PROFESSIONAL INFORMATION FOR

ALFIDA

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ALFIDA

(**Dolutegravir 50 mg, Emtricitabine 200 mg and Tenofovir alafenamide fumarate 25 mg**) **film coated tablets.**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir, 200 mg emtricitabine and tenofovir alafenamide fumarate equivalent to 25 mg tenofovir alafenamide.

Contains Sugar: mannitol 145 mg per film coated tablet.

For full list of excipients, (**see section 6.1)**

3. PHARMACEUTICAL FORM

ALFIDA film coated tablets:

Pink coloured capsule shaped, biconvex film coated tablet debossed with “Cipla” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

ALFIDA is indicated:

- for use alone as a complete regimen for the treatment of human immunodeficiency virus - 1 (HIV-1) infection in adults and paediatric patients weighing at least 40 kg.

4.2. Posology and method of administration

ALFIDA therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

Prior to initiation of ALFIDA , patients should be tested for hepatitis B virus infection (**see section 4.4**).

Estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating ALFIDA therapy and should be monitored during therapy in all patients (**see section 4.4**).

Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in all individuals.

Posology:

Treatment of HIV-1 infection in adults and paediatric patients weighing at least 40 kg

The dose of ALFIDA is one tablet once daily taken with or without food.

(**see section 4.5**)

Special Populations

Elderly patients

Dolutegravir

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure. Pharmacokinetic data for dolutegravir in subjects of > 65 years old are limited. In general, caution should be exercised in the administration of dolutegravir in elderly patients reflecting the

greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other medicine therapy. (**see section 4.4 and 4.5**)

Emtricitabine and Tenofovir

Pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in the elderly (> 65 years). (**see section 4.4**).

Clinical studies of emtricitabine and tenofovir disoproxil fumarate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be done with caution, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other medicine therapy.

In clinical trials, 80 subjects out of the 97 subjects enrolled aged 65 years and over received emtricitabine (FTC), tenofovir alafenamide (TAF), elvitegravir (EVG) and cobicistat (COBI). No differences in safety or efficacy have been observed between elderly subjects and adults between 18 and less than 65 years of age.

Renal Impairment

ALFIDA tablets are not recommended for patients with severe renal impairment (estimated creatinine clearance below 30 mL per min) because ALFIDA tablets are a fixed-dose combination and the dosage of the individual components cannot be adjusted. No dosage adjustment of ALFIDA tablets is recommended in patients with mild or moderate renal impairment (estimated creatinine clearance greater than or equal to 30 mL per minute).

Hepatic Impairment

Dolutegravir

No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh grade A). ALFIDA is contra-indicated in patients with moderate or severe hepatic impairment (**see section 4.3**).

Tenofovir

The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir disoproxil fumarate have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. No change in tenofovir disoproxil fumarate dosing is required in patients with hepatic impairment.

Emtricitabine and Tenofovir

The pharmacokinetics of tenofovir and emtricitabine or emtricitabine has not been studied in patients with hepatic impairment; however, emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment should be limited.

No dosage adjustment of dolutegravir, emtricitabine and tenofovir alafenamide tablets is recommended in patients with mild (Child-Pugh Class A) hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of dolutegravir, emtricitabine and tenofovir alafenamide has not been studied.

Therefore, ALFIDA tablets are not recommended for use in patients with moderate or severe hepatic impairment (**see section 4.3**).

Paediatric Population

ALFIDA should only be administered to adolescents patients with a body weight of at least 40 kg because it is a fixed-dose combination that cannot be adjusted. The safety and efficacy have been established for the individual components in this weight group.

Method of administration

ALFIDA film coated tablets is a fixed dose combination that cannot be adjusted. ALFIDA is taken orally with or without food.

4.3. Contraindications

- ALFIDA is contraindicated in patients with previously demonstrated hypersensitivity to dolutegravir, emtricitabine and tenofovir alafenamide or any of the components of ALFIDA (**see section 6.1**).
- ALFIDA is contraindicated in combination with dofetilide. (**See section 4.5**)
- ALFIDA is contraindicated in combination with pilsicainide. (**See section 4.5**)
- ALFIDA is contraindicated in patients taking metformin (**See section 4.5**)
- ALFIDA should not be co-administered with other tenofovir-containing medicines, or with other emtricitabine-containing medicines.
- ALFIDA should not be administered with lamivudine - containing medicines due to similarities between emtricitabine and lamivudine.
- ALFIDA is contraindicated in moderate and severe hepatic impairment.
- ALFIDA is contraindicated in severe renal impairment, creatinine clearance < 30 mL/min (renal impairment).
- Antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation
- ALFIDA is contraindicated in Pregnancy and lactation.

4.4. Special warnings and precautions for use

Hypersensitivity reactions

Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir and were characterised by rash, constitutional findings and sometimes, organ dysfunction, including liver injury. Discontinue ALFIDA and other suspect medicines immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash

accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia and angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with ALFIDA or other suspect medicines after the onset of hypersensitivity may result in a life-threatening reaction.

Risk of Adverse Reactions or Loss of Virologic Response Due to Interactions

The concomitant use of ALFIDA tablets and other medicines may result in known or potentially significant interactions, some of which may lead to loss of therapeutic effect of ALFIDA tablets and possible development of resistance and possible clinically significant adverse reactions from greater exposures of concomitant medicine (**see section 4.3 and section 4.8**).

Consider the potential for interactions prior to and during therapy with ALFIDA tablets; review concomitant medicines during therapy with ALFIDA tablets; and monitor for the adverse reactions associated with the concomitant medicines.

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/severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been

reported with the use of nucleoside analogues including emtricitabine, a component of ALFIDA tablets, and tenofovir disoproxil fumurate, another prodrug of tenofovir, alone or in combination with other antiretrovirals.

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Tenofovir alafenamide, one component of ALFIDA tablets, is approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued medicines containing tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of ALFIDA tablets. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue ALFIDA tablets. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

This is caused by mitochondrial dysfunction. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues such as ALFIDA to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with ALFIDA film coated tablets should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

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 to 5 mmol/L with minimum symptoms: Switch to medicines that are less likely to cause lactic acidosis.

• Lactate 5 to 10 mmol/L with symptoms and/or with reduced standard bicarbonate:

Stop ALFIDA 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 ALFIDA to patients with known risk factors for liver disease. Treatment with ALFIDA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues such as emtricitabine and tenofovir disoproxil fumarate 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 post-natally to nucleoside analogues, these have predominantly concerned treatment with regimens containing zidovudine and may be the case with ALFIDA. 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 signs and symptoms.

Immune Reconstitution Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART and occurs more commonly in patients with low CD4 counts.

Relevant examples are tuberculosis, cytomegalovirus retinitis, generalised and/or focal atypical mycobacterial infections and Pneumocystis jiroveci (P. carinii) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Auto-immune disorders (such as Graves' disease, polymyositis and Guillain- Barre 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 and sometimes can be an atypical presentation.

Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of dolutegravir therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection.

Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B co-infected patients (**see section 4.8**).

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.

Hepatoxicity

The unbound fraction of dolutegravir in the blood is doubled in patients with moderate hepatic impairment. Dolutegravir is not recommended in patients with moderate or hepatic impairment (**see section 4.3**) Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir, emtricitabine and tenofovir alafenamide tablets. In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver failure have been reported in patients receiving a dolutegravir-containing regimen without pre-existing hepatic disease or other identifiable risk factors. Medicine-induced liver injury leading to liver transplant has been reported with fixed-dose abacavir, dolutegravir, and lamivudine. Monitoring for hepatotoxicity is recommended.

The use of emtricitabine and tenofovir disoproxil fumarate can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of emtricitabine and tenofovir disoproxil fumarate has not been established in patients with significant underlying liver disorders/diseases. 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.

Co-infection with Hepatitis B or C

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.

Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy.

Dolutegravir

In Phase III studies, patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn. This may occur with ALFIDA as dolutegravir is a component thereof.

Emtricitabine and Tenofovir

Tenofovir alafenamide, one component of ALFIDA film coated tablets, is approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are co-infected with HIV-1 and HBV and have discontinued products containing tenofovir disoproxil fumarate (TDF) or emtricitabine and may occur with ALFIDA film coated tablets. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients co-infected with HIV-1 and HBV who discontinue emtricitabine or tenofovir, which are components of ALFIDA film coated tablets.

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.

Opportunistic infections

Patients receiving ALFIDA may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by medical practitioners experienced in the treatment of these associated HIV diseases. Regular monitoring of viral load and CD4 counts needs to be done.

Transmission of infection

Patients should be advised that current antiretroviral therapy, including ALFIDA, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken. ALFIDA are not indicated for use as preexposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.

Pancreatitis

Pancreatitis has been observed in some patients receiving emtricitabine and tenofovir disoproxil fumarate and may occur in ALFIDA.

Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of ALFIDA until diagnosis of pancreatitis is excluded.

Renal impairment

Emtricitabine and tenofovir disoproxil fumarate are principally eliminated by the kidney. In patients with moderate to severe renal impairment, the terminal half-life of tenofovir disoproxil fumarate is increased due to decreased clearance. Estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating ALFIDA film coated tablets therapy. All patients

should be monitored during therapy with ALFIDA . 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 prodrugs in both animal toxicology studies and human trials (**see section 4.3**). Calculated creatinine clearance and serum phosphorus should be routinely monitored in patients with chronic kidney disease because these patients are at greater risk of developing Fanconi syndrome on tenofovir prodrugs (**see section 4.3**).

Discontinue ALFIDA in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. ALFIDA should be avoided with concurrent or recent use of a nephrotoxic medicines including non-steroidal anti-inflammatory medicines are at increased risk of developing renal-related adverse reactions. ALFIDA should not be administered to patients with creatinine clearance below 50 mL/min or patients requiring haemodialysis (**see section 4.3**).

Renal impairment in adults can be determined using the South African Renal Society modification of the Cockroft and Gault formula for calculation of creatinine clearance: Use the eCrCl mL/min=[(140-age) x weight (kg) x 0.85 (if female)] divided by serum creatinine (micromoles/litre).

Renal impairment is classified accordingly:

- mild renal impairment: CrCl ≥ 50-80 mL/min
- moderate renal impairment CrCl > 30-50 mL/min
- severe renal impairment CrCl < 30 mL/min.

Bone effects

Bone mineral density monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Tenofovir combination therapy is associated with decreased bone mineral density. During therapy with emtricitabine and tenofovir disoproxil fumarate assessment of bone mineral density (BMD) should be considered for patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. The effect of supplementation with calcium and vitamin D was not studied, such supplementation

may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

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 or renal function in at-risk patients. These manifest as bone pain or pain in extremities and which may contribute to fractures, and have been reported in association with the use of tenofovir disoproxil fumarate and may occur in ALFIDA (**see section 4.8**).

In clinical trials of HIV-1 uninfected individuals, decreases in BMD were also observed. In a pre-exposure trial of men having sex with men (MSM), a sub study of 503 subjects found mean changes from baseline in BMD ranging from -0,4 % to -1,0 % across total hip, spine, femoral neck, and trochanter in the emtricitabine and tenofovir disoproxil fumarate group compared with the placebo group. Bone fractures were reported in 1,7 % of the emtricitabine and tenofovir disoproxil fumarate group compared with 1,4 % in the placebo group. No correlation between BMD and fractures was noted. A pre-exposure study in heterosexual couples where one of the partners was HIV-1 infected, found similar fracture rates between treatment and placebo groups (0,8 % and 0,6 %, respectively). No BMD evaluations were conducted during this trial.

Cases of hypophosphatemia and osteomalacia (associated with proximal renal tubulopathy) have been reported in association with the use of tenofovir disoproxil fumarate (**see section 4.8**) and may occur with ALFIDA.

Paediatric population

Safety and effectiveness in paediatric patients have not been established and should only be administered to adolescents patients with a body weight of at least 40 kg because it is are a fixed-dose combination that cannot be adjusted. The safety and efficacy have been established for the individual components in this weight group.

Elderly population

Dolutegravir

Clinical trials of dolutegravir did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of dolutegravir in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other medicine therapy.

Emtricitabine and Tenofovir Alafenamide

In clinical trials, 80 of the 97 subjects enrolled aged 65 years and over received FTC + TAF and EVG + COBI. No differences in safety or efficacy have been observed between elderly subjects and adults between 18 and less than 65 years of age.

4.5. Interaction with other medicines and other forms of interaction

Dolutegravir

Caution should be given to co-administering medications (prescription and non-prescription) that may change the exposure of dolutegravir which is a component of ALFIDA or medications that may have their exposure changed by dolutegravir, which is a component of ALFIDA (**see section 4.3**).

Dolutegravir should not be co-administered with polyvalent cation-containing antacids.

Dolutegravir is recommended to be administered 2 hours before or 6 hours after these agents.

Emtricitabine or tenofovir

ALFIDA should not be co-administered with other medicines containing emtricitabine or tenofovir (**see section 4.3**).

Due to similarities between emtricitabine and lamivudine, ALFIDA should not be co-administered with other medicines containing lamivudine, including lamivudine and zidovudine co-formulation, lamivudine for HIV, lamivudine for HBV, abacavir sulfate and lamivudine co - formulation or abacavir sulfate, lamivudine and zidovudine co-formulation (**see section 4.3**).

Co-administration of didanosine buffered tablet formulation with ALFIDA should be under fasted conditions.

Co-administration of ALFIDA and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine associated adverse events (**see section 4.8**).

Patients receiving atazanavir and lopinavir/ritonavir and ALFIDA should be monitored for ALFIDA -associated adverse events. ALFIDA should be discontinued in patients who develop ALFIDA -associated adverse events (**see section 4.8**).

Tenofovir decreases the AUC and C_{min} of atazanavir. When co-administered with ALFIDA, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be co-administered with ALFIDA. Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of ALFIDA with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated medicines. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, aciclovir, valaciclovir, ganciclovir and valganciclovir.

The concomitant use of dolutegravir, emtricitabine and tenofovir alafenamide tablets and other medicines may result in known or potentially significant medicine interactions, some of which may lead to (**see section 4.3**):

• Loss of therapeutic effect of dolutegravir, emtricitabine and tenofovir alafenamide tablets and possible development of resistance.

• Possible clinically significant adverse reactions from greater exposures of concomitant medicines.

For concomitant medicines for which the interaction can be mitigated, please see Table 6 for steps to prevent or manage these possible and known significant medicine interactions, including dosing recommendations. Consider the potential for medicine interactions prior to and during therapy with dolutegravir, emtricitabine and tenofovir alafenamide tablets; review concomitant medications during therapy with dolutegravir, emtricitabine and tenofovir alafenamide tablets; and monitor for the adverse reactions associated with the concomitant medicines.

Dolutegravir, emtricitabine and tenofovir alafenamide tablets ALFIDA alone are not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in ALFIDA film coated tablets is insufficient in these subpopulations.

Dolutegravir, emtricitabine and tenofovir alafenamide tablets ALFIDA are not indicated for use as preexposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.

Effect of Dolutegravir on the Pharmacokinetics of Other Medicines

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC_{50} = 1,93 microM) and multimedicine and toxin extrusion transporter (MATE) 1 (IC_{50} = 6,34 microM). *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of medicines eliminated via OCT2 or MATE1 (dofetilide and metformin, Table 6) (**see section 4.3**)

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC_{50} = 2,12 microM) and OAT3 (IC_{50} = 1,97 microM). However, *in vivo*, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

In vitro, dolutegravir did not inhibit (IC_{50} greater than 50 microM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1), UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multimedicine resistance protein (MRP)2, or MRP4.

In vitro, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4. Based on these data and the results of medicine interaction trials, dolutegravir is not expected to affect the pharmacokinetics of medicines that are substrates of these enzymes or transporters.

Based on these data, dolutegravir is not expected to affect the pharmacokinetics of medicines that are substrates of these enzymes or transporters (e.g., reverse transcriptase and protease inhibitors, opioid analgesics, antidepressants, statins, azole antifungals (such as fluconazole, itraconazole, clotrimazole), proton pump inhibitors (such as esomeprazole, lansoprazole, omeprazole), anti-erectile dysfunction agents (such as sildenafil, tadalafil, vardenafil), aciclovir, valaciclovir, sitagliptin, adefovir).

In interaction trials, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following medicines: daclatasvir, methadone, midazolam, rilpivirine, telaprevir, tenofovir, and oral contraceptives containing norgestimate and ethinyl estradiol.

Using cross- study comparisons to historical pharmacokinetic data for each interacting medicine, dolutegravir did not appear to affect the pharmacokinetics of the following medicines: atazanavir, darunavir, efavirenz, etravirine, fosamprenavir, lopinavir, ritonavir, and boceprevir.

Effect of Other Medicines on the Pharmacokinetics of Dolutegravir or Emtricitabine and Tenofovir Alafenamide

Dolutegravir

Dolutegravir, one component of ALFIDA , is metabolised by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp *in vitro*. Certain medicines including efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir that induce those enzymes and transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir and may require dose adjustment.

Coadministration of dolutegravir and other medicines that inhibit these enzymes may increase dolutegravir plasma concentration.

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir (Table 6)**.** *In vitro*, dolutegravir was not a substrate of OATP1B1 or OATP1B3. Based on interaction trial results, the following medicines can be co-administered with dolutegravir without a dose adjustment: atazanavir/ritonavir, lopinavir/ritonavir, darunavir/ritonavir, daclatasvir, boceprevir, elbasvir/grazoprevir, methadone, midazolam, omeprazole, oral contraceptives containing norgestimate and ethinyl estradiol, prednisone, rifabutin, rilpivirine, ritonavir, sofosbuvir/velpatasvir, telaprevir and tenofovir. Another inducer, fosamprenavir in combination with ritonavir decreased plasma concentrations of dolutegravir but does not require a dosage adjustment.

Emtricitabine and Tenofovir Alafenamide

No clinically significant interactions have been observed between emtricitabine and famciclovir, indinavir, zidovudine, stavudine, and tenofovir disoproxil fumarate as an individual medicine (see Tables 2 and 3). Similarly, no clinically significant interactions have been observed between tenofovir disoproxil fumarate and abacavir, ribavirin, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, saquinavir/ritonavir, sofosbuvir, and tacrolimus in studies conducted in healthy volunteers. This may well be the case with ALFIDA.

Due to similarities between emtricitabine and lamivudine, ALFIDA should not be co-administered with other medicines containing lamivudine. including lamivudine and zidovudine co-formulation, lamivudine for HIV, lamivudine for HBV, abacavir sulfate and lamivudine co- formulation or abacavir sulfate, lamivudine and zidovudine co-formulation (**see section 4.3**).

Table 2
Medicine interactions: Changes in pharmacokinetics parameters for emtricitabine in the presence of the co-administered medicine[1]

Co-administered medicine	**Dose of co-administered medicine (mg)**	**Emtricitabine Dose (mg)**	**N**	**% Change of emtricitabine pharmacokinetics parameters[2] (90 % CI)**		
				C_{max}	**AUC**	**C_{min}**
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	↔	↔	↑ 20 (↑12 to ↑29)
Zidovudine	300 twice daily x 7 days	200 once daily x 7 days	27	↔	↔	↔
Indinavir	800 x 1	200 x 1	12	↔	↔	N/A
Famciclovir	500 x 1	200 x 1	12	↔	↔	N/A
Stavudine	40 x 1	200 x 1	6	↔	↔	N/A

[1] All interactions studies conducted in healthy volunteers.
[2] ↑= Increase; ↓ = Decrease, ↔ = No Effect; NA = Not Applicable

Table 3
Medicine interactions: Changes in pharmacokinetic parameters for co-administered medicine in the presence of the emtricitabine[1]

Co-administered medicine	Dose of co-administered medicine (mg)	Emtricitabine Dose (mg)	N	% Change of co-administered medicine pharmacokinetic parameters[2] (90 % CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	↔	↔	↔
Zidovudine	300 twice daily x 7 days	200 once daily x 7 days	27	↑ 17 (↑ 0 to ↑ 38)	↑ 13 (↑ 5 to ↑20	↔
Indinavir	800 x 1	200 x 1	12	↔	↔	N/A
Famciclovir	500 x 1	200 x 1	12	↔	↔	N/A
Stavudine	40 x 1	200 x 1	6	↔	↔	N/A

[1] All interactions studies conducted in healthy volunteers.
[2] ↑= Increase; ↓ = Decrease, ↔ = No Effect; NA = Not Applicable

Tenofovir Alafenamide Fumarate (TAF), one component of ALFIDA film coated tablets, is a substrate of P-gp, BCRP, OATP1B1, and OATP1B3.

Medicines that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption (see Table 6).

Medicines that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of ALFIDA and development of resistance.

Coadministration of ALFIDA with other medicines that inhibit P-gp and BCRP may increase the absorption and plasma concentration of TAF. TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. TAF is a weak inhibitor of CYP3A *in vitro*. TAF is not an inhibitor or inducer of CYP3A *in vivo*.

Based on interaction studies conducted with the components of emtricitabine and tenofovir alafenamide, no clinically significant interactions have been either observed or are expected when emtricitabine and tenofovir alafenamide is combined with the following antiretroviral medicines: atazanavir with ritonavir or cobicistat, darunavir with ritonavir or cobicistat, dolutegravir, efavirenz, ledipasvir, lopinavir/ritonavir, maraviroc, nevirapine, raltegravir, rilpivirine, and sofosbuvir. No clinically significant interactions have been either observed or are expected when emtricitabine and tenofovir alafenamide is combined with the following medicines: buprenorphine, itraconazole, ketoconazole, lorazepam, methadone, midazolam, naloxone, norbuprenorphine, norgestimate/ethinyl estradiol, and sertraline.

The effects of co-administered medicines on the exposure of TAF are shown in Table 4 and the effects of emtricitabine and tenofovir alafenamide or its components on the exposure of co-administered medicines are shown in Table 5 (these studies were conducted with fixed-dose emtricitabine and tenofovir alafenamide or the components of fixed-dose emtricitabine and tenofovir alafenamide (FTC or TAF) administered alone)

Table 4

Medicines Interactions: Changes in TAF Pharmacokinetic Parameters in the Presence of Co-administered medicines [a]

Co-administered medicines	**Co-administered medicines Dosage (once daily) (mg)**	**Tenofovir Alafenamide Dosage (once daily) (mg)**	**N**	**Mean Ratio of TAF Pharmacokinetic Parameters (90 % CI) No effect = 1,00**		
				C_{max}	**AUC**	**C_{min}**
Atazanavir	300 (+ 100 ritonavir)	10	10	1,77 (1,28; 2,44)	1,91 (1,55; 2,35)	NC

Co-administered medicines	Co-administered medicines Dosage (once daily) (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of TAF Pharmacokinetic Parameters (90 % CI) No effect = 1,00		
				C_{max}	AUC	C_{min}
Cobicistat	150	8	12	2,83 (2,20; 3,65)	2,65 (2,29; 3,07)	NC
Darunavir	800 (+ 150 cobicistat)	25 [b]	11	0,93 (0,72; 1,21)	0,98 (0,80;1,19)	NC
Darunavir	800 (+ 100 ritonavir)	10	10	1,42 (0,96; 2,09)	1,06 (0,84; 1,35)	NC
Efavirenz	600	40 [b]	11	0,78 (0,58;1,05)	0,86 (0,72; 1,02)	NC
Lopinavir	800 (+ 200 ritonavir)	10	10	2,19 (1,72; 2,79)	1,47 (1,17; 1,85)	NC
Rilpivirine	25	25	17	1,01 (0,84; 1,22)	1,01 (0,94;1,09)	NC
Sertraline	50 (dosed as a single dose)	10 [c]	19	1,00 (0,86; 1,16)	0,96 (0,89; 1,03)	NC

NC = Not Calculated
[a] All interaction studies conducted in healthy volunteers
[b] Study conducted with emtricitabine and tenofovir alafenamide (FTC/TAF)
[c] Study conducted with FTC + TAF with EVG + COBI

Table 5

Medicine Interactions: Changes in Pharmacokinetic Parameters for Co-administered Medicine in the Presence of Emtricitabine and Tenofovir Alafenamide or the Individual Components [a]

Co-administered medicine	**Co-administered Medicines Dosage (once daily) (mg)**	**Tenofovir Alafenamide Dosage (once daily) (mg)**	**N**	**Mean Ratio of TAF Co-administered Medicine Pharmacokinetic Parameters (90 % CI) No effect = 1,00**		
				C_{max}	**AUC**	**C_{min}**
Atazanavir	300 + 100 ritonavir	10	10	0,98 (0,89; 1,07)	0,99 (0,96; 1,01)	1,00 (0,96; 1,04)
Darunavir	800 + 150 cobicistat	25 [b]	11	1,02 (0,96; 1,09)	0,99 (0,92;1,07)	0,97 (0,82; 1,15)
Darunavir	800 + 100 ritonavir	10	10	0,99 (0,91; 1,08)	1,01 (0,96; 1,06)	1,13 (0,95; 1,34)
Dolutegravir	50	10	10	1,15 (1,04;1,27)	1,02 (0,97; 1,08)	1,05 (0,97; 1,13)
Lopinavir	800 + 200 ritonavir	10	10	1,00 (0,95; 1,06)	1,00 (0,92; 1,09)	0,98 (0,85; 1,12)
Midazolam [c]	2.5 (single dose, orally)	25	18	1,02 (0,92; 1,13)	1,13 (1,04; 1,23)	NC
	1 (single dose, intravenous)			0,99 (0,89; 1,11)	1,08 (1,04; 1,14)	NC
Rilpivirine	25	25	16	0,93 (0,87; 0,99)	1,01 (0,96; 1,06)	1,13 (1,04; 1,23)
Sertraline	50 (dosed as a single dose)	10 [d]	19	1,14 (0,94; 1,38)	0,93 (0,77; 1,13)	NC

NC = Not Calculated
[a] All interaction studies conducted in healthy volunteers
[b] Study conducted with emtricitabine and tenofovir alafenamide (FTC/TAF)
[c] A sensitivity CYP3A4 substrate
[d] Study conducted with FTC + TAF with EVG + COBI

Established and Other Potentially Significant Interactions

There were no interaction trials conducted with dolutegravir and fixed dose emtricitabine and tenofovir alafenamide or with the fixed-dose combination of all three components.

Information regarding potential interactions with dolutegravir, emtricitabine and tenofovir alafenamide (Table 6) are provided below.

These recommendations are based on either interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy (**see section 4.3**)

Table 6

Established and Other Potentially Significant Medicine Interactions for Dolutegravir, Emtricitabine and Tenofovir Alafenamide Fumarate (TAF): Alterations in Dose May Be Recommended Based on Interaction Trials or Predicted Interactions

Concomitant Medicine Class: Medicine Name	**Effect on concentration of Dolutegravir, TAF and/or Concomitant Medicine**	**Clinical Comment**
Antidysrhythmic: Dofetilide	↑ Dofetilide	Coadministration is contraindicated with ALFIDA (**see section 4.3**)
Antimycobacterials: Rifabutin Rifampin Rifapentine	↓ TAF	Coadministration of ALFIDA with rifabutin, rifampin, or rifapentine is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Etravirine	↓ Dolutegravir	Use of ALFIDA with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.

Concomitant Medicine Class: Medicine Name	**Effect on concentration of Dolutegravir, TAF and/or Concomitant Medicine**	**Clinical Comment**
Non-nucleoside reverse transcriptase inhibitor: Efavirenz	↓ Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from ALFIDA.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓ Dolutegravir	Avoid coadministration with ALFIDA because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir	↓ Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from ALFIDA.
Other Agents		
Carbamazepine	↓ Dolutegravir	An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from ALFIDA; however, use with ALFIDA is not recommended because of the TAF component.
Carbamazepine	↓ Dolutegravir	Consider alternative anticonvulsant.

Concomitant Medicine Class: Medicine Name	**Effect on concentration of Dolutegravir, TAF and/or Concomitant Medicine**	**Clinical Comment**
Oxcarbazepine Phenytoin Phenobarbitone	↓ TAF	
St. John's wort (*Hypericum perforatum*)	↓ Dolutegravir ↓ TAF	Coadministration of ALFIDA with St. John's wort is not recommended.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids or laxatives Sucralfate Buffered medications	↓ Dolutegravir	Administer ALFIDA 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron	↓ Dolutegravir	Administer ALFIDA 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, ALFIDA and supplements containing calcium or iron can be taken together with food.

Concomitant Medicine Class: Medicine Name	**Effect on concentration of Dolutegravir, TAF and/or Concomitant Medicine**	**Clinical Comment**
Metformin	↑ Metformin	With concomitant use, limit the total daily dose of metformin to 1000 mg either when starting metformin or ALFIDA . When stopping ALFIDA , the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of ALFIDA is recommended.

Medicines Affecting Renal Function

Because emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of ALFIDA with medicines that reduce renal function or compete for active tubular secretion may increase concentrations of emtricitabine, tenofovir, and other renally eliminated medicines and this may increase the risk of adverse reactions. Some examples of medicines that are eliminated by active tubular secretion 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**).

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

A reliable method of contraception should be used to avoid pregnancy while taking ALFIDA .

Pregnancy

ALFIDA is contraindicated in pregnancy (**see section 4.3**). A urine pregnancy test should be carried out within 24 hours before commencing treatment with dolutegravir containing medicines. Once treatment has started, pregnancy testing should be repeated every 4 weeks. Pregnancy testing and counselling should be performed if a patient misses her periods or if there are any abnormalities in the menstrual bleeding. Nucleotide analogues, as in ALFIDA may impact on mitochondrial function to a variable degree. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/ or post-natally to nucleotide analogues. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) peripheral neuropathy and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events have often been transitory. Late onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is unknown. These findings should be considered and investigated for any baby/ infant/ child exposed *in utero* to nucleos(t)ide analogues who present with severe clinical findings of unknown aetiology, particularly neurologic findings.

Breast-feeding

HIV infected women should not breastfeed their infants in order to avoid transmission of HIV. It is expected that dolutegravir and emtricitabine, which are components of ALFIDA will be secreted into human milk. Breast-feeding while taking ALFIDA is contraindicated. (**See section 4.3**)

Fertility

No fertility data is available for humans. No adverse effects on fertility and reproductive performance of male and female rats have been observed.

4.7. Effects on ability to drive and use machines

No studies on the effects of either ALFIDA on the ability to drive and use machines have been performed. The clinical status of the patient and the adverse event profile of ALFIDA should be borne in mind (**see section 4.8**).

Dizziness has been reported during treatment with either tenofovir disoproxil fumarate and emtricitabine as well as tenofovir alafenamide fumarate and emtricitabine. Dizziness has also been reported with the use of dolutegravir.

Therefore patients are advised not use machinery or drive whilst on treatment with ALFIDA as ALFIDA contains dolutegravir, emtricitabine and tenofovir alafenamide fumarate. (**see section 4.8**).

4.8. Undesirable effects

a) Summary of the safety profile

Serious adverse reaction may occur with the use of ALFIDA and are listed below:

- Hepatotoxicity
- Hypersensitivity Reactions
- Severe Acute Exacerbation of Hepatitis B
- Immune Reconstitution Syndrome
- New Onset or Worsening Renal Impairment
- Lactic Acidosis and Severe Hepatomegaly with Steatosis

The most frequently reported adverse reactions are separated according to the individual component in ALFIDA and is stated below.

Dolutegravir

The most frequent adverse reactions of moderate to severe intensity and incidence at least 2 % (in those receiving dolutegravir in any one adult trial) are insomnia, fatigue, and headache.

Emtricitabine and Tenofovir Alafenamide

Most common adverse reaction (incidence greater than or equal to 10 %, all grades) is nausea.

b) Structured listing summary of adverse reactions

List of adverse reactions

The following adverse reactions are reported corresponding to: Frequent, Less Frequent and Frequency Unknown:

Undesirable effects as a result of all three components in ALFIDA ,

Dolutegravir, Emtricitabine and Tenofovir alafenamide fumarate

Immune System Disorders

Less Frequent: Hypersensitivity, immune reconstitution syndrome

Psychiatric Disorders

Frequent: Insomnia

Less Frequent: Suicidal ideation, attempt, behaviour, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness.

Nervous System Disorders

Frequent: Headache

Gastrointestinal Disorders

Less Frequent: Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting.

Hepatobiliary disorders

Less Frequent: Hepatitis

Skin and Subcutaneous Tissue Disorders

Less Frequent: Pruritus

Musculoskeletal and connective tissue Disorders

Less Frequent: Myositis

Renal and urinary disorders

Less Frequent: Renal impairment

General disorders and administration site conditions

Frequent: Fatigue

Undesirable effects as a result of one component in ALFIDA , Dolutegravir

Immune System Disorders

Less Frequent: Hypersensitivity, immune reconstitution syndrome

Psychiatric Disorders

Frequent: Insomnia

Frequency Unknown: Anxiety

Nervous System Disorders

Frequent: Headache, dizziness and abnormal dreams

Gastrointestinal Disorders

Frequent: Nausea, diarrhoea, vomiting, flatulence and upper abdominal pain

Less Frequent: Abdominal pain and abdominal discomfort

Hepatobiliary disorders

Less Frequent: Hepatitis

Frequency Unknown: Acute liver failure, hepatotoxicity

Skin and Subcutaneous Tissue Disorders

Frequent: Rash and pruritus

Musculoskeletal and connective tissue Disorders

Frequency Unknown: Arthralgia, myalgia

General disorders and administration site conditions

Frequent: Fatigue

Undesirable effects as a result of two component in ALFIDA , Emtricitabine and Tenofovir

Blood and lymphatic system disorders

Frequent: Neutropenia

Less Frequent: Anaemia

Immune System Disorders

Frequent: Allergic reaction including angioedema

Metabolism and nutrition disorders

Frequent: Hypertriglyceridemia and hyperglycaemia

Frequency Unknown: Hypophosphataemia, lactic acidosis and hypokalaemia

Psychiatric Disorders

Frequent: Insomnia and abnormal dreams

Nervous System Disorders

Frequent: Dizziness and headache

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea

Gastrointestinal Disorders

Frequent: Diarrhoea, nausea, vomiting, flatulence, abdominal pain, amylase elevation, lipase elevation

Less Frequent: Dyspepsia

Frequency Unknown: Pancreatitis

Hepatobiliary disorders

Frequent: Hyperbilirubinemia, increased liver enzymes (including increased AST, increased ALT and/or gamma GT)

Frequency Unknown: Hepatitis and hepatic steatosis

Skin and Subcutaneous Tissue Disorders

Frequent: Rash event (rash, maculopapular rash, vesiculobullous rash, pustular rash), skin discoloration

Less Frequent: Angioedema, pruritus and urticaria

Musculoskeletal and connective tissue Disorders

Frequent: Creatine kinase elevation

Less Frequent: Arthralgia

Frequency Unknown: Myopathy, osteomalacia (both associated with proximal renal tubulopathy), rhabdomyolysis, muscular weakness

Renal and urinary disorders

Frequency Unknown: Increased creatinine. renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal tubulopathy, nephrogenic diabetes insipidus, proteinuria, acute tubular necrosis, polyuria, interstitial nephritis (including acute cases)

General disorders and administration site conditions

Frequent: Pain, asthenia and fatigue

c) Description of selected adverse reactions

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of ALFIDA . Clinical or

laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity should be suspended (**see section 4.4**).

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of Anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment (**see section 4.4**).

Hepatoxicity

Hepatotoxicity has been reported with dolutegravir, one component of ALFIDA. Laboratory monitoring for hepatoxicity during therapy with ALFIDA is recommended, especially for patients with liver disease, such as hepatitis B or C.

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to ART. The frequency of this is unknown (**see section 4.4**).

Changes in lipid laboratory tests

In studies in treatment-naïve patients, increases from baseline were observed in both the tenofovir alafenamide fumarate and tenofovir disoproxil fumarate containing treatment groups for the fasting lipid parameters total cholesterol, direct low density lipoprotein (LDL) and high-density lipoprotein (HDL)-cholesterol, and triglycerides at week 144. The median increase from baseline for those parameters was greater in the elvitegravir/cobicistat /emtricitabine/ tenofovir

alafenamide fumarate (E/C/F/TAF) group compared with the elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil (as fumarate) 245 mg (E/C/F/TDF) group at Week 144 ($p < 0.001$ for the difference between treatment groups for fasting total cholesterol, direct LDL- and HDL-cholesterol, and triglycerides). The median (Q1, Q3) change from baseline in total cholesterol to HDL-cholesterol ratio at Week 144 was 0.2 (-0.3, 0.7) in the E/C/F/TAF group and 0.1 (-0.4, 0.6) in the E/C/F/TDF group ($p = 0.006$ for the difference between treatment groups). In a study of virologically suppressed patients switching from emtricitabine/tenofovir disoproxil fumarate to emtricitabine/tenofovir alafenamide fumarate while maintaining the third antiretroviral agent (Study GS-US-311-1089), increases from baseline were observed in the fasting lipid parameters total cholesterol, direct LDL cholesterol and triglycerides in the emtricitabine/tenofovir alafenamide fumarate arm compared with little change in the emtricitabine/tenofovir disoproxil fumarate arm ($p \leq 0.009$ for the difference between groups in changes from baseline). There was little change from baseline in median fasting values for HDL cholesterol and glucose, or in the fasting total cholesterol to HDL cholesterol ratio in either treatment arm at week 96. None of the changes was considered clinically relevant.

In a study of virologically suppressed adult patients switching from abacavir/lamivudine to emtricitabine/tenofovir alafenamide fumarate while maintaining the third antiretroviral agent (Study GS-US-311-1717), there were minimal changes in lipid parameters. This may well be the case with ALFIDA.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (**see section 4.4**).

Changes in laboratory chemistries

Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 48 weeks. In treatment naïve patients a mean change from baseline of 9,96 µmol/L (range: -53 µmol/L to 54,8 µmol/L) was observed after 48 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment experienced patients. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate. Small increases in total bilirubin (without clinical jaundice) were observed on dolutegravir and raltegravir (but not efavirenz) arms in the programme. These changes are not considered clinically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway (UGT1A 1) . Asymptomatic creatine phosphokinase (CPK) elevations mainly in association with exercise have also been reported with dolutegravir therapy. This may very well be the case for ALFIDA as dolutegravir is a component thereof.

d) Paediatric population

Dolutegravir

Clinical Trials Experience in Paediatric Subjects: IMPAACT P1093 is an ongoing multi-centre, open-label, non-comparative trial of approximately 160 HIV-1-infected paediatric subjects aged 4 weeks to less than 18 years, of which 46 treatment-experienced, integrase strand transfer inhibitors (INSTI) -naïve subjects aged 6 to less than 18 years have been enrolled.

The adverse reaction profile was similar to that for adults. Grade 2 adverse reactions reported by more than one subject were decreased neutrophil count (n = 3) and diarrhoea (n = 2). There were no Grade 3 or 4 medicine-related adverse reactions reported. No adverse reactions led to discontinuation. The Grade 3 or 4 laboratory abnormalities reported in more than one subject were elevated total bilirubin (n = 3) and decreased neutrophil count (n = 2). The changes in mean serum creatinine were similar to those observed in adults.

Emtricitabine and Tenofovir

In a 24-week, open-label trial of 23 antiretroviral treatment-naïve HIV-1-infected paediatric subjects aged 12 to less than 18 years old (weighing at least 35 kg) who received emtricitabine + tenofovir alafenamide fumarate with elvitegravir + cobicistat, the safety of this combination was similar to that of adults. Among these paediatric subjects, mean bone mineral density increased from baseline to Week 24, +1.7% at the lumbar spine and +0.8% for the total body less head. Mean changes from baseline bone mineral density Z-scores were -0.10 for lumbar spine and -0.11 for total body less head at week 24. Two subjects had significant (greater than 4%) lumbar spine bone mineral density loss at Week 24.

e) Other special populations

Patients with renal impairment

The safety of emtricitabine and tenofovir alafenamide was evaluated through 144 weeks in an open-label clinical study (GS-US-292-0112) in which 248 HIV-1 infected patients who were either treatment-naïve (n = 6) or virologically suppressed (n = 242) with mild to moderate renal impairment (estimated glomerular filtration rate by Cockcroft-Gault method [eGFRCG]: 30 - 69 mL/min) received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet. The safety profile in patients with mild to moderate renal impairment was similar to that in patients with normal renal function (**see section 5.1**).

The safety of emtricitabine and tenofovir alafenamide was evaluated through 48 weeks in a single arm, open-label clinical study (GS-US-292-1825) in which 55 virologically suppressed HIV-1 infected patients with end stage renal disease (eGFRCG < 15 mL/min) on chronic haemodialysis received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet. There were no new safety issues identified in patients with end stage renal disease on chronic haemodialysis receiving emtricitabine and tenofovir

alafenamide, in combination with elvitegravir and cobicistat as a fixed-dose combination tablet (**see section 5.2**).

Patients co-infected with HIV and HBV

Dolutegravir

Hepatitis B and/or Hepatitis C Virus Co-infection: In Phase 3 trials, subjects with hepatitis B and/or C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal. Overall, the safety profile in subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C virus co-infection for all treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected compared with HIV mono-infected subjects receiving dolutegravir were observed in 18 % vs. 3 % with the 50 mg once-daily dose and 13 % vs. 8 % with the 50 mg twice-daily dose. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C at the start of therapy with dolutegravir, particularly in the setting where anti-hepatitis therapy was withdrawn.

Emtricitabine and tenofovir alafenamide

The safety of emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]) was evaluated in 72 HIV/HBV co-infected patients receiving treatment for HIV in an open-label clinical study (GS-US-292-1249), through Week 48, in which patients were switched from another antiretroviral regimen (which included tenofovir disoproxil fumarate [TDF] in 69 of 72 patients) to E/C/F/TAF. Based on these limited data, the safety profile of emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-

dose combination tablet, in patients with HIV/HBV co-infection, was similar to that in patients with HIV-1 mono infection (**see section 4.4**).

Post Marketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during post marketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to medicine exposure.

Dolutegravir

Hepatobiliary Disorders: Acute liver failure, hepatotoxicity.

Musculoskeletal: Arthralgia, myalgia.

Psychiatric: Anxiety.

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Medicine Reaction Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. In addition, suspected adverse reactions may also be reported by e-mail to medicinesafetysa@cipla.com or by telephone to 080 222 6662 (toll free).

4.9. Overdose

There is known specific treatment for overdose with ALFIDA. In overdose, side effects can be precipitated and/or be of increased severity, the patient should be monitored, and standard supportive treatment applied as required (**see section 4.8**).

Dolutegravir

As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Emtricitabine (FTC)

Limited clinical experience is available at doses higher than the recommended dose of FTC. In one clinical pharmacology study, single doses of FTC 1200 mg (6 times the recommended dose of FTC) were administered to 11 subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

Haemodialysis treatment removes approximately 30 % of the FTC dose over a 3-hour dialysis period starting within 1.5 hours of FTC dosing (blood flow rate of 400 mL per minute and a dialysate flow rate of 600 mL per minute). It is not known whether FTC can be removed by peritoneal dialysis.

Tenofovir Alafenamide (TAF)

Limited clinical experience is available at doses higher than the recommended dose of TAF. A single dose of 125 mg TAF (5 times the TAF dose in 200 mg/25 mg fixed-dose combination emtricitabine and tenofovir alafenamide) was administered to 48 healthy subjects; no serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 20.2.8 – Antiviral medicine.

ALFIDA tablets are a fixed-dose combination of antiretroviral medicines dolutegravir (DTG), emtricitabine (FTC) and tenofovir alafenamide (TAF).

5.1 Pharmacodynamic properties

Mechanism of Action:

Dolutegravir

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. In vitro, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex ($t_{1/2}$ 71 hours). Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC50 values of 2.7 nM and 12.6 nM.

Antiviral Activity in Cell Culture: Dolutegravir

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC50 values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC50 value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC50 values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC50 values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Antiviral Activity in Combination with Other Antiviral Medicines

The antiviral activity of dolutegravir was not antagonistic when combined with the INSTI, raltegravir; nonnucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz or nevirapine; the nucleoside reverse transcriptase inhibitors (NRTIs), abacavir or stavudine; the protease

inhibitors (PIs), amprenavir or lopinavir; the CCR5 co-receptor antagonist, maraviroc; or the fusion inhibitor, enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor, adefovir, or inhibited by the antiviral, ribavirin.

Resistance in Cell Culture

Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold. Passage of mutant viruses containing the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutions included T97A, E138K, G140S, and M154I. Passage of mutant viruses containing both G140S and Q148H selected for L74M, E92Q, and N155H.

Cross-Resistance

The single integrase strand transfer inhibitor-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

Resistance in vitro

Isolation from wild type HIV-1: Viruses highly resistant to dolutegravir have not been observed during HIV-1 passage. During wild type HIV-1 passage in the presence of dolutegravir integrase substitution observed were S153Y and S153F with FCs ≤ 4,1 for strain IIIB, or E92Q with FC = 3,1 and G193E with FC = 3,2 for strain NL432. Additional passage of wildtype subtype B, C and A/G viruses in the presence of dolutegravir selected for R263K, G118R, and S153T.

Anti-HIV activity Against Resistant Strains

Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent potency against 2 non-nucleoside (NN)-RTI-resistant, 3 nucleoside (N)-RTI-resistant and 2 PI-resistant HIV-1 mutant clones (1 triple and 1 sextuple) compared to the wild-type strain.

Integrase Inhibitor-Resistant HIV-1 Strains

Dolutegravir showed anti-HIV activity (susceptibility) with FC< 5 against 27 of 28 integrase inhibitor-resistant mutant viruses with single substitutions including T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R, and N155H.

Integrase Inhibitor-Resistant HIV-2 Strains

Site directed mutant HIV-2 viruses were constructed based on subjects infected with HIV-2 and treated with raltegravir who showed virologic failure. Overall the HIV-2 FCs observed were similar to HIV-1 FCs observed for similar pathway mutations.

Resistance in vivo

Integrase inhibitor naïve patients

No integrase inhibitor (INI) resistant mutations or treatment emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment – naïve studies.

Effects on Renal Function

The effect of dolutegravir on serum creatinine clearance (CrCl), glomerular filtration rate (GFR) using iohexol as the probe and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was evaluated. A small decrease of 10 – 14 % in mean serum creatinine clearance (CrCl) was observed with dolutegravir within the first week of treatment. Dolutegravir has no significant effect on glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF). In vitro studies suggest that the increases in creatinine observed in clinical studies are due to the non-pathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

Emtricitabine

Emtricitabine, a synthetic nucleoside analogue of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'- triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, Ɛ, and mitochondrial DNA polymerase γ.

Antiviral Activity in Cell Culture

The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was

assessed in T lymphoblastoid cell lines, the MAGI-CCR5 cell line, and primary peripheral blood mononuclear cells. The effective concentration at 50 % (EC50) values for FTC were in the range of 0,0013 to 0,64 micromolar. FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC50 values ranged from 0,007 to 0,075 micromolar) and showed strain specific activity against HIV-2 (EC50 values ranged from 0,007 to 1,5 micromolar).

In a study of FTC with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, non-nucleoside reverse transcriptase inhibitors [NNRTIs], integrase strand transfer inhibitors [INSTIs], and PIs) no antagonism was observed for these combinations.

Resistance

HIV-1 isolates with reduced susceptibility to FTC were selected in cell culture and in subjects treated with FTC. Reduced susceptibility to FTC was associated with M184V or I substitutions in HIV-1 RT.

Cross-Resistance

FTC-resistant viruses with the M184V or I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine.
Viruses harbouring substitutions conferring reduced susceptibility to stavudine and zidovudine thymidine analog substitutions (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to FTC. HIV-1 containing the K103N substitution or other substitutions associated with resistance to NNRTIs was susceptible to FTC.

Tenofovir Alafenamide

TAF is a phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination

Tenofovir has activity against HIV-1. Cell culture studies have shown that both tenofovir and FTC can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

Antiviral Activity in Cell Culture

The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4-T lymphocytes. The EC50 values for TAF ranged from 2.0 to 14.7 nM.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC50 values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC50 values ranged from 0.91 to 2.63 nM).

In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs, and PIs) no antagonism was observed for these combinations.

Resistance

HIV-1 isolates with reduced susceptibility to TAF were selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed.

Cross-Resistance

Tenofovir resistance substitutions K65R and K70E result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir.
HIV-1 with multiple thymidine analog substitutions (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R), or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M substitution complex including K65R, showed reduced susceptibility to TAF in cell culture.

5.2. Pharmacokinetic properties

Dolutegravir

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The Pharmacokinetic variability of dolutegravir is between low to moderate. In Phase 1 studies in healthy subjects, between-subjects CVb % for AUC and C_{max} ranged from – 20 to 40 % and C_T from 30 to 56 % across studies. The between-subject Pharmacokinetic variability of dolutegravir was higher in HIV-infected subjects than healthy subjects. Within-subjects variability (CV_w %) is lower than between-subject variability.

Absorption

Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours post-dose. With once-daily dosing, pharmacokinetic steady-state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and C24h ranging from

1,2 to 1,5. Dolutegravir is a P-gp substrate in vitro. The absolute bioavailability of dolutegravir has not been established. Dolutegravir may be taken with or without food. Food increased the extent of absorption and slowed the rate of absorption of dolutegravir. Low-, moderate-, and high-fat meals increased dolutegravir AUC(0-∞) by 33 %, 41 %, and 66 %; increased C_{max} by 46 %, 52 %, and 67 %; and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively.

Distribution

Dolutegravir is highly bound (greater than or equal to 98,9 %) to human plasma proteins based on in vivo data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50 mg once-daily administration is estimated at 17,4 L based on a population pharmacokinetic analysis.

Binding of dolutegravir to plasma proteins is independent of concentration. Total blood and plasma medicine-related radioactivity concentration ratios averaged between 0,441 to 0,535 indicating minimal association of radioactivity with blood cellular components. Free fraction of dolutegravir in plasma is estimated at approximately 0,2 to 1,1 % in healthy subjects with moderate hepatic impairment, and 0,8 to 1,0 % in subjects with severe renal impairment and 0,5 % in HIV-1 infected patients. Dolutegravir is present in cerebrospinal fluid (CSF).
In 12 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 13,2 ng per mL (range: 3,74 ng per mL to 18,3 ng per mL) 2 to 6 hours post-dose after 16 weeks of treatment. The clinical relevance of this finding has not been established.

Metabolism

Dolutegravir is primarily metabolised via UGT1A1 with some contribution from CYP3A. Dolutegravir is the predominant circulating compound in plasma. After a single oral dose of [^{14}C] dolutegravir, 53 % of the total oral dose was excreted unchanged in faeces. It is unknown if all or part of this is due to unabsorbed medicine or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-one percent of the total oral dose is excreted in the urine, represented by ether glucuronide of dolutegravir (18,9 % of total dose), N-dealkylation metabolite (3,6 % of total dose) and a metabolite formed by oxidation at the benzylic carbon (3,0 % of total dose). Renal elimination of unchanged medicine was low (less than 1 % of the dose).

Elimination

Dolutegravir has a terminal half-life of ~14 hours and an apparent oral clearance (CL/F) of 1,0 L per hour based on population pharmacokinetic analyses.

Special Populations

Renal Impairment

Renal clearance of unchanged medicine is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CLcr < 30 mL/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CLcr < 30 mL/min) and matching healthy subjects were observed, AUC, C_{max}, and C_{24} of dolutegravir were decreased by 40 %, 23 % and 43 % respectively, compared with those in matched healthy subjects. No dosage adjustment is necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Hepatic Insufficiency

Dolutegravir is primarily metabolised and eliminated by the liver. In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh category B score 7 to 9) to 8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the two groups. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in Metabolising Enzymes

There is no evidence that common polymorphisms in metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32 % lower clearance of dolutegravir and 46 % higher AUC compared with subjects with genotypes associated with normal metabolism via UGT 1A1 (n = 41). Polymorphisms in CYP3A4, CYP3A5 and NR1I2 are not associated with differences in the pharmacokinetics of dolutegravir.

Co-infection with Hepatitis B or C

Population pharmacokinetic analysis indicate that Hepatitis C virus co-infection has no clinically relevant effect on the exposure to dolutegravir. There are limited data on patients with Hepatitis B co-infection.

Elderly

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed there is no clinically relevant effect of age on dolutegravir exposure. Pharmacokinetic data for dolutegravir in subjects of >65 years old are limited.

Children and adolescents (12 to < 18 years of age)

The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 to 18 years of age) showed that dolutegravir 50 mg once daily dosage resulted in dolutegravir exposure comparable to that observed in adults who receive dolutegravir 50 mg once daily.

Table 7: Adolescent pharmacokinetic parameters

Age/weight	Dolutegravir Dose	Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (CV %)		
		$AUC_{(0-24)}$ µg•hr/mL	C_{max} µg/mL	C_{24} µg/mL
12 to < 18 years ≥ 40 kg[a]	50 mg once daily[a]	46 (43)	3,49 (38)	0,90 (59)

[a]One subject weighing 37 kg received 35 mg once daily.

Emtricitabine and Tenofovir Alafenamide

The pharmacokinetic (PK) properties of the components of emtricitabine and tenofovir alafenamide are provided in Table 8**.**

Absorption

Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose. The mean absolute bioavailability of emtricitabine is observed at 93 %. Following multiple dose oral administration of emtricitabine to 20 HIV-1 infected subjects, the (mean ± SD) steady state plasma emtricitabine peak concentrations (C_{max}) were 1.8 ± 0.7 µg/mL and the area-under the plasma

concentration-time curve over a 24-hour dosing interval (AUC) was 10.0 ± 3.1 µg•hr/mL. The mean steady state plasma trough concentration at 24 hours post-dose was equal to or greater than the mean in vitro IC90 value for anti- HIV-1 activity. Emtricitabine systemic exposure was unaffected when emtricitabine was administered with food. Following administration of food in healthy subjects, peak plasma concentrations were observed approximately 1 hour post-dose for tenofovir alafenamide administered as F/TAF (25 mg) or E/C/F/TAF (10 mg).

The mean C_{max} and AUC_{last}, (mean ± SD) under fed conditions following a single 25 mg dose of tenofovir alafenamide were 0.21 ± 0.13 *µ*g/mL and 0.25 ± 0.11 *µ*g•hr/mL, respectively. The mean C_{max} and AUC_{last} following a single 10 mg dose of tenofovir alafenamide administered in E/C/F/TAF were 0.21 ± 0.10 µg/mL and 0.25 ± 0.08 *µ*g•hr/mL, respectively. Relative to fasting conditions, the administration of tenofovir alafenamide with a high fat meal (~800 kcal, 50 % fat) resulted in a decrease in tenofovir alafenamide C_{max} (15-37 %) and an increase in AUC_{last} (17-77 %).

Distribution

In vitro binding of emtricitabine to human plasma proteins is < 4 % and is independent of concentration over the range of 0,02 to 200 *µ*g/mL.

At peak plasma concentration, the mean plasma to blood medicine concentration ratio was ~1.0 and the mean semen to plasma medicine concentration ratio was ~4.0.

In vitro binding of tenofovir to human plasma proteins is < 0.7% and is independent of concentration over the range of 0,01-25 *µ*g/mL. *Ex vivo* binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies was approximately 80 %.

Biotransformation

In vitro studies indicate that emtricitabine is not an inhibitor of human CYP enzymes. Following administration of [^{14}C]-emtricitabine, complete recovery of the emtricitabine dose was achieved in urine (~86 %) and faeces (~14 %). Thirteen percent of the dose was recovered in the urine as three putative metabolites. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~9 % of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~4 % of dose). No other metabolites were identifiable.

Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80 % of an oral dose. *In vitro* studies have shown that tenofovir alafenamide is metabolised to tenofovir (major metabolite) by cathepsin A in PBMCs (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes.

In vivo, tenofovir alafenamide is hydrolysed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite tenofovir diphosphate. In human clinical studies, a 10 mg oral dose of tenofovir alafenamide (given with emtricitabine and elvitegravir and cobicistat) resulted in tenofovir diphosphate concentrations > 4-fold higher in PBMCs and > 90 % lower concentrations of tenofovir in plasma as compared to a 245 mg oral dose of tenofovir disoproxil (as fumarate) (given with emtricitabine and elvitegravir and cobicistat).

In vitro, tenofovir alafenamide is not metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolised by CYP3A4. Upon co-administration with the moderate CYP3A inducer probe efavirenz, tenofovir alafenamide exposure was not significantly affected. Following administration of tenofovir alafenamide, plasma [^{14}C]-radioactivity showed a time-dependent profile with tenofovir alafenamide as the most abundant species in the initial few hours and uric acid in the remaining period.

Elimination

Emtricitabine is primarily excreted by the kidneys (a combination of glomerular filtration and active tubular secretion) with complete recovery of the dose achieved in urine (approximately 86 %) and faeces (approximately 14 %). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 mL/min. Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours. Renal excretion of intact tenofovir alafenamide is a minor pathway with < 1% of the dose eliminated in urine. Tenofovir alafenamide is mainly eliminated following metabolism to tenofovir. Tenofovir alafenamide and tenofovir have a median plasma half-life of 0,51 and 32,37 hours, respectively. Tenofovir is renally eliminated by both glomerular filtration and active tubular secretion.

Table 8: Pharmacokinetic properties of ALFIDA

	Emtricitabine	**Tenofovir alafenamide**
Absorption		
T_{max} (h)	3	1
Effect of high fat meal (relative to fasting)[a]	AUC ratio = 0,91 (0,89, 0,93) C_{max} ratio = 0,74 (0,69, 0,78)	AUC ratio = 1,75 (1,64, 1,88) C_{max} ratio = 0,85 (0,75, 0,95)
Distribution		
Plasma protein binding	< 4 %	Approximately 80 %
Source of protein binding data	In vitro	Ex vivo
Blood-to-plasma ratio	0,6	1,0
Biotransformation		
Metabolism	Not significantly metabolised	Cathepsin A[b] (PBMCs) CES1 (hepatocytes)

	Emtricitabine	**Tenofovir alafenamide**
		CYP3A (minimal)
Elimination		
Major route of elimination	Glomerular filtration and active tubular secretion	Metabolism (> 80 % of oral dose)
$T_{1/2}$ (h) [c]	10	0,51
% dose excreted in urine[d]	70	<1
% dose excreted in faeces[d]	13,7	31,7

PBMCs: peripheral blood mononuclear cells

CES1: carboxylesterase 1

a. Value refer to geometric mean ratio (high fat meal/ fasting) in PK parameters and 90 % CI. High calorie/high fat meal = 800 kcal, 50 % fat.

b. In vivo, TAF is hydrolysed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. In vitro studies have shown that TAF is metabolised to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes. Upon coadministration with the moderate CYP3A inducer probe efavirenz, TAF exposure was unaffected.

c. $T_{1/2}$ values refer to median terminal plasma half-life. Note that the pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

d. Dosing in mass balance studies (single dose administration of ^{14}C emtricitabine after multiple dosing of emtricitabine for 10 days and single dose of ^{14}C TAF)

Special Populations

Renal Impairment

No clinically relevant differences in tenofovir alafenamide, or tenofovir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment (estimated CrCl ≥ 15 mL/min and < 30 mL/min) in a Phase 1 study of

tenofovir alafenamide. In a separate Phase 1 study of emtricitabine alone, mean systemic emtricitabine exposure was higher in patients with severe renal impairment (estimated CrCl < 30 mL/min) (33.7 μg•hr/mL) than in subjects with normal renal function (11.8 μg•hr/mL). The safety of emtricitabine and tenofovir alafenamide has not been established in patients with severe renal impairment (estimated CrCl ≥ 15 mL/min and < 30 mL/min).

Exposures of emtricitabine and tenofovir in 12 patients with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis who received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet (E/C/F/TAF) in Study GS-US-292-1825 were significantly higher than in patients with normal renal function. No clinically relevant differences in tenofovir alafenamide pharmacokinetics were observed in patients with end stage renal disease on chronic haemodialysis as compared to those with normal renal function. There were no new safety issues identified in patients with end stage renal disease on chronic haemodialysis receiving emtricitabine and tenofovir alafenamide, in combination with elvitegravir and cobicistat as a fixed-dose combination tablet (**see section 4.8**).

There are no pharmacokinetic data on emtricitabine or tenofovir alafenamide in patients with end stage renal disease (estimated CrCl < 15 mL/min) not on chronic haemodialysis. The safety of emtricitabine and tenofovir alafenamide has not been established in these patients.

Hepatic Insufficiency

The pharmacokinetics of emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment should be limited. Clinically relevant changes in the pharmacokinetics of tenofovir alafenamide or its metabolite tenofovir were not observed in patients with mild or moderate hepatic impairment.

In patients with severe hepatic impairment, total plasma

concentrations of tenofovir alafenamide and tenofovir are lower than those seen in subjects with normal hepatic function. When corrected for protein binding, unbound (free) plasma concentrations of tenofovir alafenamide in severe hepatic impairment and normal hepatic function are similar.

Children and adolescents (< 18 years of age)

Exposures of emtricitabine and tenofovir alafenamide (given with elvitegravir and cobicistat) achieved in 24 paediatric patients aged 12 to < 18 years who received emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat in Study GS-US-292-0106 were similar to exposures achieved in treatment-naïve adults (**Table 9**).

Table 9: Pharmacokinetics of emtricitabine and tenofovir alafenamide in antiretroviral-naïve adolescents and adults

	Adolescents			**Adults**		
	FTC[a]	TAF[b]	TFV[b]	FTC[a]	TAF[c]	TFV[c]
AUC_{tau} (ng•hr/mL)	14,424.4 (23.9)	242.8 (57.8)	275.8 (18.4)	11,714.1 (16.6)	206.4 (71.8)	292.6 (27.4)
C_{max}	2,265.0 (22.5)	121.7 (46.2)	14.6 (20.0)	2,056.3 (20.2)	162.2 (51.1)	15.2 (26.1)
C_{tau}	102.4 (38.9)b	N/A	10.0 (19.6)	95.2 (46.7)	N/A	10.6 (28.5)

E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate

FTC = emtricitabine; TAF = tenofovir alafenamide fumarate; TFV = tenofovir

N/A = not applicable

Data are presented as mean (%CV).

a n = 24 adolescents (GS-US-292-0106); n = 19 adults (GS-US-292-0102)

b n = 23 adolescents (GS-US-292-0106, population PK analysis)

c n = 539 (TAF) or 841 (TFV) adults (GS-US-292-0111 and GS-US-292-0104, population PK analysis)

Hepatitis B and/or hepatitis C virus co-infection

The pharmacokinetics of emtricitabine and tenofovir alafenamide have not been fully evaluated in patients co-infected with HBV and/or HCV.

Elderly, Gender, and Race

No clinically relevant pharmacokinetic differences due to age, gender or ethnicity have been identified for emtricitabine, or tenofovir alafenamide.

Preclinical safety data

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Emtricitabine has demonstrated low carcinogenic potential in mice and rats.

Non-clinical studies of tenofovir alafenamide in rats and dogs revealed bone and kidney as the primary target organs of toxicity. Bone toxicity was observed as reduced bone mineral density (BMD) in rats and dogs at tenofovir exposures at least four times greater than those expected after administration of emtricitabine and tenofovir alafenamide. A minimal infiltration of histiocytes was present in the eye in dogs at tenofovir alafenamide and tenofovir exposures of approximately 4 and 17 times greater, respectively, than those expected after administration of emtricitabine and tenofovir alafenamide.

Tenofovir alafenamide was not mutagenic or clastogenic in conventional genotoxicity assays. Because there is a lower tenofovir exposure in rats and mice after the administration of tenofovir alafenamide compared to tenofovir disoproxil fumarate, carcinogenicity studies and a rat peri-postnatal study were conducted only with tenofovir disoproxil fumarate. No special hazard for humans was revealed in conventional studies of carcinogenic potential and toxicity

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Croscarmellose Sodium

Magnesium Stearate

Mannitol

Microcrystalline Cellulose

Povidone

Sodium Starch Glycolate

Opadry AMB Pink 80W54485 composed of:

Iron oxide red (E172)

Iron oxide yellow (E172)

Lecithin (E322)

Polyvinyl Alcohol-Part. Hydrolyzed (E1203)

Talc (E553b)

Titanium dioxide (E171)

Xanthan gum (E415)

6.2. Incompatibilities

Not applicable

6.3. Shelf Life

24 months

6.4. Special precautions for storage

Store at or below 25 °C. Keep the bottle tightly closed.

6.5. Nature and contents of container

ALFIDA film coated tablets are packed as either 28's, 30's or 90's into a white high density polyethylene (HDPE) bottle with a white high density polyethylene non child-resistant cap, together with three silica gel bags. Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du Cap

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8. REGISTRATION NUMBER

55/20.2.8/0456.455

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 July 2023

10. DATE OF REVISION OF THE TEXT

Not applicable.