, 0,96)	No dose adjustment is required.
ledipasvir + sofosbuvir (90 mg ledipasvir SD + 400 mg sofosbuvir SD, doravirine 100 mg SD)	↑ doravirine AUC 1,15 (1,07, 1,24) C_{max} 1,11 (0,97, 1,27) C_{24hr} 1,24 (1,13, 1,36)	Patients receiving doravirine/lamivudine/tenofovir disoproxil concomitantly with ledipasvir/sofosbuvir should be

	↔ 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) Expected: ↑ tenofovir	monitored for adverse reactions associated with tenofovir disoproxil.
sofosbuvir/velpatasvir	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ doravirine ↑ tenofovir	Patients receiving doravirine/lamivudine/tenofovir disoproxil concomitantly with sofosbuvir/velpatasvir should be monitored for adverse reactions associated with tenofovir disoproxil.
sofosbuvir	Interaction not studied with doravirine or	No dose adjustment is required.

	doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ doravirine	
daclatasvir	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ doravirine	No dose adjustment is required.
ombitasvir/paritaprevir/ritonavir and dasabuvir +/- ritonavir	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↑ doravirine (Inhibition of CYP3A due to ritonavir)	No dose adjustment is required.
dasabuvir	Interaction not studied with doravirine or	No dose adjustment is required.

	doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ doravirine	
glecaprevir, pibrentasvir	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↑ doravirine (inhibition of CYP3A)	No dose adjustment is required.
ribavirin	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ doravirine	No dose adjustment is required.
Herbal Supplements		
St. John's wort (*Hypericum perforatum*)	Interaction not studied with doravirine or	Co-administration is contraindicated.

	doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	
HIV Antiviral Medicines		
tenofovir disoproxil (300 mg QD, doravirine 100 mg SD)	↔ doravirine AUC 0,95 (0,80,1,12) C_{max} 0,80 (0,64,1,01) C_{24hr} 0,94 (0,78, 1,12)	No dose adjustment is required.
lamivudine + tenofovir disoproxil (300 mg lamivudine SD + 245 mg tenofovir disoproxil SD, doravirine 100 mg SD)	↔ doravirine AUC 0,96 (0,87, 1,06) C_{max} 0,97 (0,88, 1,07) C_{24hr} 0,94 (0,83, 1,06) ↔ lamivudine AUC 0,94 (0,88, 1,00) C_{max} 0,92 (0,81, 1,05) ↔ tenofovir AUC 1,11 (0,97, 1,28) C_{max} 1,17 (0,96, 1,42)	No dose adjustment is required.
Immunosuppressants		

tacrolimus sirolimus	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. 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 with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, a 100 mg dose of doravirine should be taken daily, approximately 12 hours after the dose of doravirine/lamivudine/tenofovir disoproxil.
Miscellaneous		
sorbitol solution (3,2 g, 10,2 g, 13,4 g)/lamivudine	Single dose lamivudine oral solution 300 mg lamivudine	When possible, avoid chronic co-administration of doravirine/lamivudine/tenofovir disoproxil with medicinal products containing sorbitol or other osmotic

	AUC ↓ 14 %; 32 %; 35 % C_{max} ↓ 28 %; 52 %; 55 %	acting poly-alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.
Opioid Analgesics		
methadone (20 to 200 mg QD individualised dose, doravirine 100 mg QD)	↓ doravirine AUC 0,74 (0,61, 0,90) C_{max} 0,76 (0,63, 0,91) C_{24hr} 0,80 (0,63, 1,03) ↔ R-methadone AUC 0,95 (0,90, 1,01) C_{max} 0,98 (0,93, 1,03) C_{24hr} 0,95 (0,88, 1,03) ↔ S-methadone AUC 0,98 (0,90, 1,06) C_{max} 0,97 (0,91, 1,04) C_{24hr} 0,97 (0,86, 1,10)	No dose adjustment is required.
buprenorphine naloxone	Interaction not studied with doravirine or	No dose adjustment is required.

	doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ buprenorphine ↔ naloxone	
Oral Contraceptives		
0,03 mg ethinylestradiol/0,15 mg levonorgestrel SD, doravirine 100 mg QD	↔ ethinylestradiol AUC 0,98 (0,94, 1,03) C_{max} 0,83 (0,80, 0,87) ↑ levonorgestrel AUC 1,21 (1,14, 1,28) C_{max} 0,96 (0,88, 1,05)	No dose adjustment is required.
norgestimate/ethinylestradiol	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ norgestimate/ethinylestradiol	No dose adjustment is required.
Psychostimulants		

modafinil	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, a 100 mg dose of doravirine should be taken daily, approximately12 hours after the dose of doravirine/lamivudine/tenofovir disoproxil.
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 with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ rosuvastatin ↔ simvastatin	No dose adjustment is required.

↑ = increase, ↓ = decrease, ↔ = no change

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of doravirine in pregnant women. A large amount of data on pregnant women (more than 3 000 outcomes from first trimester) taking the individual active component lamivudine in combination with other antiretrovirals indicates no malformative toxicity. A moderate amount of data on pregnant women (between 300 to 1 000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil.

Antiretroviral pregnancy registry

To monitor maternal-foetal outcomes in patients exposed to antiretroviral medicinal products while pregnant, an Antiretroviral Pregnancy Registry has been established. Medical practitioners 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).

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

Animal studies with lamivudine showed an increase in early embryonic deaths in rabbits but not in rats (see section 5.3). Placental transfer of lamivudine has been shown to occur in humans. Lamivudine may inhibit cellular DNA replication (see section 5.3). The clinical relevance of this finding is unknown.

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

Breastfeeding

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

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).

Lamivudine has been identified in breastfed newborns/infants of treated women. Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (< 4 % of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age. There are no data available on the safety of lamivudine when administered to babies < 3 months old.

Tenofovir is excreted in human milk. There is insufficient information on the effects of tenofovir in newborns/infants.

Fertility

No human data on the effect of DELSTRIGO on fertility are available. Animal studies do not indicate harmful effects of doravirine, lamivudine or tenofovir disoproxil 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

DELSTRIGO may have 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 DELSTRIGO (see section 4.8). This should be considered when assessing a patient's ability to drive or operate machinery.

4.8 Undesirable effects

a. Summary of the safety profile

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

b. Tabulated summary of adverse reactions

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

Table 2: Tabulated summary of adverse reactions associated with doravirine/lamivudine/tenofovir disoproxil

Frequency	Adverse reactions
Blood and lymphatic systems disorders	
Uncommon	neutropenia*, anaemia*, thrombocytopenia*
Very rare	pure red cell aplasia*
Infections and infestations	
Rare	rash pustular

Metabolism and nutrition disorders	
Uncommon	hypophosphatemia, hypokalaemia*
Rare	hypomagnesaemia, lactic acidosis*
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
Very rare	peripheral neuropathy (or paraesthesia)*
Vascular disorders	
Uncommon	hypertension
Respiratory, thoracic and mediastinal disorders	
Common	cough*, nasal symptoms*
Rare	dyspnoea, tonsillar hypertrophy
Gastrointestinal disorders	
Common	nausea, diarrhoea, abdominal pain[4], vomiting, flatulence

Uncommon	constipation, abdominal discomfort[5], abdominal distension, dyspepsia, faeces soft[6], gastrointestinal motility disorder[7], pancreatitis*
Rare	rectal tenesmus
Hepatobiliary disorders	
Rare	hepatic steatosis*, hepatitis*
Skin and subcutaneous tissue disorders	
Common	alopecia*, rash[8]
Uncommon	pruritus
Rare	dermatitis allergic, rosacea, angioedema*
Musculoskeletal and connective tissue disorders	
Common	muscle disorders*
Uncommon	myalgia, arthralgia, rhabdomyolysis*,†, muscular weakness*,†
Rare	musculoskeletal pain, osteomalacia (manifested as bone pain and infrequently contributing to fractures)*, myopathy*
Renal and urinary disorders	
Uncommon	increased creatinine*, proximal renal tubulopathy (including Fanconi syndrome)*
Rare	acute kidney injury, renal disorder, calculus urinary, nephrolithiasis, acute renal failure*, renal failure*, acute tubular necrosis*,

	nephritis (including acute interstitial)*, nephrogenic diabetes insipidus*
General disorders and administration site conditions	
Common	fatigue, fever*
Uncommon	asthenia malaise
Rare	chest pain, chills, pain, thirst
Investigations	
Common	alanine aminotransferase increased[9]
Uncommon	aspartate aminotransferase increased, lipase increased, amylase increased, haemoglobin decreased
Rare	blood creatine phosphokinase increased

*This adverse reaction was not identified as an adverse reaction associated with doravirine from the Phase 3 clinical studies (DRIVE-FORWARD, DRIVE-AHEAD, DRIVE-SHIFT), but is included in this table as an adverse reaction based on the Summary of Product Characteristics of 3TC and/or TDF. The highest frequency category reported in the 3TC or TDF Summary of Product Characteristics is used.

†This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil in the absence of this condition.

[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

Paediatric population

The safety of doravirine/lamivudine/tenofovir disoproxil was evaluated in 45 HIV-1 infected virologically suppressed or treatment-naïve paediatric patients 12 to < 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Doravirine

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

Lamivudine

Because a negligible amount of lamivudine was removed via (4-hour) haemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous haemodialysis would provide clinical benefit in a lamivudine overdose event.

Tenofovir disoproxil

Tenofovir disoproxil is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %. Following a single 245 mg dose of tenofovir disoproxil, a 4-hour haemodialysis session removed approximately 10 % of the administered tenofovir dose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, ATC code: J05AG24

Mechanism of action

Doravirine

Doravirine is a pyridinone non-nucleoside reverse transcriptase inhibitor of HIV-1 and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT). The inhibitory concentration at 50 % (IC50) of doravirine for RNA-dependent DNA polymerisation of recombinant wild-type HIV-1 RT in a biochemical assay was 12.2±2.0 nM (n=3). Doravirine does not inhibit the human cellular DNA polymerases α, ß and mitochondrial DNA polymerase γ.

Lamivudine

Lamivudine is a nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5´-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of

action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue.

Tenofovir disoproxil

Tenofovir disoproxil is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir disoproxil requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylation's by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5´-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β and mitochondrial DNA polymerase γ.

Antiviral activity in cell culture

Doravirine

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. The antiviral activity of doravirine was not antagonistic when combined with lamivudine and tenofovir disoproxil.

Lamivudine

The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and peripheral blood mononuclear cells (PBMCs) using standard susceptibility assays. EC_{50} values were in the range of 0,003 to 15 µM (1 µM = 0,23 µg per mL). The median EC_{50} values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60

nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM) and 30 nM (range: 20 to 90 nM) against HIV-1 clades A to G and group O viruses (n=3 except n=2 for clade B) respectively. Ribavirin (50 µM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3,5-fold in MT-4 cells.

Tenofovir disoproxil

The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} values for tenofovir were in the range of 0,04 to 8,5 µM. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G and O (EC_{50} values ranged from 0,5 to 2,2 µM).

Resistance

In cell culture

Doravirine

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, F227I, F227C, 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, and 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).

Lamivudine

Lamivudine-resistant variants of HIV-1 have been selected in cell culture and in subjects treated with lamivudine. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 RT at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

Tenofovir disoproxil

HIV-1 isolates selected by tenofovir expressed a K65R substitution in HIV-1 RT and showed a 2- to 4-fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 RT has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine and tenofovir.

In clinical trials

Treatment naïve adult subjects

Doravirine

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

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

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

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

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

**The subject received FTC/TDF

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

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

Lamivudine and tenofovir disoproxil

In a pooled analysis of antiretroviral-naïve subjects who received doravirine, lamivudine and tenofovir disoproxil, genotyping was performed on plasma HIV-1 isolates from all subjects

with HIV-1 RNA > 400 copies per mL at confirmed virologic failure, at Week 48 or at time of early study drug discontinuation. Genotypic resistance developed in 7 evaluable subjects. The resistance-associated substitutions that emerged were RT M41L (n=1), K65R (n=2) and M184V/I (n=4).

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, lamivudine or tenofovir was detected.

Cross-resistance

No significant cross-resistance has been demonstrated between doravirine-resistant HIV-1 variants and lamivudine/emtricitabine or tenofovir or between lamivudine- or tenofovir-resistant variants and doravirine.

Doravirine

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

Laboratory strains of HIV-1 harbouring the common NNRTI-associated mutations K103N, Y181C or K103N/Y181C substitutions in RT exhibit < a 3-fold decrease in susceptibility to doravirine compared to wild-type virus when evaluated in the presence of 100 % normal human serum. In *in vitro* studies, doravirine was able to suppress the following NNRTI-associated substitutions; K103N, Y181C and G190A under clinically relevant concentrations.

A panel of 96 diverse clinical isolates containing NNRTI-associated mutations was evaluated for susceptibility to doravirine in the presence of 10 % foetal bovine serum. Clinical isolates containing the Y188L substitution or V106 substitutions in combination with A98G, H221Y, P225H, F227C or Y318F showed a >100-fold reduced susceptibility to doravirine. Other substitutions yielded a fold change of 5 to 10 (G190S (5,7); K103N/P225H (7,9),

V108I/Y181C (6,9), Y181V (5,1)). The clinical relevance of a 5- to 10-fold change 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.

Lamivudine

Cross-resistance has been observed among NRTIs. The M184I/V lamivudine resistance substitution confers resistance to emtricitabine. Lamivudine-resistant HIV-1 mutants were also cross resistant to didanosine (ddI). In some subjects treated with zidovudine plus didanosine, isolates resistant to multiple RT inhibitors, including lamivudine, have emerged.

Tenofovir disoproxil

Cross-resistance has been observed among NRTIs. The K65R substitution in HIV-1 RT selected by tenofovir is also selected in some HIV-1 infected patients treated with abacavir or didanosine. HIV-1 isolates with the K65R substitution also showed reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these NRTIs may occur in patients whose virus harbours the K65R substitution. The K70E substitution selected clinically by tenofovir disoproxil results in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine and tenofovir. HIV-1 isolates from patients (n=20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N) showed a 3,1-fold decrease in the susceptibility to tenofovir. Subjects whose virus expressed an L74V RT substitution without zidovudine resistance-associated substitutions (n=8) had reduced response to tenofovir disoproxil. Limited data are available for patients whose virus expressed a Y115F substitution (n=3),

Q151M substitution (n=2) or T69 insertion (n=4) in HIV-1 RT, all of whom had a reduced response in clinical trials.

Clinical experience

Treatment-naïve adult subjects

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

In DRIVE-FORWARD, 766 subjects were randomised and received at least 1 dose of either doravirine 100 mg or darunavir + ritonavir 800 + 100 mg once daily, each in combination with emtricitabine/tenofovir disoproxil (FTC/TDF) or abacavir/lamivudine (ABC/3TC) selected by the investigator. At baseline, the median age of subjects was 33 years (range 18 to 69 years), 86 % had CD4+ T-cell count > 200 cells per mm^3, 84 % were male, 27 % were non-white, 4 % had hepatitis B and/or C virus co-infection, 10 % had a history of AIDS, 20 % had HIV-1 RNA > 100 000 copies per mL, 13 % received ABC/3TC and 87 % received FTC/TDF; these characteristics were similar between treatment groups.

In DRIVE-AHEAD, 728 subjects were randomised and received at least 1 dose of either doravirine/lamivudine/tenofovir disoproxil 100/300/245 mg (DOR/3TC/TDF) or efavirenz/emtricitabine/tenofovir disoproxil (EFV/FTC/TDF) once daily. At baseline, the median age of subjects was 31 years (range 18 to 70 years), 85 % were male, 52 % were non-white, 3 % had hepatitis B or C co-infection, 14 % had a history of AIDS, 21 % had HIV-1 RNA > 100 000 copies per mL and 12 % had CD4+ T-cell count < 200 cells per mm^3; these characteristics were similar between treatment groups.

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

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

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

TDF/FTC	276/316 (87 %)	267/312 (86 %)	NA	
ABC/3TC	43/48 (90 %)	36/43 (84 %)	NA	
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.

Virologically suppressed adult subjects

The efficacy of switching from a baseline regimen consisting of two nucleoside reverse transcriptase inhibitors in combination with a ritonavir- or cobicistat-boosted PI, or cobicistat-boosted elvitegravir, or an NNRTI to DELSTRIGO was evaluated in a 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 Resistance section. Subjects were randomised to either switch to DELSTRIGO at baseline [N=447, Immediate Switch Group (ISG)] or stay on their baseline regimen until Week 24, at which point they switched to DELSTRIGO [N=223, Delayed Switch Group (DSG)]. At baseline, the median age of subjects was 43 years, 16 % were female and 24 % were Non-White.

In the DRIVE-SHIFT trial, an immediate switch to DELSTRIGO was demonstrated to be non-inferior at Week 48 compared to continuation of the baseline regimen at Week 24 as assessed by the proportion of subjects with HIV-1 RNA < 40 copies/mL. Treatment results are shown in Table 5. Consistent results were seen for the comparison at Study Week 24 in each treatment group.

Table 5: Efficacy response (Snapshot approach) in the DRIVE-SHIFT study

Outcome	**DELSTRIGO Once Daily ISG**	**Baseline Regimen DSG**
	Week 48 N=447	**Week 24 N=223**
HIV-1 RNA < 40 copies/mL	90 %	93 %
ISG-DSG, Difference (95 % CI)*	-3,6 % (-8,0 %, 0,9 %)	
Proportion (%) of Subjects With HIV-1 RNA < 40 copies/mL by Baseline Regimen Received		
Ritonavir- or Cobicistat-boosted PI	280/316 (89 %)	145/156 (93 %)
Cobicistat-boosted elvitegravir	23/25 (92 %)	11/12 (92 %)
NNRTI	98/106 (92 %)	52/55 (95 %)
Proportion (%) of Subjects With HIV-1 RNA < 40 copies/mL by Baseline CD4+ T-cell Count (cells/mm^3)		

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

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

[†]Includes subjects who discontinued study drug or study before Week 48 for ISG or before Week 24 for DSG for lack or loss of efficacy and subjects with HIV-1 RNA ≥ 40 copies/mL in the Week 48 window for ISG and in the Week 24 window for DSG.

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

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

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

Discontinuation due to adverse events

In DRIVE-AHEAD, a lower proportion of subjects who discontinued due to an adverse event by Week 48 was seen for the DELSTRIGO group (3,0 %) compared with the EFV/FTC/TDF group (6,6 %).

Paediatric population

The efficacy of DOR/3TC/TDF was evaluated in an open-label, single-arm trial in HIV-1 infected paediatric patients 12 to < 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.

5.2 Pharmacokinetic properties

Single-dose administration of one doravirine/lamivudine/tenofovir disoproxil tablet to healthy subjects (N=24) under fasted conditions provided comparable exposures of doravirine, lamivudine and tenofovir to administration of doravirine tablets (100 mg) plus lamivudine tablets (300 mg) plus tenofovir disoproxil tablets (245 mg). The administration of a single DELSTRIGO tablet with a high-fat meal to healthy subjects resulted in a 26 % increase in doravirine C_{24hr}, while AUC and C_{max} were not significantly affected. Lamivudine C_{max}

decreased by 19 % with a high-fat meal, while AUC was not significantly affected. Tenofovir C_{max} decreased by 12 % and AUC increased by 27 % with a high-fat meal. These differences in pharmacokinetics are not clinically relevant.

Doravirine

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

Parameter GM (% CV)	AUC_{0-24hr} µg.h/mL	C_{max} µg/mL	C_{24hr} µg/mL
Doravirine 100 mg once daily	16,1 (29)	0,962 (19)	0,396 (63)
GM: geometric mean, % CV: Geometric coefficient of variation			

Absorption

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

Distribution

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

Biotransformation

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

Elimination

Doravirine

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.

Lamivudine

Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy subjects, steady-state C_{max} ($C_{max,ss}$) was 2,04 ± 0,54 µg per mL (mean ± SD) and the 24-hour steady-state AUC ($AUC_{24hr,ss}$) was 8,87 ± 1,83 µg•hour per mL. Binding to plasma protein is low. Approximately 71 % of an intravenous dose of lamivudine is recovered as unchanged medicinal product in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5 % of an oral dose after 12 hours). In most single-dose trials in HIV-1 infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours. In HIV-1 infected subjects, total clearance was 398,5 ± 69,1 mL per min (mean ± SD).

Tenofovir disoproxil

Following oral administration of a single 245 mg dose of tenofovir disoproxil to HIV-1 infected subjects in the fasted state, C_{max} was achieved in 1 hour. C_{max} and AUC values were 0,30 ± 0,09 µg per mL and 2,29 ± 0,69 µg•hr per mL, respectively. The oral bioavailability of tenofovir from tenofovir disoproxil in fasted subjects is approximately 25 %. Less than 0,7 %

of tenofovir binds to human plasma proteins *in vitro* over the range of 0,01 to 25 µg per mL. Approximately 70 to 80 % of the intravenous dose of tenofovir is recovered as unchanged medicinal product in the urine within 72 hours of dosing. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with CrCl > 80 mL per minute of 243,5 ± 33,3 mL per minute (mean ± SD). Following oral administration, the terminal half-life of tenofovir is approximately 12 to 18 hours. *In vitro* studies have determined that neither tenofovir disoproxil nor tenofovir are substrates for the CYP450 enzymes.

Renal impairment

Doravirine

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).

Lamivudine

Studies with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. Based on the lamivudine data, DELSTRIGO is not recommended for patients with CrCl of < 50 mL/min.

Tenofovir disoproxil

Pharmacokinetic parameters of tenofovir were determined following administration of a single dose of tenofovir disoproxil 245 mg to 40 non-HIV-infected adult subjects with varying degrees of renal impairment defined according to baseline CrCl (normal renal function when CrCl > 80 mL/min; mild with CrCl = 50 to 79 mL/min; moderate with CrCl = 30 to 49 mL/min and severe with CrCl = 10 to 29 mL/min). Compared with subjects with normal renal function, the mean (% CV) tenofovir exposure increased from 2 185 (12 %) ng·h/mL in subjects with CrCl > 80 mL/min to respectively 3 064 (30 %) ng·h/mL, 6 009 (42 %) ng·h/mL and 15 985 (45 %) ng·h/mL in subjects with mild, moderate and severe renal impairment.

The pharmacokinetics of tenofovir in non-haemodialysis adult subjects with CrCl < 10 mL/min and in subjects with end-stage renal disease managed by peritoneal or other forms of dialysis have not been studied.

Hepatic impairment

Doravirine

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).

Lamivudine

The pharmacokinetic properties of lamivudine have been determined in subjects with moderate to severe hepatic impairment. Pharmacokinetic parameters were not altered by

diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Tenofovir disoproxil

The pharmacokinetics of tenofovir following a 245 mg dose of tenofovir disoproxil have been studied in healthy subjects with moderate to severe hepatic impairment. No clinically relevant differences in tenofovir pharmacokinetics were observed between subjects with hepatic impairment and healthy subjects.

Paediatric population

Mean doravirine exposures were similar in 54 paediatric patients aged 12 to < 18 years and weighing at least 35 kg who received doravirine or doravirine/lamivudine/tenofovir disoproxil IMPAACT 2014 (Protocol 027) relative to adults following administration of doravirine or doravirine/lamivudine/tenofovir disoproxil. Exposures of lamivudine and tenofovir in paediatric subjects following the administration of doravirine/lamivudine/tenofovir disoproxil were similar to those in adults following administration of lamivudine and tenofovir disoproxil (Table 6).

Table 6: Steady-state pharmacokinetics for doravirine, lamivudine, and tenofovir following administration of doravirine or doravirine/lamivudine/tenofovir disoproxil in HIV infected paediatric patients aged 12 to < 18 years and weighing at least 35 kg

Parameter*	Doravirine†	Lamivudine‡	Tenofovir‡
AUC_{0-24} (µg•h/mL)	16,4 (24)	11,3 (28)	2,55 (14)
C_{max} (µg/mL)	1,03 (16)	2,1 (24)	0,293 (37)

C_{24} (µg/mL)	0,379 (42)	0,0663 (55)	0,0502 (9)

*Presented as geometric mean (%CV: geometric coefficient of variation)

†From population PK analysis (n=54)

‡From intensive PK analysis (n=10)

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 < 65 years of age in a Phase 1 trial or in a population pharmacokinetic analysis. The pharmacokinetics of lamivudine and tenofovir have not been studied in subjects older than 65 years. No dose adjustment is required.

Gender

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

Race

Doravirine

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.

Lamivudine

There are no significant or clinically relevant racial differences in pharmacokinetics of lamivudine.

Tenofovir disoproxil

There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following the administration of tenofovir disoproxil.

5.3 Preclinical safety data

Reproductive toxicity

Doravirine

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.

Lamivudine

Lamivudine was not teratogenic in animal studies but there were indications of an increase in early embryonic deaths in rabbits at relatively low systemic exposures, comparable to those achieved in humans. A similar effect was not seen in rats even at very high systemic exposure.

Tenofovir disoproxil

Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil reduced the viability index and weight of pups in a peri-postnatal toxicity study at maternally toxic doses.

Carcinogenesis

Doravirine

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.

Lamivudine

Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 12 times (mice) and 57 times (rats) the human exposures at the RHD.

Tenofovir disoproxil

Oral carcinogenicity studies in rats and mice only revealed a low incidence of duodenal tumours at an extremely high-dose in mice. These tumours are unlikely to be of relevance to humans.

Mutagenesis

Doravirine

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

Lamivudine

Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a

microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Tenofovir disoproxil

Tenofovir disoproxil was mutagenic in the *in vitro* mouse lymphoma assay and negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, tenofovir disoproxil was negative when administered to male mice.

Impairment of fertility

Doravirine

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

Lamivudine

Lamivudine did not affect male or female fertility in rats.

Tenofovir disoproxil

Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters.

Repeat dose toxicity

Doravirine

Administration of doravirine in animal toxicity studies was not associated with toxicity.

Lamivudine

Administration of lamivudine in animal toxicity studies at high-doses was not associated with any major organ toxicity. At the highest dosage levels, minor effects on indicators of liver and

kidney function were seen together with occasional reductions in liver weight. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia.

Tenofovir disoproxil

Findings in repeat-dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use included kidney and bone changes and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures ≥ 5-fold the exposure in paediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (≥ 40-fold the exposure in patients). Findings in the rat and monkey studies indicated that there was a substance related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium (E468), Hypromellose acetate succinate, Magnesium stearate (E470b), Microcrystalline cellulose (E460), Silica, colloidal anhydrous (E551) and Sodium stearyl fumarate

Film-coating

Carnauba wax (E903), Hypromellose (E464), Iron oxide yellow (E172), Lactose monohydrate, Titanium dioxide (E171) and Triacetin (E1518)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the original bottle and keep the bottle tightly closed in order to protect from moisture.

Do not remove the desiccant.

6.5 Nature and contents of container

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

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

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

53/20.2.8/0233

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 August 2021

10 DATE OF REVISION OF THE TEXT

23 May 2025