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

AUSTRALIAN PRODUCT INFORMATION

DELSTRIGO® 100/300/300

(doravirine, lamivudine, and tenofovir disoproxil fumarate) Tablets

1 NAME OF THE MEDICINE

doravirine

lamivudine

tenofovir disoproxil fumarate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DELSTRIGO® is a fixed-dose combination, film-coated tablet containing doravirine, lamivudine, and tenofovir disoproxil fumarate (tenofovir DF) for oral administration.

Active Ingredient

Each tablet contains 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir DF (equivalent to 245 mg of tenofovir disoproxil) as active ingredients.

Inactive Ingredients (List of Excipients)

List of excipients with known effect:

- lactose (as monohydrate).

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

Doravirine is practically insoluble in water.

Lamivudine is soluble in water.

Tenofovir DF is slightly soluble in water.

3 PHARMACEUTICAL FORM

DELSTRIGO (doravirine/lamivudine/tenofovir disoproxil fumarate) is available as a yellow, oval-shaped, film-coated tablet, 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 HIV-1 infection in adults who are antiretroviral therapy (ART)-naïve with no known substitutions associated with resistance to doravirine, lamivudine, or tenofovir.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adult Patients

The recommended dosage regimen of DELSTRIGO in adults is one tablet taken orally once daily with or without food.

Missed Dose

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

Paediatric Patients

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

Elderly Patients

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

Renal Impairment

Because DELSTRIGO is a fixed-dose combination tablet and the dosage of lamivudine and tenofovir DF cannot be altered, patients with estimated creatinine clearance less than 50 mL/min should not receive DELSTRIGO (see sections 4.4 and 5.2*, Special populations*).

Hepatic Impairment

No dose adjustment of DELSTRIGO is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. DELSTRIGO has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see sections 4.4 and 5.2*, Special populations*).

Co-administration with Moderate CYP3A Inducers

If DELSTRIGO is co-administered with rifabutin, one tablet of doravirine-PIFELTRO® should be taken approximately 12 hours after each dose of DELSTRIGO (see section 4.5 and 5.2*, Drug interaction studies*).

Co-administration of doravirine/lamivudine/tenofovir disoproxil with other moderate CYP3A inducers has not been evaluated. If co-administration with other moderate CYP3A inducers (e.g. dabrafenib, lesinurad, bosentan, thioridazine, nafcillin, modafinil, telotristat ethyl) cannot be avoided, a 100 mg dose of doravirine should be administered daily, approximately 12 hours after the administration of doravirine/lamivudine/tenofovir disoproxil dose (see section 4.5).

4.3 CONTRAINDICATIONS

DELSTRIGO should not be co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of DELSTRIGO (see section 5.2*, Drug Interaction Studies*). These drugs include, but are not limited to, the following:

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

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV

All patients with HIV-1 should be tested for the presence of HBV before initiating antiretroviral therapy. DELSTRIGO is not approved for the treatment of chronic HBV infection, and the safety and efficacy of DELSTRIGO have not been established in patients coinfected with HIV-1 and HBV.

Severe acute exacerbations of hepatitis B (e.g., liver decompensated and liver failure) have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued lamivudine or tenofovir DF, two of the components of DELSTRIGO. Patients who are coinfected with HIV-1 and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with DELSTRIGO. If appropriate, initiation of anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

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 DF, a component of DELSTRIGO.

DELSTRIGO should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple nonsteroidal anti-inflammatory drugs [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 DF. 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 creatinine clearance 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 creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of DELSTRIGO and periodically during DELSTRIGO therapy.

The lamivudine and tenofovir DF components of DELSTRIGO are primarily excreted by the kidney. DELSTRIGO should be discontinued if estimated creatinine clearance declines below 50 mL per minute as dose interval adjustment required for lamivudine and tenofovir DF cannot be achieved with the fixed-dose combination tablet (see section 4.2).

Drug Interactions

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

Bone Loss and Mineralization Defects

Bone Mineral Density

In clinical trials in HIV-1 infected adults, tenofovir DF (a component of DELSTRIGO) was associated with slightly greater 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 DF. For additional information, consult the tenofovir DF prescribing information.

The effects of tenofovir DF-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.

Mineralization 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 DF. 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 products containing tenofovir DF.

Co-administration with Other Products

DELSTRIGO is a fixed-dose combination of doravirine, lamivudine, and tenofovir DF. Do not co-administer DELSTRIGO with other medicinal products containing lamivudine, or with medicinal products containing tenofovir DF or tenofovir alafenamide, or with adefovir dipivoxil. DELSTRIGO should not be administered with doravirine-PIFELTRO unless needed for dose adjustment (e.g., with rifabutin) (see sections 4.2 and 4.5).

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus,

Pneumocystis jirovecii pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

Use in hepatic impairment

No dose adjustment of DELSTRIGO is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. DELSTRIGO has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see section 5.2*, Special populations*).

Use in renal impairment

Because DELSTRIGO is a fixed-dose combination tablet and the dosage of lamivudine and tenofovir DF cannot be altered, patients with estimated creatinine clearance less than 50 mL/min should not receive DELSTRIGO (see sections 4.4 and 5.2*, Special populations*).

Use in the elderly

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

Paediatric use

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

Effects on laboratory tests

See section 4.8, *Laboratory abnormalities*

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

DELSTRIGO is a complete regimen for the treatment of HIV-1 infection; therefore, DELSTRIGO should not be administered with other antiretroviral medications for the treatment of HIV-1 infection. Information regarding potential drug-drug interactions with other antiretroviral medications is not provided.

Drugs Affecting Renal Function

Because lamivudine and tenofovir are primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion, co-administration of DELSTRIGO with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of lamivudine, tenofovir, and/or other renally eliminated drugs. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, aciclovir, cidofovir, ganciclovir, valaciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs (see section 4.4).

Co-administration of Other Medicinal Products

Exposure to didanosine is significantly increased following co-administration with tenofovir DF that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported with concomitant use of tenofovir DF and didanosine.

Established and Other Potentially Significant Drug Interactions

Doravirine is primarily metabolised by CYP3A, and drugs that induce or inhibit CYP3A may affect the clearance of doravirine. Co-administration of DELSTRIGO and drugs that induce CYP3A may result in decreased plasma concentrations of doravirine and reduce the therapeutic effect of doravirine (see sections 4.3, 4.4 and 5.2*, Drug interaction studies*). Co-administration of DELSTRIGO with strong inducers of CYP3A is contraindicated (see section 4.3). Co-administration of DELSTRIGO and drugs that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine.

Doravirine at a dose of 100 mg once daily is not likely to have a clinically relevant effect on the plasma concentrations of drugs metabolised by CYP enzymes.

Table 1 shows the established and other potentially significant drug interactions with the components of DELSTRIGO, but is not inclusive. For additional potential drug interactions with lamivudine or tenofovir DF (see sections 4.4 and 5.2*, Special populations*).

Table 1: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Antibiotic		
nafcillin	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil MSD. Expected:	

	disoproxil MSD. Expected: (Induction of CYP3A)	
Antimycobacterials		
rifabutin*	doravirine	Concomitant use of DELSTRIGO with rifabutin may cause a decrease in the plasma concentrations of doravirine (induction of CYP3A enzymes). If DELSTRIGO is co-administered with rifabutin, one tablet of doravirine-PIFELTRO should be taken approximately 12 hours after the dose of DELSTRIGO (see DOSAGE AND ADMINISTRATION).
Antipsychotics		
thioridazine	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil MSD. Expected: (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 h after the dose of doravirine/lamivudine/tenofovir disoproxil.
Azole Antifungal Agents		
fluconazole itraconazole ketoconazole* posaconazole voriconazole	agents	Concomitant use of DELSTRIGO with azole antifungal agents may cause an increase in the plasma concentrations of DELSTRIGO (inhibition of CYP3A enzymes). No doravirine dose adjustment is required when DELSTRIGO is co-administered with azole antifungal agents.
Endothelin Receptor Antagonists		
bosentan	Interaction not studied. Expected: (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, a 100 mg dose of doravirine should be taken daily, approximately12 h after the dose of doravirine/lamivudine/tenofovir disoproxil.
Kinase Inhibitors		
dabrafenib	Interaction not studied. Expected: (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 h after the dose of doravirine/lamivudine/tenofovir disoproxil
Hepatitis C Antiviral Agents		
ledipasvir/sofosbuvir sofosbuvir/velpatasvir		Patients receiving DELSTRIGO concomitantly with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir should be monitored for adverse reactions associated with tenofovir DF.
Psychostimulants		
modafinil	Interaction not studied. Expected: (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 h after the dose of doravirine/lamivudine/tenofovir disoproxil

OTHER AGENTS		
Sorbitol solution (3.2 g, 10.2 g, 13.4 g)		When possible, avoid chronic co-administration of sorbitol-containing medicines with lamivudine. Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.

*The interaction between doravirine and the drug was evaluated in a clinical study.
All other drug-drug interactions shown are anticipated based on the known metabolic and elimination pathways.

Drugs with No Observed or Predicted Interactions with DELSTRIGO

Drug-drug interactions with doravirine and the following drugs were evaluated in clinical studies and no dose adjustment is needed for either drug (see section 5.2*, Drug interaction studies*): aluminium hydroxide/magnesium hydroxide/simethicone-containing antacid, pantoprazole, atorvastatin, an oral contraceptive containing ethinylestradiol and levonorgestrel, metformin, methadone, midazolam, or elbasvir/grazoprevir.

No clinically relevant drug-drug interaction is expected when DELSTRIGO is co-administered with buprenorphine, naloxone, daclatasvir, simeprevir, diltiazem, verapamil, rosuvastatin, simvastatin, canagliflozin, liraglutide, sitagliptin, lisinopril, or omeprazole.

Based on the results of *in vitro* experiments and the known elimination pathways of tenofovir, the potential for CYP-mediated interactions involving tenofovir DF with other medicinal products is low (see section 5.2*, Drug interaction studies*).

No clinically significant drug interactions have been observed between tenofovir DF and the following medications: entecavir, methadone, oral contraceptives, sofosbuvir, or tacrolimus in studies conducted in healthy subjects.

Lamivudine is not significantly metabolised by CYP enzymes nor does it inhibit or induce this enzyme system; therefore, it is unlikely that clinically significant drug interactions will occur through these pathways (see section 5.2*, Drug interaction studies*).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Lamivudine: Lamivudine did not affect male or female fertility in rats at doses associated with exposures (based on C_{max}) up to 70 times higher than the exposures in humans at the RHD.

Tenofovir DF: There were no effects on fertility, mating performance or early embryonic development when tenofovir DF was administered to male rats at a dose (600 mg/kg/day) equivalent to 5 times the RHD based on AUC comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day 7 of gestation. There was, however, an alteration of the oestrous cycle in female rats.

Use in pregnancy (Category B3)

Antiretroviral Pregnancy Registry

To monitor maternal-foetal outcomes of pregnant patients exposed to DELSTRIGO, an International Antiretroviral Pregnancy Registry (APR) has been established. Physicians are

encouraged to register patients via email at SM_APR@INCResearch.com or via facsimile at +1-910-256-0637.

No adequate human data are available to establish whether or not DELSTRIGO poses a risk to pregnancy outcomes. Doravirine use in women during pregnancy has not been evaluated; however, lamivudine and tenofovir DF use during pregnancy has been evaluated in a limited number of women reported to the APR.

Doravirine: Adequate and well controlled studies with doravirine have not been conducted in pregnant women. Reproduction studies performed in rats and rabbits at exposures up to approximately 8 times the exposure in humans at the RHD did not indicate harmful effects of doravirine with respect to pregnancy or embryofoetal or pre/postnatal development. Doravirine was administered orally at up to 300 mg/kg/day to pregnant rabbits on gestation days 7 to 20, and up to 450 mg/kg/day to rats on gestation days 6 to 20, and also to rats on gestation day 6 to lactation/postpartum day 20. Studies in pregnant rats and rabbits showed that doravirine is transferred to the foetus through the placenta, with foetal plasma concentrations of up to 40% (rabbits) and 52% (rats) that of maternal concentrations observed on gestation day 20.

Lamivudine: Reproduction studies performed in rats and rabbits showed no evidence of teratogenicity. Evidence of early embryolethality was seen in the rabbit at exposure levels (based on AUC) less than those observed in humans, but there was no indication of this effect in the rat at exposure levels (based on C_{max}) up to 40 times that at the RHD. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the foetus through the placenta.

Tenofovir DF: Reproduction studies have been performed in rats and rabbits at respective exposures (AUC) of 4-13 and 66-fold the human exposure and revealed no harm to the foetus.

Subcutaneous treatment of pregnant rhesus monkeys with a dose of 30 mg/kg/day of the tenofovir base during the last half of pregnancy resulted in reduced foetal serum phosphorus concentrations.

Use in lactation

Studies in humans have shown that both lamivudine and tenofovir are excreted in human milk. It is unknown whether doravirine is excreted in human milk. Because of the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving DELSTRIGO.

Doravirine: Doravirine was excreted into the milk of lactating rats following oral administration (450 mg/kg/day) from gestation day 6 to lactation day 14, with milk concentrations approximately 1.5 times that of maternal plasma concentrations observed 2 hours post dose on lactation day 14.

Lamivudine: Lamivudine is excreted in human breast milk.

Tenofovir DF: Samples of breast milk obtained from 5 HIV-1-infected mothers in the first postpartum week show that tenofovir is excreted in human milk. The impact of this exposure in breastfed infants is unknown.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of DELSTRIGO on the ability to drive or operate machinery have been performed. Patients should be informed that dizziness has been reported during

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials Experience

Treatment-Emergent Adverse Drug Reactions

The safety assessment of DELSTRIGO in antiretroviral treatment-naïve, HIV-1 infected subjects, is based on the analyses of data through 48 weeks from two Phase 3, randomised, international, multicentre, double-blind, active-controlled trials (DRIVE-FORWARD (Protocol 018) and DRIVE-AHEAD (Protocol 021)).

In DRIVE-FORWARD, 766 adult subjects received either doravirine-PIFELTRO® 100 mg (n=383) or darunavir 800 mg + ritonavir 100 mg (DRV+r) (n=383) once daily, each in combination with emtricitabine/tenofovir DF (FTC/TDF) or abacavir/lamivudine (ABC/3TC). By Week 48, 1.6% in the doravirine-PIFELTRO group and 3.1% in the DRV+r group had adverse events leading to discontinuation of study medication.

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

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

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

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

	DRIVE-FORWARD		DRIVE-AHEAD	
	Doravirine-PIFELTRO +2 NRTIs Once Daily	DRV+r +2 NRTIs Once Daily	DELSTRIGO Once Daily	EFV/FTC/TDF Once Daily
	N=383	N=383	N=364	N=364
Gastrointestinal Disorders				
Abdominal pain upper	2%	<1%	<1%	<1%
Diarrhea	5%	13%	3%	5%
Nausea	7%	8%	5%	7%
Vomiting	2%	1%	2%	3%
General Disorders and Administration Site Conditions				
Fatigue	5%	2%	4%	3%
Nervous System Disorders				
Dizziness	3% 6%	2%	7%	32%

Headache Sleep disorder Somnolence	2% 0%	3% <1% <1%	4% <1% 3%	4% 2% 7%
Psychiatric Disorders Abnormal dreams Insomnia Nightmare	 1% 1% <1%	 <1% 2% <1%	 5% 4% 2%	 9% 5% 4%
Skin and Subcutaneous Disorders Rash	 <1%	 <1%	 2%	 9%
Frequencies of adverse reactions are based on all adverse events attributed to trial drugs by the investigator. †No doravirine. NRTIs=nucleoside reverse transcriptase inhibitor. NRTIs = FTC/TDF or ABC/3TC.				

Laboratory Abnormalities

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

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

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

Grade 2 Grade 3-4	2.5 - <5.0 x ULN	<1% 0%	<1% 0%	0% 0%	<1% <1%
Lipase					
Grade 2 Grade 3-4	1.5 - <3.0 x ULN	4% 3%	5% 2%	5% 1%	4% 2%
Creatine kinase (IU/l					
Grade 2 Grade 3-4	6.0 - <10.0 x ULN	2% 3%	3% 4%	2% 2%	2% 3%
ULN = Upper limit of normal range. Note: NRTIs = FTC/TDF or ABC/3TC.					

Change in Lipids from Baseline

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

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

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

	DRIVE-FORWARD		DRIVE-AHEAD	
Laboratory Parameter Preferred Term	**Doravirine-PIFELTRO +2 NRTIs Once Daily**	**DRV+r +2 NRTIs Once Daily**	**DELSTRIGO Once Daily**	**EFV/FTC/TDF Once Daily**
	N=320	**N=311**	**N=320**	**N=307**
LDL-Cholesterol (mg/dL)*	-4.6	9.5	-2.1	8.3
Non-HDL Cholesterol (mg/dL)*	-5.4	13.7	-4.1	12.7
Total Cholesterol (mg/dL)	-1.4	18.0	-2.2	21.1
Triglycerides (mg/dL)	-3.1	24.5	-12.0	21.6
HDL-Cholesterol (mg/dL)	4.0	4.3	1.8	8.4
Subjects on lipid-lowering agents at baseline were excluded from these analyses (in DRIVE-FORWARD: doravirine-PIFELTRO n=12 and DRV+r n=14; in DRIVE-AHEAD: DELSTRIGO n=15 and EFV/FTC/TDF n=10). Subjects initiating a lipid-lowering agent post-baseline had their last fasted on-treatment value (prior to starting the agent) carried forward (in DRIVE-FORWARD: doravirine-PIFELTRO n=6 and DRV+r n=4; in DRIVE-AHEAD: DELSTRIGO n=3 and EFV/FTC/TDF n=8). *P-values for the pre-specified hypothesis testing for treatment difference were <0.0001 in both DRIVE-FORWARD and DRIVE-AHEAD. Note: NRTIs = FTC/TDF or ABC/3TC.				

Neuropsychiatric Adverse Events

For DRIVE-AHEAD, the analysis of subjects with neuropsychiatric adverse events by Week 48 is presented in Table 5. A statistically significantly lower proportion of DELSTRIGO-treated subjects compared to EFV/FTC/TDF-treated subjects reported neuropsychiatric adverse events by Week 48 in the three pre-specified categories of dizziness, sleep disorders and disturbances, and altered sensorium.

Table 5: DRIVE-AHEAD - Analysis of Subjects with Neuropsychiatric Adverse Events (Week 48)

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

*The 95% CIs were calculated using Miettinen and Nurminen's method.
†Inability to think clearly or concentrate.
‡Not pre-specified for statistical testing.

Discontinuation due to Adverse Events

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

Postmarketing Experience

There are no postmarketing data available for doravirine. See the full prescribing information for lamivudine and tenofovir DF for postmarketing information on these products.

Reporting suspected adverse effects

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

4.9 OVERDOSE

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

Doravirine: There is no known specific treatment for 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 DF: Tenofovir DF is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir DF, a 4-hour haemodialysis session removed approximately 10% of the administered tenofovir dose.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

Lamivudine and Tenofovir DF are HIV-1 nucleoside analogue reverse transcriptase inhibitors (NRTI).

DELSTRIGO is a fixed-dose combination of the antiviral drugs doravirine, lamivudine, and tenofovir DF.

Doravirine: Doravirine is a pyridinone non-nucleoside reverse transcriptase inhibitor of HIV-1 and inhibits HIV-1 replication by allostericinhibition of HIV-1 reverse transcriptase (RT).

Lamivudine: Lamivudine is a synthetic 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 DF: Tenofovir DF is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the -triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA

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 (NHS) using MT4-GFP reporter cells. Doravirine demonstrated antiviral activity against a broad panel of primary HIV-1 isolates (A, A1, AE, AG, B, BF, C, D, G, H) with EC_{50} values ranging from 0.6 nM to 10.0 nM. The antiviral activity of doravirine was not antagonistic when combined with lamivudine and tenofovir DF.

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 microM (1 microM = 0.23 mcg 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-G and group O viruses (n = 3 except n =

2 for clade B) respectively. Ribavirin (50 microM) 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 DF: 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 0.04–8.5 microM. 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 0.5–2.2 microM).

Effects on Electrocardiogram

At a doravirine dose of 1200 mg, which provides approximately 4 times the peak concentration observed following the maximum approved dose, doravirine does not prolong the QT interval to any clinically relevant extent.

Microbiology

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, F227C, F227V, H221Y, M230I, L234I, P236L, and Y318F.

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 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

Tenofovir DF: HIV-1 isolates selected by tenofovir *in vitro* expressed a K65R substitution in HIV-1 RT and showed a 3–4- 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 tenofovir and reduced susceptibility to abacavir, emtricitabine, and lamivudine.

In Clinical Trials

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

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

Lamivudine and Tenofovir DF: In a pooled analysis of antiretroviral-naïve subjects who received doravirine, lamivudine, and tenofovir DF, genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-1 RNA greater than 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).

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: Laboratory strains of HIV-1 harbouring the common NNRTI-associated mutations K103N, Y181C, or K103N/Y181C substitutions in RT exhibit less than a 3-fold decrease in susceptibility to doravirine compared to wild-type virus when evaluated in the presence of 100% NHS. Doravirine was able to suppress the following NNRTI-associated substitutions: K103N, Y181C, G190A, and E138K mutants under clinically relevant concentrations.

A panel of 96 diverse clinical isolates containing NNRTI-associated mutations was evaluated for susceptibility to doravirine in the presence of 10% foetal bovine serum. Clinical isolates containing the Y188L substitution alone or Y188L or V106A substitutions in combination with E138K, F227L, G190A, K103N and/or M230L showed a greater than 100-fold reduced susceptibility to doravirine.

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

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 reverse transcriptase inhibitors, including lamivudine, have emerged.

Tenofovir DF: 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 harbors the K65R substitution. The K70E substitution selected clinically by tenofovir DF 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 DF. 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 trials

Treatment-Naïve Adult Subjects

The efficacy of DELSTRIGO is based on the analyses of 48-week data from two randomized, multicentre, double-blind, active controlled Phase 3 trials, (DRIVE-FORWARD and DRIVE-AHEAD) in antiretroviral treatment-naïve, HIV-1 infected subjects (n=1494).

In DRIVE-FORWARD, 766 subjects were randomized and received at least 1 dose of either doravirine-DELSTRIGO once daily or DRV+r 800/100 mg once daily each in combination with emtricitabine/tenofovir DF (FTC/TDF) or abacavir/lamivudine (ABC/3TC) selected by the investigator. At baseline, the median age of subjects was 33 years, 16% were female, 27% were non-white, 4% had hepatitis B and/or C virus co-infection, 10% had a history of AIDS, 20% had HIV-1 RNA greater than 100,000 copies/mL, 86% had CD4+ T-cell count greater than 200 cells/mm^3, 13% received ABC/3TC and 87% received FTC/TDF; these characteristics were similar between treatment groups.

In DRIVE-AHEAD, 728 subjects were randomised and received at least 1 dose of either DELSTRIGO or EFV/FTC/TDF once daily. At baseline, the median age of subjects was 31 years, 15% were female, 52% were non-white, 3% had hepatitis B or C co-infection, 14% had a history of AIDS, 21% had HIV-1 RNA greater than 100,000 copies/mL, and 88% had CD4+ T-cell count greater than 200 cells/mm^3; these characteristics were similar between treatment groups.

Week 48 outcomes for DRIVE-FORWARD and DRIVE-AHEAD are provided in Table 6. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

In DRIVE-FORWARD, doravirine-PIFELTRO demonstrated consistent efficacy across demographic and baseline prognostic factors, including gender, race, ethnicity, NRTI background therapy, baseline HIV- -cell count, and viral subtypes. Mean CD4+ T-cell counts in the doravirine-PIFELTRO and DRV+r groups increased from baseline by 193 and 186 cells/mm^3, respectively.

In DRIVE-AHEAD, DELSTRIGO demonstrated consistent efficacy across demographic and baseline prognostic factors, including gender, race, ethnicity, baseline HIV- or >100,000 copies/mL), CD4+ T-cell count, and viral subtypes. Mean CD4+ T-cell counts in the DELSTRIGO and EFV/FTC/TDF groups increased from baseline by 198 and 188 cells/mm^3, respectively.

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

Outcome	DRIVE-FORWARD		DRIVE-AHEAD	
	Doravirine-PIFELTRO + 2 NRTIs Once Daily	**DRV+r + 2 NRTIs Once Daily**	**DELSTRIGO Once Daily**	**EFV/FTC/TDF Once Daily**
	N=383	**N=383**	**N=364**	**N=364**
HIV-1 RNA <50 copies/mL	84%	80%	84%	81%
Treatment Differences (95% CI)*	3.9% (-1.6%, 9.4%)		3.5% (-2.0%, 9.0%)	
HIV- †	11%	13%	11%	10%
No Virologic Data at Week 48 Window	5%	7%	5%	9%
Reasons				
Discontinued study due to AE or Death‡	1%	3%	2%	7%

Discontinued study for Other Reasons[§]	3%	4%	2%	2%
On study but missing data in window	<1%	<1%	0	<1%
Proportion (%) of Subjects With HIV-1 RNA <50 copies/mL at Week 48 by Baseline and Demographic Category				
Gender				
Male	84%	82%	84%	80%
Female	81%	67%	85%	83%
Race				
White	87%	83%	84%	81%
Non-White	75%	73%	84%	80%
Ethnicity				
Hispanic or Latino	88%	81%	83%	84%
Not Hispanic or Latino	82%	79%	85%	79%
NRTI Background Therapy				
FTC/TDF	83%	81%	-	-
ABC/3TC	86%	75%	-	-
Baseline HIV-1 RNA (copies/mL)				
	86%	81%	86%	83%
>100,000 copies/mL	77%	74%	77%	72%
CD4+ T-cell Count (cells/mm^3)				
	81%	66%	66%	78%
>200 cells/mm3	84%	83%	87%	81%
Viral Subtype				
Subtype B	84%	82%	84%	80%
Subtype Non-B	83%	76%	85%	83%

*The 95% CIs for the treatment differences were calculated using stratum-adjusted Mantel-Haenszel method.

[†]Includes subjects who discontinued study drug or study before Week 48 for lack or loss of efficacy and subjects with HIV-1 RNA equal to or above 50 copies/mL in the Week 48 window (relative day 295-378).

[‡]Includes subjects who discontinued because of adverse event (AE) or death if this resulted in no virologic data in the Week 48 window.

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

Note: NRTIs = FTC/3TC or ABC/3TC.

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

At Week 48, the proportion of subjects with HIV-1 RNA less than 50 copies/mL was 79% (85/108) and 82% (89/108) for doravirine-PIFELTRO 100 mg and EFV, respectively (FDA Snapshot Approach). At Week 96, the proportion of subjects with HIV-1 RNA less than 50 copies/mL was 76% (82/108) and 76% (82/108) for doravirine-PIFELTRO 100 mg and EFV, respectively. At Week 48, mean CD4+ T-cell counts in the doravirine-PIFELTRO 100 mg and EFV groups increased from baseline by 192 and 195 cells/mm^3, respectively. At Week 96, mean CD4+ T-cell counts in the doravirine-PIFELTRO 100 mg and EFV groups increased from baseline by 259 and 264 cells/mm^3, respectively.

5.2 PHARMACOKINETIC PROPERTIES

Single-dose administration of one DELSTRIGO 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 DF tablets (300 mg).

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 is generally achieved by Day 2 of once daily dosing, with accumulation ratios of 1.2 to 1.4 for AUC_{0-24}, C_{max}, and C_{24}. Doravirine steady state pharmacokinetics following administration of 100 mg once daily to HIV-1 infected subjects, based on a population pharmacokinetic analysis, are provided below.

Parameter GM (%CV)	**AUC_{0-24}**	**C_{max}**	**C_{24} nM**
Doravirine 100 mg once daily	37.8 (29)	2.26 (19)	930 (63)
GM: geometric mean, %CV: Geometric coefficient of variation			

Absorption

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

Distribution

Based on administration of an IV microdose, the volume of distribution of doravirine is 60.5 L. Doravirine is approximately 76% bound to plasma proteins.

Metabolism

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

Excretion

Doravirine: Doravirine has a terminal half-life ($t_{1/2}$) of approximately 15 hours. Doravirine is primarily eliminated via oxidative metabolism. Excretion of unchanged drug via urinary excretion is minor. Biliary excretion of unchanged drug is not expected to be significant.

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 mcg per mL (mean ± SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg•hour per mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug 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, HBV-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 DF: Following oral administration of a single 300 mg dose of tenofovir DF to HIV-1-infected subjects in the fasted state, C_{max} was achieved in one 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 DF 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 70-80% of the intravenous dose of tenofovir is recovered as unchanged drug 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 creatinine clearance greater than 80 mL per minute of 243.5 ± 33.3 mL per minute (mean ± SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Effect of Food on Oral Absorption

The administration of a single DELSTRIGO tablet with a high-fat meal to healthy subjects resulted in a 26% increase in doravirine C_{24}, 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.

Special populations

Renal Impairment

Doravirine: Renal excretion of doravirine is minor: approximately 6% of the administered dose is excreted unchanged in urine. In a study comparing 8 subjects with severe (eGFR 15-<30 mL/min/1.73 m^2) renal impairment to 8 subjects without renal impairment, the single dose exposure of doravirine was 43% higher in subjects with severe renal impairment. In a population pharmacokinetic analysis, renal function did not have a clinically relevant effect on doravirine pharmacokinetics. No dose adjustment is required in patients with mild, moderate or severe (eGFR 15-<30 mL/min/1.73 m^2) renal impairment. Doravirine has not been studied in patients with end-stage renal disease or in patients undergoing dialysis (see section 4.4).

Lamivudine: The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-1–infected adults with impaired renal function (Table 7).

Table 7: Pharmacokinetic Parameters (Mean ± SD) After a Single 300-mg Oral Dose of Lamivudine in 3 Groups of Adults with Varying Degrees of Renal Function

	Creatine Clearance Criterion (Number of Subjects)		
Parameter	**>60 mL/min**	**10-30 mL/min**	**<10 mL/min**
	N=6	**N=4**	**N=6**
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C_{max} (mcg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

Tenofovir DF: The pharmacokinetics of tenofovir are altered in subjects with renal impairment. In subjects with creatinine clearance below 50 mL per minute or with end stage renal disease requiring dialysis, C_{max} and AUC of tenofovir were increased (see section 4.4).

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 (Child-Pugh score B) to 8 subjects without hepatic impairment. No dose adjustment is required in patients with mild or moderate hepatic impairment. Doravirine has not been studied in subjects with severe hepatic impairment (Child-Pugh score C) (see section 4.4).

Lamivudine: The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. 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 DF: The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir DF 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

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

Elderly

No clinically relevant differences in the pharmacokinetics of doravirine have been identified in subjects at least 65 years of age compared to subjects less than 65 years of age in a Phase 1 trial or in a population pharmacokinetic analysis. The pharmacokinetics of lamivudine and tenofovir have not been studied in subjects older than 65 years. The pharmacokinetics of doravirine have been studied in a limited number of subjects (n=4) over 75 years or age (see section 4.4).

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 DF: 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 DF.

Gender

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

Drug Interaction Studies

DELSTRIGO is a complete regimen for the treatment of HIV-1 infection; therefore, DELSTRIGO should not be administered with other HIV-1 antiretroviral medications. Information regarding potential drug-drug interactions with other antiretroviral medications is not provided.

The drug interaction trials described were conducted with doravirine, lamivudine and/or tenofovir DF, as single entities; no drug interaction trials have been conducted using the combination of doravirine lamivudine and tenofovir DF. No clinically relevant drug interactions were observed between doravirine, lamivudine and tenofovir DF128.

Doravirine

Doravirine is primarily metabolised by CYP3A, and drugs that induce or inhibit CYP3A may affect the clearance of doravirine. Co-administration of doravirine and drugs that induce CYP3A may result in decreased plasma concentrations of doravirine. Co-administration of doravirine and drugs that inhibit CYP3A may result in increased plasma concentrations of doravirine.

Doravirine is not likely to have a clinically relevant effect on the exposure of medicinal products metabolised by CYP enzymes. Drug interaction studies were performed with doravirine and other drugs likely to be co-administered or commonly used as probes for pharmacokinetic interactions. The effects of co-administration of other drugs on the C_{max}, AUC, and C_{24} values of doravirine are summarised in Table 8. The effects of co-administration of doravirine on the C_{max} and AUC values of other drugs are summarised in Table 9 (see section 4.5).

Table 8: Drug Interactions: Changes in Pharmacokinetic Parameter Values of Doravirine in the Presence of Co-administered Drug

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Doravirine	N	Geometric Mean Ratio (90% CI) of Doravirine Pharmacokinetics with/without Co-administered Drug (No Effect=1.00)		
				AUC*	C_{max}	C_{24}
Azole Antifungal Agents						
ketoconazole	400 mg QD	100 mg SD	10	3.06 (2.85, 3.29)	1.25 (1.05, 1.49)	2.75 (2.54, 2.98)
Antimycobacterials						
rifampin	600 mg SD	100 mg SD	11	0.91 (0.78, 1.06)	1.40 (1.21, 1.63)	0.90 (0.80, 1.01)
	600 mg QD	100 mg SD	10	0.12 (0.10, 0.15)	0.43 (0.35, 0.52)	0.03 (0.02, 0.04)
rifabutin	300 mg QD	100 mg SD	12	0.50 (0.45, 0.55)	0.99 (0.85, 1.15)	0.32 (0.28, 0.35)
HIV Antiviral Agents						
tenofovir DF	300 mg QD	100 mg SD	7	0.95 (0.80, 1.12)	0.80 (0.64, 1.01)	0.94 (0.78, 1.12)
lamivudine + tenofovir DF	300 mg lamivudine SD + 300 mg tenofovir DF SD	100 mg SD	15	0.96 (0.87, 1.06)	0.97 (0.88, 1.07)	0.94 (0.83, 1.06)
Hepatitis C Antiviral Agents						

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Doravirine	N	Geometric Mean Ratio (90% CI) of Doravirine Pharmacokinetics with/without Co-administered Drug (No Effect=1.00)		
				AUC*	C_{max}	C_{24}
elbasvir + grazoprevir	50 mg elbasvir QD + 200 mg grazoprevir QD	100 mg QD	12	1.56 (1.45, 1.68)	1.41 (1.25, 1.58)	1.61 (1.45, 1.79)
ledipasvir + sofosbuvir	90 mg ledipasvir SD + 400 mg sofosbuvir SD	100 mg SD	14	1.15 (1.07, 1.24)	1.11 (0.97, 1.27)	1.24 (1.13, 1.36)
Acid-Reducing Agents						
antacid (aluminium and magnesium hydroxide oral suspension)	20 mL SD	100 mg SD	14	1.01 (0.92, 1.11)	0.86 (0.74, 1.01)	1.03 (0.94, 1.12)
pantoprazole	40 mg QD	100 mg SD	13	0.83 (0.76, 0.91)	0.88 (0.76, 1.01)	0.84 (0.77, 0.92)
Opioid Analgesics						
methadone	20-200 mg QD individualized dose	100 mg QD	14	0.74 (0.61, 0.90)	0.76 (0.63, 0.91)	0.80 (0.63, 1.03)

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

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

Table 9: Drug Interactions: Changes in Pharmacokinetic Parameter Values for Co-administered Drugs in the Presence of Doravirine

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Doravirine	N	Geometric Mean Ratio [90% CI] Drug Pharmacokinetics with/without Co-administered Doravirine (No Effect=1.00)		
				AUC*	C_{max}	C_{24}
CYP3A Substrate						
midazolam	2 mg SD	120 mg QD	7	0.82 (0.70, 0.97)	1.02 (0.81, 1.28)	-
HIV-Antiviral Agents						
lamivudine	300 mg lamivudine SD + 300 mg tenofovir DF SD	100 mg SD	15	0.94 (0.88, 1.00)	0.92 (0.81, 1.05)	-
tenofovir DF				1.11 (0.97, 1.28)	1.17 (0.96, 1.42)	-
HCV-Antiviral Agents						
elbasvir	50 mg elbasvir QD + 200 mg grazoprevir QD	100 mg QD	12	0.96 (0.90, 1.02)	0.96 (0.91, 1.01)	0.96 (0.89, 1.04)
grazoprevir				1.07 (0.94, 1.23)	1.22 (1.01, 1.47)	0.90 (0.83, 0.96)
ledipasvir	90 mg ledipasvir SD + 400 mg sofosbuvir SD	100 mg SD	14	0.92 (0.80, 1.06)	0.91 (0.80, 1.02)	--
sofosbuvir				1.04 (0.91, 1.18)	0.89 (0.79, 1.00)	--

GS-331007†				1.03 (0.98, 1.09)	1.03 (0.97, 1.09)	--
Oral Contraceptives						
ethinyl estradiol	0.03 mg ethinyl estradiol + 0.15 mg levonorgestrel (Nordette®-28) SD	100 mg QD	19	0.98 (0.94, 1.03)	0.83 (0.80, 0.87)	--
levonorgestrel				1.21 (1.14, 1.28)	0.96 (0.88, 1.05)	--
Statins						
atorvastatin	20 mg SD	100 mg QD	14	0.98 (0.90, 1.06)	0.67 (0.52, 0.85)	-
Antidiabetics						
metformin	1000 mg SD	100 mg QD	14	0.94 (0.88, 1.00)	0.94 (0.86, 1.03)	-
Opioid Analgesics						
methadone (R-methadone)	20-200 mg QD individualized dose	100 mg QD	14	0.95 (0.90, 1.01)	0.98 (0.93, 1.03)	0.95 (0.88, 1.03)
methadone (S-methadone)				0.98 (0.90, 1.06)	0.97 (0.91, 1.04)	0.97 (0.86, 1.10)

CI = Confidence interval; SD = Single Dose; QD = Once Daily.

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

†The predominant circulating nucleoside metabolite of sofosbuvir.

Lamivudine

Trimethoprim/Sulfamethoxazole: Lamivudine and trimethoprim/sulfamethoxazole (TMP/SMX) were co-administered to 14 HIV-positive patients in a single-centre, open-label, randomised, crossover study. Each patient received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design. Co-administration of TMP/SMX with lamivudine resulted in an increase of 43% ±23% (mean

decrease of 30% ±36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by co-administration with lamivudine.

Tenofovir DF

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, co-administration of tenofovir DF with drugs that are eliminated by active tubular secretion may increase concentrations of tenofovir, and/or the co-administered drug (see section 4.4 and 4.5).

Drug interaction studies were performed for tenofovir DF and the following medications: entecavir, methadone, oral contraceptives (ethinylestradiol/norgestimate), and tacrolimus. Tacrolimus increased the C_{max}
effect on the tenofovir AUC and C_{min}. Tenofovir had no effect on the C_{max}, AUC, and C_{min} of tacrolimus.

The C_{max}, AUC, and C_{min} of tenofovir were not affected in the presence of entecavir.

effect on the entecavir C_{max} and C_{min}.

Tenofovir had no effect on the C_{max}, AUC, and C_{min} of methadone or ethinyl estradiol/norgestimate.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

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, and in an assay for unscheduled DNA synthesis in rat liver.

Tenofovir DF: Tenofovir DF was mutagenic in the *in vitro* mouse lymphoma assay and in an ex vivo assay for unscheduled DNA synthesis in rat hepatocytes, but it was negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, tenofovir DF was negative when administered to male mice.

Carcinogenicity

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

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 DF: Long-term oral carcinogenicity studies of tenofovir DF in mice and rats were carried out at doses up to 600 and 300 mg/kg/day, respectively, resulting in exposures up to approximately 15 times (mice) and 5 times (rats) those observed in humans at the RHD (based on AUC). At the high dose (600 mg/kg/day) in female mice, liver adenomas were increased at exposures 15 times of that in humans. These were associated with a high incidence of duodenal mucosal hyperplasia, which was also observed with a dose of 300 mg/kg/day. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the RHD.

Animal Toxicology

No animal studies have been conducted with DELSTRIGO. The following data are based on findings in separate studies with the individual components of DELSTRIGO (doravirine, lamivudine, and tenofovir disoproxil fumarate).

Chronic Toxicity

Doravirine: In repeat-dose oral toxicity studies, doravirine was very well tolerated in all animal species up to the highest doses tested. There were no adverse effects or target organs of toxicity identified in rats dosed for 6 months with 450 mg/kg/day, or in dogs dosed with 1000 mg/kg/day for 9 months (approximately 7 times and 18 times, respectively, above the exposure at the RHD).

Lamivudine: In repeat-dose toxicity studies, lamivudine was very well tolerated in the rat at oral doses up to 2000 mg/kg b.i.d. for 6 months and in dogs up to 1000 mg/kg/b.i.d for up to 12 months. In dogs, deaths were seen in females dosed with 1500 mg/kg b.i.d. in a 3-month study. Treatment-related effects in chronic toxicity studies were restricted to minor haematological (mainly red cell parameters), clinical chemistry and urinalysis changes, and mucosal hyperplasia of the cecum (in rats). Haematological changes included reductions in

red cell counts at all dose levels, associated with increased MCV and MCH, and reductions in total leucocyte, neutrophil and lymphocyte counts in high-dose animals, but with no effect on bone marrow cytology. The no (toxicologically important) effect level was 450 mg/kg b.i.d in rats and 45 mg/kg/day in dog, which is approximately 17-fold and 9-fold respectively above the human exposure at the RHD.

Tenofovir DF: Tenofovir and tenofovir DF administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in the 4 animal species tested. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet includes the following inactive ingredients: colloidal anhydrous silica, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, sodium stearylfumarate, and carnauba wax. The tablets are film coated with a coating material containing the following inactive ingredients: hypromellose, iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store DELSTRIGO in the original bottle. Keep the bottle tightly closed to protect from moisture. Do not remove the desiccants.

Store DELSTRIGO below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

DELSTRIGO (doravirine/lamivudine/tenofovir disoproxil fumarate) is available in HDPE (high density polyethylene) bottles of 30 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

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

The chemical name for doravirine is 3-chloro-5-[[1-[(4,5-dihydro-4-methyl-5-oxo-1*H*-1,2,4-triazol-3-yl)methyl]-1,2-dihydro-2-oxo-4-(trifluoromethyl)-3-pyridinyl]oxy]benzonitrile. It has a molecular formula of $C_{17}H_{11}ClF_3N_5O_3$ and a molecular weight of 425.75.

Lamivudine: Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine and is an HIV-1 nucleoside analogue reverse transcriptase inhibitor.

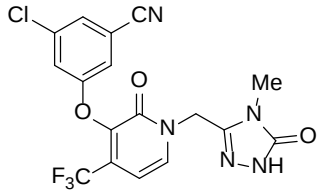
The chemical name for lamivudine is (-)-1-[(*2R,5S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-cytosine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.26.

Tenofovir DF: Tenofovir DF (a prodrug of tenofovir) is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. *In vivo* tenofovir DF is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analogue of adenosine 5'-monophosphate. Tenofovir diphosphate is an HIV-1 reverse transcriptase inhibitor.

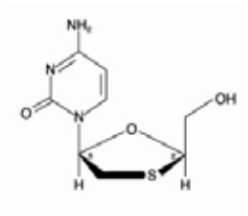
The chemical name for tenofovir DF is 9-[(*R*)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy] phosphinyl]- methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}$ P·$C_4H_4O_4$ and a molecular weight of 635.52.

Chemical structure

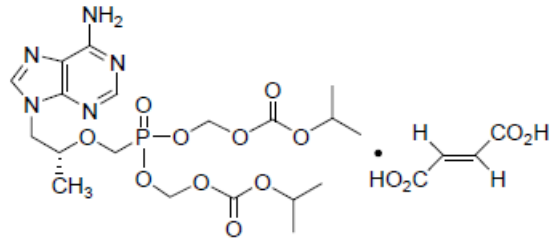
Doravirine:



Lamivudine:



Tenofovir DF:



CAS number

Doravirine: 1338225-97-0

Lamivudine: 134678-17-4

Tenofovir DF: 202138-50-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4).

8 SPONSOR

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www.msd-australia.com.au

9 DATE OF FIRST APPROVAL

18 January 2019

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