Professional Information

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

DOLTRITAF film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Dolutegravir sodium equivalent to dolutegravir 50 mg

Emtricitabine 200 mg

Tenofovir alafenamide fumarate equivalent to tenofovir alafenamide 25 mg

Contains sugar: lactose monohydrate 120 mg per tablet and mannitol 145,400 mg per tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

A white to off white, film-coated, oval shaped, biconvex bevelled edge tablet debossed with M on one side of the tablet and TD1 on the other side; and with the following dimensions (length: 18,00 mm; width: 9,00 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Testing prior to initiation of DOLTRITAF Tablets

Prior to initiation of **DOLTRITAF** tablets, 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 **DOLTRITAF** tablets 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.

Adults and paediatric patients weighing at least 40 kg

The recommended dosage of **DOLTRITAF** is one tablet taken orally once daily with or without food in adults and paediatric patients weighing at least 40 kg and creatinine clearance greater than or equal to 30 mL per minute.

Paediatric use

DOLTRITAF tablets should only be administered to paediatric patients with a body weight of at least 40 kg because they 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

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. 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.

Hepatic impairment

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

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

Renal impairment

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

or moderate renal impairment (estimated creatinine clearance greater than or equal to 30 mL per minute).

4.3 Contraindications

DOLTRITAF tablets are contraindicated in patients:

- with previous hypersensitivity reaction to dolutegravir [see section 4.4]
- receiving dofetilide and pilsicainide
- with moderate and severe hepatic impairment (Child-Pugh B or C)
- with severe renal impairment, CrCl < 30 ml/min
- Metformin is contraindicated in patients taking **DOLTRITAF**.
- Antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation

DOLTRITAF is contraindicated in pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

WARNING:

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS.

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Tenofovir alafenamide, one component of DOLTRITAF 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 products containing tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of DOLTRITAF 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 DOLTRITAF tablets. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Hepatotoxicity

Safety of the mono-component medicines are well established, but the safety of the FDC combination have not been established. Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of **DOLTRITAF** tablets [see section 4.8]. 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.

Hypersensitivity reactions

Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1 % of subjects receiving dolutegravir in Phase 3 clinical trials.

Discontinue **DOLTRITAF** tablets 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 or peeling of the skin, oral blisters or lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with **DOLTRITAF** tablets or other suspect medicines after the onset of hypersensitivity may result in a life-threatening reaction. **DOLTRITAF** tablets are contraindicated in patients who have experienced a previous hypersensitivity reaction to dolutegravir.

Risk of adverse reactions or loss of virologic response due to interactions

The concomitant use of **DOLTRITAF** tablets and other medicines may result in known or potentially significant interactions, some of which may lead to [see section 4.3 and section 4.5]:

- Loss of therapeutic effect of **DOLTRITAF** tablets and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant medicines.

Consider the potential for interactions prior to and during therapy with **DOLTRITAF** tablets; review concomitant medications during therapy with

DOLTRITAF 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.

Immune Reconstitution Inflammatory Syndrome

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

limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART).

Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Bone mineral density

During therapy with **DOLTRITAF** 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. If bone abnormalities are suspected then appropriate consultation should be obtained.

Opportunistic infections

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

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, including DOLTRITAF, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

New onset or worsening renal impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials of FTC + TAF with cobicistat (COBI) plus elvitegravir (EVG), there have been no cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT).

In clinical trials of FTC + TAF with EVG + COBI in treatment-naïve subjects and in virally suppressed subjects switched to FTC + TAF with EVG + COBI with eGFRs greater than 50 mL per minute, renal serious adverse events or discontinuations due to renal adverse reactions were encountered in less than 1 % of participants treated with FTC + TAF with EVG + COBI. In a study of virally suppressed subjects with baseline eGFRs between 30 and 69 mL per minute treated with FTC + TAF with EVG + COBI for a median duration of 43 weeks, FTC + TAF with EVG + COBI was permanently discontinued due to worsening renal function in two of 80 (3 %) subjects with a baseline eGFR between 30 and 50 mL per minute [see section 4.8]. **DOLTRITAF** tablets are not recommended in patients with estimated creatinine clearance below 30 mL per minute because data in this population are insufficient (see section 4.3).

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic medicines including non-steroidal anti-inflammatory medicines are at increased risk of developing renal-related adverse reactions.

Estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating **DOLTRITAF** tablets therapy and should be monitored during therapy in all patients.
Serum phosphorus should be monitored in patients with chronic kidney disease because these patients are at greater risk of developing Fanconi syndrome on tenofovir prodrugs. Discontinue **DOLTRITAF** tablets in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

Lactic acidosis/hyperlactataemia

Use of **DOLTRITAF** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/ℓ) and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/ℓ with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.
- Lactate 5-10 mmol/ℓ with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.

- Lactate> 10 mmol/ℓ: STOP all therapy (80 % mortality).

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

Caution should be exercised when administering **DOLTRITAF** to patients with known risk factors for liver disease.

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

Mitochondrial dysfunction

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

There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or post-natally to nucleoside analogues.

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

Pancreatitis

Pancreatitis has been observed in some patients receiving **DOLTRITAF**.

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

Patients with moderate to severe renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of **DOLTRITAF** is increased due to decreased clearance. The dose of **DOLTRITAF** should therefore be adjusted (see section 4.2).

Liver disease

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

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

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

Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines.

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

Excipient warnings

DOLTRITAF contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, total lactase deficiency, glucose-galactose malabsorption should not take **DOLTRITAF. DOLTRITAF** also contains mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

Effect of dolutegravir on the pharmacokinetics of other medicines

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC50 > 50 µm) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1), UGT2B7, or the transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2.

In vitro, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4.

In vivo, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. 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), alafenamide, valaciclovir, sitagliptin, adefovir).

In medicine interaction studies, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, telaprevir and oral contraceptives containing norgestimate and ethinyl estradiol.

In vitro. Dolutegravir inhibited the renal organic cation transporter 2 (OCT2). Based on this observation, dolutegravir may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, metformin).

Effect of other medicines on the pharmacokinetics of dolutegravir or emtricitabine and tenofovir alafenamide

Dolutegravir: Dolutegravir, one component of **DOLTRITAF** tablets, is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp *in vitro*. Medicines that induce those enzymes and transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir.

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.

In vitro, dolutegravir was not a substrate of OATP1B1 or OATP1B3.

Based on interaction trial results, the following medicines can be coadministered 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, and sofosbuvir/velpatasvir.

Emtricitabine and tenofovir alafenamide: TAF, one component of **DOLTRITAF** 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 below). 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 **DOLTRITAF** tablets and development of resistance.

Coadministration of **DOLTRITAF** tablets 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.

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 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].

Established and other potentially significant interactions for dolutegravir, emtricitabine and tenofovir alafenamide:

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 **DOLTRITAF** tablets [see section 4.3].
Antimycobacterials: Rifabutin Rifampin Rifapentine	↓ TAF	Coadministration of **DOLTRITAF** tablets with rifabutin, rifampin, or rifapentine is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Etravirine	↓ Dolutegravir	Use of **DOLTRITAF** tablets with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
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 **DOLTRITAF** tablets.
Non-nucleoside reverse transcriptase inhibitor:	↓ Dolutegravir	Avoid coadministration with **DOLTRITAF** tablets because there are insufficient data to make dosing recommendations.

Nevirapine		
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 **DOLTRITAF** tablets.
Other Medicines		
Carbamazepine	↓ Dolutegravir	An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from **DOLTRITAF** tablets; however, use with **DOLTRITAF** tablets is not recommended because of the TAF component.
Carbamazepine Oxcarbazepine Phenytoin Phenobarbitone	↓ Dolutegravir ↓ TAF	Consider alternative anticonvulsant.
St. John's wort *(Hypericum perforatum)*	↓ Dolutegravir ↓ TAF	Coadministration of **DOLTRITAF** tablets with St. John's wort is not recommended.
Medications containing polyvalent cations (e.g. Mg or Al): Cation-containing	↓ Dolutegravir	Administer **DOLTRITAF** tablets 2 hours before or 6 hours after taking medications containing polyvalent cations.

antacids or laxatives Sucralfate Buffered medications		
Oral calcium or iron supplements, including multivitamins containing calcium or iron	↓ Dolutegravir	Administer **DOLTRITAF** tablets 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, **DOLTRITAF** tablets and supplements containing calcium or iron can be taken together with food.
Metformin	↑ Metformin	Co-administration of dolutegravir (as in **DOLTRITAF** increased metformin plasma concentration. Metformin is contraindicated in patients taking **DOLTRITAF** (see section 4.3).

Medicines affecting renal function

Because FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of **DOLTRITAF** tablets with medicines that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, 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:

Women of childbearing potential should be counselled about the potential risk of neural tube defects with dolutegravir (see below), including consideration of using effective contraceptive measures.

Perform pregnancy testing before initiation of **DOLTRITAF** in women of childbearing potential to exclude inadvertent (unintentional) use of **DOLTRITAF** during the first trimester of pregnancy.

If a woman plans pregnancy, the benefits and the risks of starting or continuing treatment with dolutegravir versus using another antiretroviral regimen should be discussed with her.

Pregnancy:

DOLTRITAF is contraindicated during pregnancy (see section 4.3)

A urine pregnancy test should be carried out within 24 hours before commencing treatment with dolutegravir containing medicines.

Use of dolutegravir during pregnancy was associated with a small increase in the prevalence of neural tube defects (0.19 %) compared to non-dolutegravir regimens (0.11 %). Most neural tube defects occur within the first 4 weeks of embryonic development after conception (approximately 6 weeks after the last menstrual period).

If a pregnancy is confirmed in the first trimester while on dolutegravir, the benefits and risks of continuing dolutegravir versus switching to another antiretroviral regimen should be discussed with the patient, taking the gestational age and the critical time period of neural tube defect development into account.

Dolutegravir may be used during the second and third trimester of pregnancy when the expected benefit outweighs the potential risk to the

foetus. Dolutegravir was shown to cross the placenta in humans, leading to significant exposure to the foetus, but the implications of such exposure are not yet known.

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 **DOLTRITAF** 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-1-infected mothers should not breastfeed their infants to avoid risking transmission of HIV-1 or follow appropriate guidelines.

Dolutegravir is excreted in human breast milk, and there is significant exposure to the neonate/infants due to slow elimination; the half-life of dolutegravir in the new born was 33 hr compared to 14 hr in the adults. There is insufficient information on the effects of dolutegravir in neonates/infants.

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants) and (3) adverse reactions in a breastfed infant similar to those seen in adults, mothers should not breastfeed if they are receiving **DOLTRITAF** tablets.

Fertility:

There are no data on the effects of dolutegravir on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

The clinical status of the patient and the adverse event profile of **DOLTRITAF** should be borne in mind when considering the patient's ability to drive or operate machinery.

Dizziness has been reported during treatment with emtricitabine.

4.8 Undesirable effects

Clinical trial data

Adverse reactions identified in an analysis of pooled data from clinical studies are listed below by system organ class and by frequency.

Blood and the lymphatic system disorders	Frequent	Neutropenia
	Frequency unknown	Anaemia
Immune system disorders	Frequent	Allergic reaction, including angioedema

	Less frequent	Hypersensitivity, Immune Reconstitution Syndrome (see section 4.4**)**
Metabolism and nutrition disorders	Frequent	Hypertriglyceridaemia, hyperglycaemia
	Frequency unknown	Hypophosphataemia, lactic acidosis, hypokalaemia
Psychiatric disorders	Frequent	Insomnia, abnormal dreams, 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, dizziness
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, vomiting, flatulence, upper abdominal pain, Dyspepsia, amylase elevation, lipase elevation
	Less frequent	Abdominal pain, abdominal discomfort

	Frequency unknown	Pancreatitis
Hepatobiliary disorders	Frequent	Hyperbilirubinaemia, increased liver enzymes (including increased AST, increased ALT and/or gamma GT)
	Less frequent	Hepatitis
	Frequency unknown	Hepatic steatosis
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, skin discolouration
Musculoskeletal, connective tissue and bone disorders	Frequent	Creatine kinase elevation, myositis
	Frequency unknown	Myopathy, osteomalacia, rhabdomyolysis, muscular weakness
Renal and urinary disorders	Frequent	Renal impairment
	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

General disorders and administration site conditions	Frequent	Fatigue, pain, asthenia

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 with dolutegravir. These changes are not considered clinically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1).

Asymptomatic creatine phosphokinase (CPK) elevations mainly in association with exercise have also been reported with dolutegravir therapy.

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 enrol 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 [see section 4.4].

Not for use in subjects < 40 kg.

Postmarketing experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use.

Psychiatric disorders:

Frequency unknown: Anxiety.

Hepatobiliary disorders:

Frequency unknown: Acute liver failure, hepatotoxicity.

Musculoskeletal disorders:

Frequency unknown: Arthralgia, myalgia.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions & Quality Problem Reporting Form”, found online under SAHPRA’s publications:

https://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

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

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.

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. Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %.

5 PHARMACOLOGICAL PROPERTIES

Pharmacological classification: Category A, 20.2.8 Antiviral agents.

DOLTRITAF 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. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2,7 nM and 12,6 nM.

Emtricitabine: FTC, 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.

Tenofovir alafenamide: TAF is a phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). 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:

***Dolutegravir*:** Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} 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 EC_{50} 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 EC_{50} values ranging from 0,02 nM to 2,14 nM for HIV-1. Dolutegravir EC_{50} values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0,09 nM to 0,61 nM.

Emtricitabine: 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 EC_{50} 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 (EC_{50} values ranged from 0,007 to 0,075 micromolar) and showed strain specific activity against HIV-2 (EC_{50} 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 medicines (NRTIs, non-nucleoside reverse transcriptase inhibitors [NNRTIs], integrase strand transfer inhibitors [INSTIs], and PIs) no antagonism was observed for these combinations.

Tenofovir alafenamide: 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 EC_{50} 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 (EC_{50} values ranged from 0,10 to 12,0 nM) and strain specific activity against HIV-2 (EC_{50} 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 medicines (NRTIs, NNRTIs, INSTIs, and PIs) no antagonism was observed for these combinations.

Antiviral activity in combination with other antiviral medicines:

Dolutegravir: 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*: 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.
Emtricitabine: 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.

Tenofovir alafenamide: 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.

In clinical trials: *Emtricitabine and tenofovir alafenamide*:

The resistance profile of emtricitabine and tenofovir alafenamide in combination with other antiretroviral medicines for the treatment of HIV-1 infection is based on studies of FTC + TAF with EVG + COBI in the treatment of HIV-1 infection. In a pooled analysis of antiretroviral-naïve subjects, genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-1 RNA greater than 400 copies per mL at confirmed virologic failure, at Week 48, or at time of early study medicine discontinuation. Genotypic resistance developed in 7 of 14 evaluable subjects. The resistance-associated substitutions that emerged were M184V/I (N = 7) and K65R (N = 1). Three subjects had virus with emergent R, H, or E at the polymorphic Q207 residue in reverse transcriptase.

One subject was identified with emergent resistance to FTC or TAF (M184M/I) out of 4 virologic failure subjects in a clinical study of virologically-suppressed subjects who switched from a regimen containing FTC + TDF to FTC + TAF with EVG + COBI (N = 799).

Cross-resistance*:*

Dolutegravir: 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.

Emtricitabine: FTC-resistant viruses with the M184V or I substitution were cross-resistant to lamivudine, but retained *in vitro* sensitivity to didanosine, stavudine, tenofovir, zidovudine and NNRTIs (delavirdine, efavirenz, and nevirapine).

Viruses harbouring substitutions conferring reduced susceptibility to stavudine and zidovudine-ethymidine analogue 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*:** 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

Absorption, distribution, metabolism, and excretion: *Dolutegravir:*

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 C_{24h} 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 $AUC_{(0-\infty)}$ 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.

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.

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

Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A. After a single oral dose of [^{14}C] dolutegravir, 53 % of the total oral dose was excreted unchanged in faeces. Thirty-one percent of the total oral dose was excreted in urine, represented by an ether glucuronide of dolutegravir (18,9 % of total dose), a metabolite formed by

oxidation at the benzylic carbon (3,0 % of total dose), and its hydrolytic N-dealkylation product (3,6 % of total dose). Renal elimination of unchanged medicine was low (less than 1 % of the dose).

In a meta-analysis of healthy subject trials, 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 UGT1A1 (n = 41).

The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1-infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1-infected subjects. The non-linear exposure of dolutegravir following 50 mg twice daily compared with 50 mg once daily in HIV-1-infected subjects was attributed to the use of metabolic inducers in the background antiretroviral regimens of subjects receiving dolutegravir 50 mg twice daily in clinical trials. Dolutegravir was administered without regard to food in these trials.

Emtricitabine and tenofovir alafenamide:

The pharmacokinetic (PK) properties of the components of emtricitabine and tenofovir alafenamide are provided in the table below.

	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)	AUC Ratio = 1,75 (1,64; 1,88)

	C_{max} Ratio = 0,74 (0,69; 0,78)	C_{max} Ratio = 0,85 (0,75; 0,95)
Distribution		
% Bound to human plasma proteins	< 4	~ 80
Source of protein binding data	*In vitro*	*Ex vivo*
Blood-to-plasma ratio	0.6	1.0
Metabolism		
Metabolism	Not significantly metabolized	Cathepsin A[b] (PBMCs) CES1 (hepatocytes) 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
% Of dose excreted in urine[d]	70	< 1,0
% Of dose excreted in faeces[d]	13,7	31,7

PBMCs = peripheral blood mononuclear cells; CES1 = carboxylesterase 1

[a] Values refer to geometric mean ratio [High-fat meal/fasting] in PK parameters and (90 % confidence interval). High-calorie/high-fat meal = ~ 800 kcal, 50 % fat.

[b] *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized 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 to 180 hours within PBMCs.

[d] Dosing in mass balance studies: FTC (single dose administration of [^{14}C] emtricitabine after multiple dosing of emtricitabine for ten days); TAF (single dose administration of [^{14}C] tenofovir alafenamide).

The multiple dose PK parameters of FTC and TAF and its metabolite tenofovir following oral administration with food in HIV-Infected adults are provided in the table below.

Parameter Mean (CV %)	**Emtricitabine[a]**	**Tenofovir Alafenamide[b]**	**Tenofovir[c]**
C_{max} (microgram per mL)	2,1 (20,2)	0,16 (51,1)	0,02 (26,1)
AUC_{tau} (microgram•hour per mL)	11,7 (16,6)	0,21 (71,8)	0,29 (27,4)
C_{trough} (microgram per mL)	0,10 (46,7)	NA	0,01 (28,5)

CV = Coefficient of Variation; NA = Not Applicable

[a] From Intensive PK analysis in a phase 2 trial in HIV-infected adults treated with FTC + TAF and EVG + COBI.

[b] From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC + TAF with EVG + COBI (N = 539).

[c] From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC + TAF with EVG + COBI (N = 841).

Effects of food on oral absorption of dolutegravir, emtricitabine and tenofovir alafenamide:

The pharmacokinetics of dolutegravir, emtricitabine and tenofovir are not affected by food, hence **DOLTRITAF** tablets can be administered with or without food.

Specific populations:

Patients with hepatic impairment:

Dolutegravir: Dolutegravir is primarily metabolised and eliminated by the liver. In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh Class B) to 8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the 2 groups. No dosage adjustment is necessary for patients with mild hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of dolutegravir has not been studied.

Emtricitabine: The pharmacokinetics of FTC has not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of hepatic impairment should be limited.

Tenofovir alafenamide: Clinically relevant changes in tenofovir pharmacokinetics in subjects with hepatic impairment were not observed in subjects with mild to moderate (Child-Pugh Class A and B) hepatic impairment.

Patients with renal impairment:

DOLTRITAF tablets are not recommended for patients with severe renal impairment (estimated creatinine clearance below 30 mL per min) because dolutegravir, emtricitabine and tenofovir alafenamide tablets are a fixed-dose combination and the dosage of the individual components cannot be adjusted [see section 4.2].

Hepatitis B (HBV) and/or Hepatitis C Virus (HCV) Co-infection:

Emtricitabine and tenofovir alafenamide: The pharmacokinetics of FTC and TAF have not been fully evaluated in subjects coinfected with hepatitis B and/or C virus.

Dolutegravir: Population analyses using pooled pharmacokinetic data from adult trials indicated no clinically relevant effect of HCV co-infection on the pharmacokinetics of dolutegravir. There were limited data on HBV co-infection.

Gender and Race:

Dolutegravir: Population analyses using pooled pharmacokinetic data from adult trials indicated gender or race had no clinically relevant effect on the exposure of dolutegravir.

Emtricitabine and tenofovir alafenamide: Based on population pharmacokinetic analyses, no dosage adjustment is recommended based on gender or race.

Elderly Patients:

Dolutegravir: Population analyses using pooled pharmacokinetic data from adult trials indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir.

Emtricitabine and tenofovir alafenamide: Pharmacokinetics of FTC and TAF have not been fully evaluated in the elderly (65 years of age and older). Population pharmacokinetics analysis of HIV-infected subjects in Phase 2 and Phase 3 trials of FTC + TAF and EVG + COBI showed that age did not have a clinically relevant effect on exposures of TAF up to 75 years of age.

Paediatric patients:

DOLTRITAF tablets should not be administered to paediatric patients weighing less than 40 kg.

Dolutegravir: The pharmacokinetics of dolutegravir in HIV-1-infected children (n = 14) weighing at least 40 kg were similar to those observed in HIV-1-infected adults who received dolutegravir 50 mg once daily.

Emtricitabine and tenofovir alafenamide: Exposures of FTC and TAF in 24 paediatric subjects aged 12 to less than 18 years who received FTC + TAF and EVG + COBI were decreased (23 % for AUC) compared to exposures achieved in treatment-naïve adults following administration of this dosage regimen. These exposure differences are not thought to be clinically significant based on exposure-response relationships.

Interaction Trials:

The interaction trials described were conducted with dolutegravir, emtricitabine, and/or tenofovir alafenamide as single entities; no

interaction trials have been conducted using the fixed-dose combination of dolutegravir, emtricitabine and tenofovir alafenamide.

Dolutegravir: Interaction trials were performed with dolutegravir and other medicines likely to be coadministered or commonly used as probes for pharmacokinetic interactions. The effects of dolutegravir on the exposure of coadministered medicines are summarized in the table below.

Coadministered medicine(s) and dose(s)	Dose of dolutegravir	n	Geometric Mean Ratio (90 % CI) of pharmacokinetic parameters of coadministered medicine with/without dolutegravir No Effect = 1.00		
			C_{max}	AUC	C_T or C_{24}
Daclatasvir 60 mg once daily	50 mg once daily	12	1,03 (0,84 to 1,25)	0,98 (0,83 to 1,15)	1,06 (0,88 to 1,29)
Ethinyl estradiol 0,035 mg	50 mg once daily	15	0,99 (0,91 to 1,08)	1,03 (0,96 to 1,11)	1,02 (0,93 to 1,11)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1,66 (1,53 to 1,81)	1,79 (1,65 to 1,93)	-
Metformin 500 mg twice daily	50 mg once daily	15[a]	2,11 (1,91 to 2,33)	2,45 (2,25 to 2,66)	-
Methadone 16 to 150 mg	50 mg once daily	11	1,00 (0,94 to 1,06)	0,98 (0,91 to 1,06)	0,99 (0,91 to 1,07)
Midazolam	50 mg	10	-	0,95	-

3 mg	once daily			(0,79 to 1,15)	
Norelgestromin 0,25 mg	50 mg once daily	15	0,89 (0,82 to 0,97)	0,98 (0,91 to 1,04)	0,93 (0,85 to 1,03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1,10 (0,99 to 1,22)	1,06 (0,98 to 1,16)	1,21 (1,07 to 1,38)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1,09 (0,97 to 1,23)	1,12 (1,01 to 1,24)	1,19 (1,04 to 1,35)
[a] The number of subjects represents the maximum number of subjects that were evaluated.					

The effects of coadministered medicines on the pharmacokinetics of dolutegravir are summarized below.

Coadministered medicine(s) and dose(s)	Dose of dolutegravir	n	Geometric Mean Ratio (90 % CI) of dolutegravir pharmacokinetic parameters with/without coadministered medicines No Effect = 1.00		
			C_{max}	AUC	C_{τ} or C_{24}
Atazanavir 400 mg once daily	30 mg once daily	12	1,50 (1,40 to 1,59)	1,91 (1,80 to 2,03)	2,80 (2,52 to 3,11)
Atazanavir/ritonavir 300 mg/100 mg once daily	30 mg once daily	12	1,34 (1,25 to 1,42)	1,62 (1,50 to 1,74)	2,21 (1,97 to 2,47)
Darunavir/ritonavir	30 mg	15	0,89	0,78	0,62

600 mg/100 mg twice daily	once daily		(0,83 to 0,97)	(0,72 to 0,85)	(0,56 to 0,69)
Efavirenz 600 mg once daily	50 mg once daily	12	0,61 (0,51 to 0,73)	0,43 (0,35 to 0,54)	0,25 (0,18 to 0,34)
Etravirine 200 mg twice daily	50 mg once daily	16	0,48 (0,43 to 0,54)	0,29 (0,26 to 0,34)	0,12 (0,09 to 0,16)
Etravirine + darunavir/ritonavir 200 mg + 600 mg/100 mg twice daily	50 mg once daily	9	0,88 (0,78 to 1,00)	0,75 (0,69 to 0,81)	0,63 (0,52 to 0,76)
Etravirine + lopinavir/ritonavir 200 mg + 400 mg/100 mg twice daily	50 mg once daily	8	1,07 (1,02 to 1,13)	1,11 (1,02 to 1,20)	1,28 (1,13 to 1,45)
Fosamprenavir/ ritonavir 700 mg/100 mg twice daily	50 mg once daily	12	0,76 (0,63 to 0,92)	0,65 (0,54 to 0,78)	0,51 (0,41 to 0,63)
Lopinavir/ritonavir 400 mg/100 mg twice daily	30 mg once daily	15	1,00 (0,94 to 1,07)	0,97 (0,91 to 1,04)	0,94 (0,85 to 1,05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1,13 (1,06 to 1,21)	1,12 (1,05 to 1,19)	1,22 (1,15 to 1,30)
Tenofovir 300 mg once daily	50 mg once daily	15	0,97 (0,87 to 1,08)	1,01 (0,91 to 1,11)	0,92 (0,82 to 1,04)
Tipranavir/ritonavir	50 mg	14	0,54	0,41	0,24

500 mg/200 mg twice daily	once daily		(0,50 to 0,57)	(0,38 to 0,44)	(0,21 to 0,27)
Antacid (MAALOX®) Simultaneous administration	50 mg single dose	16	0,28 (0,23 to 0,33)	0,26 (0,22 to 0,32)	0,26 (0,21 to 0,31)
Antacid (MAALOX) 2 h after dolutegravir	50 mg single dose	16	0,82 (0,69 to 0,98)	0,74 (0,62 to 0,90)	0,70 (0,58 to 0,85)
Boceprevir 800 mg every 8 hours	50 mg once daily	13	1,05 (0,96 to 1,15)	1,07 (0,95 to 1,20)	1,08 (0,91 to 1,28)
Calcium carbonate 1200 mg simultaneous administration (fasted)	50 mg single dose	12	0,63 (0,50 to 0,81)	0,61 (0,47 to 0,80)	0,61 (0,47 to 0,80)
Calcium carbonate 1200 mg simultaneous administration (fed)	50 mg single dose	11	1,07 (0,83 to 1,38)	1,09 (0,84 to 1,43)	1,08 (0,81 to 1,42)
Calcium carbonate 1200 mg 2 h after dolutegravir	50 mg single dose	11	1,00 (0,78 to 1,29)	0,94 (0,72 to 1,23)	0,90 (0,68 to 1,19)
Carbamazepine 300 mg twice daily	50 mg once daily	16[c]	0,67 (0,61 to 0,73)	0,51 (0,48 to 0,55)	0,27 (0,24 to 0,31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1,29 (1,07 to 1,57)	1,33 (1,11 to 1,59)	1,45 (1,25 to 1,68)

Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0,43 (0,35 to 0,52)	0,46 (0,38 to 0,56)	0,44 (0,36 to 0,54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1,03 (0,84 to 1,26)	0,98 (0,81 to 1,20)	1,00 (0,81 to 1,23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0,99 (0,81 to 1,21)	0,95 (0,77 to 1,15)	0,92 (0,74 to 1,13)
Multivitamin (One-A-Day®) simultaneous administration	50 mg single dose	16	0,65 (0,54 to 0,77)	0,67 (0,55 to 0,81)	0,68 (0,56 to 0,82)
Omeprazole 40 mg once daily	50 mg single dose	12	0,92 (0,75 to 1,11)	0,97 (0,78 to 1,20)	0,95 (0,75 to 1,21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1,06 (0,99 to 1,14)	1,11 (1,03 to 1,20)	1,17 (1,06 to 1,28)
Rifampin[a] 600 mg once daily	50 mg twice daily	11	0,57 (0,49 to 0,65)	0,46 (0,38 to 0,55)	0,28 (0,23 to 0,34)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	1,18 (1,03 to 1,37)	1,33 (1,15 to 1,53)	1,22 (1,01 to 1,48)
Rifabutin 300 mg once daily	50 mg once daily	9	1,16 (0,98 to 1,37)	0,95 (0,82 to 1,10)	0,70 (0,57 to 0,87)

[a] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.

[b] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.

[c] The number of subjects represents the maximum number of subjects that were evaluated.

Emtricitabine and tenofovir alafenamide: The effects of coadministered medicines on the exposure of TAF are shown in the table below.

Interactions: Changes in TAF Pharmacokinetic Parameters in the Presence of Coadministered Medicine(s)[a]

Coadministered medicine	Coadministered medicine(s) dosage (once daily) (mg)	Tenofovir alafenamide dosage (once daily) (mg)	N	Mean Ratio of TAF PK 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
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) 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.

The effects of emtricitabine and tenofovir alafenamide or its components on the exposure of coadministered medicines are shown in the table below [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]. For information regarding clinical recommendations, see section 4.5.

Interactions: Changes in PK Parameters for Coadministered Medicines in the Presence of Emtricitabine and Tenofovir Alafenamide or the Individual Components[a]

Coadministered medicine	Coadministered medicine(s) dosage (once daily) (mg)	Tenofovir alafenamide dosage (once daily) (mg)	N	Mean ratio of coadministered medicine PK 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 mg	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)	
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 sensitive CYP3A4 substrate.

[d] Study conducted with FTC + TAF with EVG + COBI.

Dosing or regimen recommendations as a result of established and other potentially significant interactions with dolutegravir are provided in section 4.5.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium

Lactose monohydrate 120 mg per tablet

Magnesium stearate

Mannitol 145,400 mg per tablet

Microcrystalline cellulose

Povidone

Sodium starch glycolate.

Film coating

Macrogol

Polyvinyl alcohol

Talc (E553b)

Titanium dioxide (E171, CI 77891)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life 2 years

6.4 Special precautions for storage

Store at or below 30 °C in original container.

6.5 Nature and contents of container

Blue, opaque, HDPE bottle with blue opaque PP screw closure with aluminium induction sealing liner and desiccant canister/sachet.

Pack sizes of 30’s, 90’s & 180’s (Not all packs may be marketed).

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

MYLAN (PTY) LTD

4 Brewery Street

Isando

Gauteng

Republic of South Africa

8 REGISTRATION NUMBERS

DOLTRITAF: 53/20.2.8/0469.468

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 January 2021

10 DATE OF REVISION OF THE TEXT: 04/04/2022