PROFESSIONAL INFORMATION FOR

DIDIVIR

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DIDIVIR, 200 mg / 300 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg.

Contains sugar: Lactose monohydrate 87 mg.

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

WARNINGS:

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 (SEE SECTION 4.4).

DIDIVIR IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF DIDIVIR HAS NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED DIDIVIR.

HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY, WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP, FOR AT LEAST SEVERAL MONTHS IN PATIENTS INFECTED WITH HBV WHO DISCONTINUE THE COMBINATION TABLET. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE SECTION 4.4).

DIDIVIR USED FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) MUST ONLY BE PRESCRIBED TO INDIVIDUALS CONFIRMED TO BE HIV-NEGATIVE IMMEDIATELY PRIOR TO INITIATING AND PERIODICALLY (AT LEAST EVERY 3 MONTHS) DURING USE. RESISTANT HIV-1 VARIANTS HAVE BEEN IDENTIFIED WITH USE OF DIDIVIR FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) FOLLOWING UNDETECTED ACUTE HIV-1 INFECTION.

DO NOT INITIATE DIDIVIR FOR THE PrEP INDICATION IF SIGNS OR SYMPTOMS OF ACUTE HIV-1 INFECTION ARE PRESENT, UNLESS NEGATIVE INFECTION STATUS IS CONFIRMED (SEE SECTION 4.4).

3. PHARMACEUTICAL FORM

Film-coated tablets.

Blue coloured, capsule-shaped, biconvex, film-coated tablets plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of HIV-1 Infections

DIDIVIR is indicated in combination with other antiretroviral medicines (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infections in adults.

Pre-Exposure Prophylaxis (PrEP)

DIDIVIR is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) in proven HIV-1 uninfected adults, to reduce the risk of sexually acquired HIV-1 in adults at high risk, provided maximum treatment compliance can be monitored.

4.2 Posology and method of administration

Posology

Dosage in adults for treatment of HIV-1 infection

The dose of DIDIVIR is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily.

Dosage for Pre-exposure prophylaxis (PrEP)

The dose of DIDIVIR in HIV-1 uninfected adults is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily.

Significantly increased medicine exposures to emtricitabine and tenofovir occur when DIDIVIR is administered to patients with moderate to severe renal impairment (see **section 4.3**).

Table 1: Dosage for HIV-1 infected adult patients with creatinine clearance ≥ 50 mL/min.

	Creatinine Clearance (mL/ min)[a] >50
Recommended dosing interval	Every 24 hours

[a] Calculated using ideal (lean) body weight

Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in all individuals (see **section 4.3** and **4.4**).

Pre-exposure prophylaxis: Do not use DIDIVIR for PrEP in HIV-1 uninfected individuals with a creatinine clearance below 60 mL/ min (See **section 4.3 a**nd **4.4**).

Paediatric population

Treatment of HIV-1 infection

The dose of DIDIVIR in paediatric patients 12 years of age and older with body weight greater than or equal to 35 kg is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken.

Method of administration

Oral use

It is recommended that DIDIVIR be swallowed whole with water.

DIDIVIR can usually be taken with food or without food.

4.3 Contraindications

DIDIVIR is contraindicated in:

- patients with known hypersensitivity to tenofovir, emtricitabine or to any of the excipients in DIDIVIR (see **section 6.1**).
- creatinine clearance < 60 mL/ min when used for HIV PrEP
- creatinine clearance < 50 mL/ min when used for HIV-1 treatment
- individuals with unknown or positive HIV-1 status, for PrEP use
- DIDIVIR should not be used for PrEP in individuals not fully committed to full treatment compliance
- patients who are pregnant or breastfeeding (see **section 4.6**)
- DIDIVIR should not be co-administered with other tenofovir-containing products, or with other products containing emtricitabine
- DIDIVIR should not be administered with lamivudine-containing products due to similarities between emtricitabine and lamivudine.

4.4 Special warnings and precautions for use

Patients with HIV-1 harbouring mutations

DIDIVIR should be avoided in antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation (see **section 5.1**).

Overall HIV-1 infection prevention strategy

DIDIVIR is not always effective in preventing the acquisition of HIV-1. The time to onset of protection after commencing DIDIVIR disoproxil is unknown.

DIDIVIR should only be used for pre-exposure prophylaxis as part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (e.g. consistent and correct condom use, knowledge of HIV-1 status, regular testing for other sexually transmitted infections).

Risk of resistance with undetected HIV-1 infection

DIDIVIR should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV negative (see **section 4.3**). Individuals should be re-confirmed to be HIV-negative at frequent intervals (e.g. at least every 3 months) using a combined antigen/antibody test while taking DIDIVIR for pre-exposure prophylaxis.

DIDIVIR alone does not constitute a complete regimen for the treatment of HIV-1 and HIV-1 resistance mutations have emerged in individuals with undetected HIV-1 infection who are only taking DIDIVIR.

If clinical symptoms consistent with acute viral infection are present and recent (< 1 month) exposures to HIV-1 are suspected, use of DIDIVIR should be delayed for at least one month and HIV-1 status reconfirmed before starting DIDIVIR for pre-exposure prophylaxis.

Importance of adherence

The effectiveness of DIDIVIR in reducing the risk of acquiring HIV 1 is strongly correlated with adherence as demonstrated by measurable drug levels in blood (see **section 5.1**). HIV-1 uninfected individuals should be counselled at frequent intervals to strictly adhere to the recommended DIDIVIR daily dosing schedule.

Patients with hepatitis B or C virus infection

See boxed “WARNINGS”

HIV-1 infected patients with chronic hepatitis B or C 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 management of HIV infection in patients co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV).

The safety and efficacy of DIDIVIR for pre-exposure prophylaxis in patients with HBV or HCV infection has not been established.

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products. See also under Use with ledipasvir and sofosbuvir or sofosbuvir and velpatasvir below.

Discontinuation of DIDIVIR therapy in patients infected with HBV may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue DIDIVIR should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Lactic acidosis / Severe hepatomegaly with steatosis

See boxed “WARNINGS”

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues such as DIDIVIR alone or in combination with other antiretrovirals. The 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 DIDIVIR 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 DIDIVIR should be suspended in any patient or uninfected individual 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 DIDIVIR 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, 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 DIDIVIR to patients with known risk factors for liver disease.
Treatment with DIDIVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Pancreatitis

Pancreatitis has been observed in some patients receiving DIDIVIR.

Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers.

Discontinue treatment with DIDIVIR until diagnosis of pancreatitis is excluded.

Liver disease

Treatment with DIDIVIR can cause hepatomegaly due to non-alcoholic fatty liver disease (hepatitis steatosis).

The safety and efficacy of DIDIVIR has not been established in patients with significant underlying liver disorders/diseases.

The pharmacokinetics of tenofovir has been studied in patients with hepatic impairment and no dose adjustment is required. The pharmacokinetics of emtricitabine has not been studied in patients with hepatic impairment. Based on minimal hepatic metabolism and the renal route of elimination for emtricitabine, it is unlikely that a dose adjustment would be required for DIDIVIR in patients with hepatic impairment (see **section 5.2**).

HIV-1 infected patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Mitochondrial dysfunction following exposure in utero

Nucleoside and nucleotide analogues such as DIDIVIR have been demonstrated *in vitro* and *in vivo* to cause variable degree of damage to mitochondriae.

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, convulsions, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. These findings should be considered for any foetus exposed *in utero* to nucleoside and nucleotide analogues, including HIV-negative infants/children, who present with severe clinical findings of unknown etiology, particularly neurologic findings.

Renal impairment

Emtricitabine and tenofovir, the active ingredients in DIDIVIR, are principally eliminated by the kidney by a combination of glomerular filtration and active tubular secretion.

Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) (renal tubular injury with severe hypophosphataemia), have been reported in association with the use of tenofovir disoproxil (see **section 4.3** and **4.8**).

Prior to initiating DIDIVIR for the treatment of HIV-1 infection or for use in pre-exposure prophylaxis, it is recommended that creatinine clearance should be calculated in all individuals.

Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients without risk factors for renal impairment after two to four weeks of use, after three months of use and every three to six months thereafter (see **section 4.3**).

In individuals at risk for renal disease more frequent monitoring of renal function is required.

See also under Co-administration of other medicinal products below.

Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic medicines should be carefully monitored for changes in serum creatinine and phosphorus.

DIDIVIR should not be administered to patients with creatine below 50 mL/min or patients requiring haemodialysis or for pre-exposure prophylaxis in patients with creatine clearance below 60 mL/min.
Interrupting treatment with DIDIVIR should also be considered in case of progressive decline of renal function when no other cause has been identified.

Bone mineral density
DIDIVIR decreased bone mineral density (BMD). During therapy bone monitoring should be considered for HIV infected patients and HIV-1 uninfected individuals who have a history of pathologic bone fracture or other risk factors for osteopenia, osteoporosis or bone loss.
The effect of supplementation with calcium and vitamin D has not been studied. Such supplementation may be beneficial for all patients. If bone abnormalities are suspected, appropriate consultation should be obtained.

If bone abnormalities are suspected or detected then appropriate consultation should be obtained.

Bone mineral density monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk of osteopenia. Tenofovir combination therapy associated with decrease in bone mineral density.

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 / tenofovir disoproxil group compared with the placebo group. Bone fractures were reported in 1,7 % of the Emtricitabine / tenofovir disoproxil 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 osteomalacia (associated with proximal renal tubulopathy) have been reported in association with the use of tenofovir disoproxil fumarate (tenofovir disoproxil fumarate), such as DIDIVIR (see **section 4.8**).

When using DIDIVIR for pre-exposure prophylaxis individuals should be reassessed at each visit to ascertain whether they remain at high risk of HIV-1 infection. The risk of HIV-1 infection should be balanced against the potential for renal and bone effects with long-term use of DIDIVIR.

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.

Mineralisation defects

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of tenofovir disoproxil fumarate as in DIDIVIR (see **section 4.8**)

During therapy with DIDIVIR 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 has not been studied. If bone abnormalities are suspected, appropriate consultation should be obtained.

In cases of proximal renal tubulopathy, arthralgias and muscle pain or weakness have also been reported. Hypophosphataemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir disoproxil fumarate (see **section 4.4** *Renal impairment*).

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy such as DIDIVIR 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 “cushingoid appearance” and elevated serum lipid and glucose levels in HIV patients. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

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 syndrome (IRIS)

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 first few weeks or months of initiation of cART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, cryptococcal meningitis, and atypical mycobacterial infections and Pneumocystis jiroveci pneumonia (PCP).

Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. 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 and autoimmune hepatitis have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Opportunistic infections

Patients receiving DIDIVIR 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.

Co-administration of other medicinal products

Use of DIDIVIR should be avoided with concurrent or recent use of a nephrotoxic medicinal product (see **section 4.5**). If concomitant use with nephrotoxic medicine is unavoidable, renal function should be monitored weekly.

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in HIV-1 infected patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If DIDIVIR is co-administered with an NSAID, renal function should be monitored adequately.

A higher risk of renal impairment has been reported in HIV-1 infected patients receiving tenofovir disoproxil in combination with a ritonavir or cobicistat boosted protease inhibitor. Close monitoring of renal function is required in these patients (see **section 4.5).** In HIV-1 infected patients with renal risk factors, the co-administration of tenofovir disoproxil with a boosted protease inhibitor should be carefully evaluated.

DIDIVIR should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil, tenofovir alafenamide, or other cytidine analogues, such as lamivudine (see **section 4.5**). DIDIVIR should not be administered concomitantly with adefovir dipivoxil.

Use with ledipasvir and sofosbuvir, sofosbuvir and velpatasvir or sofosbuvir, velpatasvir and voxilaprevir

Co-administration of tenofovir disoproxil with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/ voxilaprevir has been shown to increase plasma concentrations of tenofovir, especially when used together with an HIV regimen containing tenofovir disoproxil and a pharmacokinetic enhancer (ritonavir or cobicistat).

The safety of tenofovir disoproxil when co-administered with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/ velpatasvir/voxilaprevir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration should be considered, particularly in patients at increased risk of renal dysfunction.

Patients receiving ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir concomitantly with tenofovir disoproxil and a boosted HIV protease inhibitor should be monitored for adverse reactions related to tenofovir disoproxil.

Co-administration of tenofovir disoproxil and didanosine

Co-administration of tenofovir disoproxil and didanosine is not recommended (see **section 4.5**).

Triple nucleoside therapy

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage in HIV-1 infected patients when tenofovir disoproxil was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen. There is close structural similarity between lamivudine and emtricitabine and similarities in the pharmacokinetics and pharmacodynamics of these two medicines. Therefore, the same problems may be seen if DIDIVIR is administered with a third nucleoside analogue.

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, including DIDIVIR**,** does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination.

Appropriate precautions should continue to be employed.

Comprehensive management to reduce the risk of acquiring HIV-1

Use DIDIVIR for pre-exposure prophylaxis only as part of a comprehensive prevention strategy that includes other preventative measures, such as safer sex practices, because DIDIVIR is not always effective in preventing the acquisition of HIV-1.

- Counsel uninfected individuals about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhoea).
- Inform uninfected individuals about and support their efforts in reducing sexual risk behaviour.

Use DIDIVIR to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV negative.

HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only DIDIVIR, because DIDIVIR alone does not constitute a complete treatment regime for HIV-1 treatment. Therefore, care should be taken to avoid DIDIVIR exposure in HIV-infected individuals (see section 4.3).

- **Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating DIDIVIR for a PrEP indication, evaluate seronegative individuals for current or recent signs or symptoms consistent with acute viral infections (e.g., fever, fatigue, myalgia, skin rash, etc.) and ask about potential exposure events (e.g. unprotected sex, or condom broken during sex with an HIV-1 infected partner) that may have occurred within the last month.**
- **If clinical symptoms consistent with acute viral infection are present and recent (< 1 month) exposures are suspected, delay starting PrEP for at least one month and reconfirm HIV-1 status or use an approved test as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection.**
- **While using DIDIVIR for a PrEP indication, HIV-1 screening tests should be repeated at least once every 3 months. If symptoms consistent with acute HIV-1 infection develop**

following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed, using an approved test as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection.

Counsel uninfected individuals to strictly adhere to the recommended DIDIVIR dosing schedule. The effectiveness of DIDIVIR in reducing the risk of acquiring HIV-1 is strongly correlated with adherence, as demonstrated by measurable levels of tenofovir and emtricitabine in clinical trials.

Paediatric population

Safety and effectiveness of DIDIVIR in paediatric patients have not been established.

DIDIVIR should only be administered to HIV-1 infected paediatric patients 12 years of age and older with body weight greater than or equal to 35 kg. Because it is a fixed-dose combination tablet, DIDIVIR cannot be adjusted for patients of lower age and weight.

Geriatric use

Clinical studies of fixed dose combinations of emtricitabine and tenofovir, as in DIDIVIR, 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 cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other medicinal therapy.

Lactose

DIDIVIR contains lactose.

Patients with rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take DIDIVIR.

4.5 Interaction with other medicines and other forms of interaction

No medicine interaction studies have been conducted using DIDIVIR tablets.

Emtricitabine and tenofovir disoproxil fumarate

The steady state pharmacokinetics of emtricitabine and tenofovir, as in DIDIVIR, were unaffected when administered together versus each medicine dosed alone.

In vitro and clinical pharmacokinetic interaction studies have shown the potential for CYP450-mediated interactions involving emtricitabine and tenofovir, as in DIDIVIR, with other medicines is low.

DIDIVIR are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No interactions due to competition for renal excretion have been observed. However, co-administration of DIDIVIR with medicines that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the co-administered medicine, and is therefore not recommended.

Medicines that decrease renal function may increase concentrations of emtricitabine and/or tenofovir.

Co-administration of tenofovir disoproxil fumarate and ledipasvir/sofosbuvir or sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir has been shown to increase tenofovir exposure. Patients receiving a regimen containing tenofovir disoproxil fumarate concomitantly with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir should be monitored for adverse reactions associated with tenofovir disoproxil fumarate.

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 (see Tables 4 and 5).

Table 2: Medicine interactions: Changes in pharmacokinetic 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 pharmacokinetic parameters[2] (90 % CI)**		
				C_{max}	**AUC**	**C_{min}**
Tenofovir disoproxil fumarate	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 interaction 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 emtricitabine[1].

Co-administered medicine	**Dose of co-administered medicine (mg)**	**Emtricitabine Dose (mg)**	**N**	**% Change of emtricitabine pharmacokinetic parameters[2] (90 % CI)**		
				C_{max}	**AUC**	**C_{min}**
Tenofovir disoproxil fumarate	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 interaction studies conducted in healthy volunteers.

[2.] = ↑Increase; ↓= Decrease; ⇔ = No Effect; NA = Not Applicable

Table 4: Medicine interactions: Changes in pharmacokinetic parameters for tenofovir[1] in the presence of the co-administered medicine

Co-administered medicine	**Dose of co-administered medicine (mg)**	**N**	**% Change of tenofovir pharmacokinetic parameters[2] (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	⇔	⇔	NC
Atazanavir[3]	400 once daily x 14 days	33	↑ 14 (↑ 8 to ↑20)	↑ 24 (↑ 21 to ↑28)	↑ 22 (↑ 15 to ↑30)
Didanosine (enteric- coated)	400 once	25	⇔	⇔	⇔
Didanosine (buffered)	250 or 400 once daily x 7 days	14	⇔	⇔	⇔
Efavirenz	600 once daily x 14 days	29	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 three times daily x 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔

Lamivudine	150 twice daily x 7 days	15	⇔	⇔	⇔
Ledipasvir/ Sofosbuvir [4,5]	90/400 once daily x 10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑ 42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/ Sofosbuvir [4,6]		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/ Sofosbuvir [7]	90/400 once daily x 14 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to ↑ 197)
Ledipasvir/ Sofosbuvir [8]	90/400 once daily x 10 days	14	↑ 32 (↑ 25 to ↑ 39)	↑ 40 (↑ 31 to ↑ 50)	↑ 91 (↑ 74 to ↑ 110)
Ledipasvir/ Sofosbuvir [9]	90/400 once daily x 10 days	29	↑ 61 (↑ 51 to ↑ 72)	↑ 65 (↑ 59 to ↑ 71)	↑ 115 (↑ 105 to ↑ 126)
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Nelfinavir	1 250 twice daily X 14 days	29	⇔	⇔	⇔
Saquinavir/ Ritonavir	1 000/100 twice daily x 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)
Sofosbuvir[10]	400 single dose	16	↑ 25 (↑ 8 to ↑ 45)	⇔	⇔

Sofosbuvir/ Velpatasvir[11]	400/100 once daily	24	↑ 55 (↑ 43 to ↑ 68)	↑ 30 (↑ 24 to ↑ 36)	↑ 39 (↑ 31 to ↑ 48)
Sofosbuvir/ Velpatasvir[12]	400/100 once daily	29	↑ 55 (↑ 45 to ↑ 66)	↑ 39 (↑ 33 to ↑ 44)	↑ 52 (↑ 45 to ↑ 59)
Sofosbuvir/ Velpatasvir[13]	400/100 once daily	15	↑ 77 (↑ 53 to ↑ 104)	↑ 81 (↑ 68 to ↑ 94)	↑ 121 (↑ 100 to ↑ 143)
Sofosbuvir/ Velpatasvir[14]	400/100 once daily	24	36 (↑ 25 to ↑ 47)	↑ 35 (↑ 29 to ↑ 42)	↑ 45 (↑ 39 to ↑ 51)
Sofosbuvir/ Velpatasvir[15]	400/100 once daily	24	↑ 44 (↑ 33 to ↑ 55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑ 76 to ↑ 92)
Sofosbuvir/ Velpatasvir[16]	400/100 once daily	30	↑ 46 (↑ 39 to ↑ 54)	↑ 40 (↑ 34 to ↑ 45)	↑ 70 (↑ 61 to ↑ 79)
Sofosbuvir/ Velpatasvir/ Voxilaprevir[17]	400/100/100 + Voxilaprevir[18] 100 once daily	29	↑ 48 (↑ 36 to ↑ 61)	↑ 39 (↑ 32 to ↑ 46)	↑ 47 (↑ 38 to ↑ 56)
Tacrolimus	0,05 mg/kg twice daily x 7 days	21	↑ 13 (↑ 1 to ↑	⇔	⇔

			27)		

[1.] Patients received tenofovir disoproxil fumarate 300 mg once daily.

[2.] Increase = ↑; Decrease = ↓; No Effect = ⇔; NC = Not calculated

[3.] Atazanavir South African Prescribing Information

[4.] Data generated from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provided similar results.

[5.] Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate.

[6.] Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate.

[7.] Study conducted with efavirenz/emtricitabine/tenofovir disoproxil fumarate co-administered with ledipasvir/sofosbuvir.

[8.] Study conducted with emtricitabine/rilpivirine/tenofovir disoproxil fumarate co-administered with ledipasvir/sofosbuvir.

[9.] Study conducted with emtricitabine/tenofovir disoproxil fumarate + dolutegravir co administered with ledipasvir/sofosbuvir.

[10.] Study conducted with efavirenz/emtricitabine/tenofovir disoproxil fumarate co-administered with sofosbuvir.

[11.] Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate.

[12.] Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate.

[13.] Study conducted with efavirenz/emtricitabine/tenofovir disoproxil fumarate co-administered with sofosbuvir/velpatasvir.

[14.] Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate

co- administered with sofosbuvir/velpatasvir.

15. Study conducted with emtricitabine/rilpivirine/tenofovir disoproxil fumarate co-administered with sofosbuvir/velpatasvir.

16. Administered as raltegravir + emtricitabine/tenofovir disoproxil fumarate

17. Comparison based on exposures when administered as darunavir + ritonavir + emtricitabine/tenofovir disoproxil fumarate.

18. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposure expected in HCV-infected patients.

Table 5: Medicine interactions: Changes in pharmacokinetic parameters for co-administered medicine in the presence of tenofovir

Co-administered medicine	**Dose of co-administered medicine (mg)**	**N**	**% Change of co-administered medicine pharmacokinetic parameters[1] (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	⇔	N/A
Atazanavir[2]	400 once daily x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[2]	Atazanavir/Ritonavir 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[3] (↓ 42 to ↓ 3)	↓ 23[3] (↓ 46 to ↑ 10)

Efavirenz	600 once daily x 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 three times daily x 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/ Ritonavir 400/100 twice daily x 14 days	24	⇔	⇔	⇔
Methadone[4]	40 to 110 once daily x 14 days[5]	13	⇔	⇔	⇔
Nelfinavir M8 metabolite	1 250 twice daily x 14 days	29	⇔ ⇔	⇔ ⇔	⇔ ⇔
Oral Contraceptives[6]	Ethinyl Estradiol 0,035 mg/ Norgestimate 0,25 mg once daily x 7 days	20	⇔	⇔	⇔
Ribavirin	600 once daily	22	⇔	⇔	N/A
Saquinavir	Saquinavir/	32	↑ 22 (↑ 6 to	↑ 29[7] (↑ 12 to	↑ 47[7] (↑ 23 to

Ritonavir	Ritonavir 1 000/100 twice daily x 14 days		↑ 41) ⇔	↑ 48) ⇔	↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Sofosbuvir GS-331007 Velpatasvir Voxilaprevir	Sofosbuvir/ Velpatasvir/ Voxilaprevir 400/100/100 + Voxilaprevir[8] 100 once daily	29	↓ 30[9] (↓ 38 to ↓ 22) ⇔[9] ⇔[9] ↑ 72[9] (↑ 51 to ↑ 97)	⇔[9] ⇔[9] ⇔[9] ↑ 143[9] (↑ 115 to ↑ 175)	N/A N/A ⇔[9] ↑ 300[9] (↑ 244 to ↑ 365)

Increase = ↑; Decrease = ↓; No Effect =⇔; NA = Not Applicable

2. Atazanavir South African Prescribing Information

3. In HIV-infected patients, addition of tenofovir disoproxil fumarate to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and Cmin values of atazanavir that were 2, 3 and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.

4. R-(active), S- and total methadone exposures were equivalent when dosed alone or with tenofovir disoproxil fumarate.

5. Individual subjects were maintained on their stable methadone dose. No pharmacodynamics alterations (opiate toxicity or withdrawal signs or symptoms) were reported.

[6.] Ethinyl estradiol 0,035 mg and 17-deacetyl norgestimate 0,25 mg (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir disoproxil fumarate.

[7.] Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir disoproxil fumarate and ritonavir-boosted saquinavir are co- administered.

[8.] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

[9.] Comparison based on exposures when administered as darunavir + ritonavir + emtricitabine/tenofovir disoproxil fumarate.

Following multiple dosing to HIV negative subjects receiving either chronic methadone maintenance therapy or oral contraceptives, or single doses of ribavirin, steady state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of clinically significant interactions between these medicine and tenofovir disoproxil fumarate.

Co-administration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Table 6 summarises the effects of tenofovir disoproxil fumarate on the pharmacokinetics of didanosine. Concomitant dosing of tenofovir disoproxil fumarate with didanosine buffered tablets or enteric coated capsules significantly increases the Cmax and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown.

Table 6: Medicine interactions: Pharmacokinetic parameters for didanosine in the presence of tenofovir.

Didanosine[1] dose (mg)/Method of administration[2]	**Tenofovir method of administration[2]**	**N**	**% Difference (90 % CI) vs. didanosine 400 mg alone, fasted[3]**	
			Cmax	**AUC**
Buffered tablets				
400 once daily 4 x 7 days	Fasted 1 hour after didanosine	14	↑ 28 (↑ 11 to ↑ 48)	↑ 44 (↑ 31 to ↑ 59)
Enteric-coated capsules				
400 once, fasted	With food, 2 hr after didanosine	26	↑ 48 (↑ 25 to ↑ 76)	↑ 48 (↑ 31 to ↑ 67)
400 once, with food	Simultaneously with didanosine	26	↑ 64 (41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)
250 once, fasted	With food, 2 hr after didanosine	28	↓ 10 (↓ 22 to ↑ 3)	⇔
250 once, fasted	Simultaneously with didanosine	28	⇔	↑ 14 (0 to ↑ 31)
250 once, with food	Simultaneously with didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓ 11 (↓ 23 to ↑ 2)

[1.] See **section 4.4** for use regarding use of didanosine with tenofovir

[2.] Administration with food was with a light meal (~ 373 kcal, 20 % fat).

[3.] Increase = ↑; Decrease = ↓; No Effect = ⇔

[4.] Includes 4 subjects weighing < 60 kg receiving ddL 250 mg.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

DIDIVIR should not be used during pregnancy as safety and efficacy have not been established (see **section 4.3**).

If an uninfected individual becomes pregnant while taking DIDIVIR for a PrEP indication, careful consideration should be given to whether use of DIDIVIR should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy.

Breastfeeding

HIV-infected mothers should not breastfeed their infants, to avoid risking postnatal transmission of HIV. Animal studies show that tenofovir is excreted in milk. It is not known whether tenofovir and emtricitabine are excreted in human milk.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed their infants if they are receiving DIDIVIR.

Fertility

No human data on the effect of DIDIVIR are available. Reported animal studies do not indicate harmful effects of emtricitabine or tenofovir disoproxil on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects of either tenofovir disoproxil fumarate or emtricitabine on the ability to drive and use machines have been performed. However, dizziness has been reported during

treatment with both tenofovir disoproxil fumarate and emtricitabine. If this happens, patients must avoid driving or operating machinery.

4.8 Undesirable effects

HIV-1 infection: The most frequently reported adverse reactions considered possibly or probably related to emtricitabine and/or tenofovir disoproxil as contained in DIDIVIR were nausea and diarrhoea in a clinical study in adults. The safety profile of emtricitabine and tenofovir disoproxil as contained in DIDIVIR in this study was consistent with the previous experience with these medicines when each was administered with other antiretroviral medicine.

Pre-exposure prophylaxis: No new adverse reactions to tenofovir disoproxil/emtricitabine as contained in DIDIVIR were identified from reported studies in which HIV-1 uninfected adults received tenofovir disoproxil /emtricitabine as contained in DIDIVIR once daily for pre-exposure prophylaxis. The most frequent adverse reaction reported in the study was headache.

Tabulated list of adverse reactions: Emtricitabine and Tenofovir disoproxil

Frequency	**Emtricitabine**	**Tenofovir disoproxil**
Blood and lymphatic system disorders		
Frequent	Neutropenia	
Less frequent	Anaemia[2]	
Frequency unknown		Haematuria
Immune system disorders		
Frequent	Allergic reactions, including angioedema.	Angioedema.
Metabolism and nutrition disorders		

Frequent	Hypertriglyceridermia, hyperglycaemia	Hypophosphataemia.
Less Frequent		Lactic acidosis and hypokalaemia.[1]
Psychiatric disorders		
Frequent	Abnormal dreams, insomnia).	
Frequency unknown		Depression, insomnia, anxiety
Nervous system disorders		
Frequent	Headache, dizziness.	Headache, dizziness.
Less frequent	Neuritis, paraesthesia, and peripheral neuropathy.	
Frequency unknown		Peripheral neuropathy (including peripheral neuritis and neuropathy).
Respiratory, thoracic and mediastinal disorders		
Frequent	Increased cough, rhinitis, dyspnoea.	Dyspnoea.
Frequency unknown		Chest pain, pneumonia.
Gastrointestinal disorders		
Frequent	Nausea, diarrhoea, vomiting, flatulence, dyspepsia, abdominal pain, elevated amylase including elevated pancreatic amylase, elevated serum lipase.	Nausea, vomiting, diarrhoea, abdominal pain, abdominal distension, and flatulence.
Less frequent		Raised serum amylase concentrations, pancreatitis, abdominal pain, and flatulence.

Frequency unknown		Dyspepsia.
Hepatobiliary disorders		
Frequent	Elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT) and hyperbilirubinaemia.	Increased transaminases
Less frequent		Hepatotoxicity, including lactic acidosis, hepatic steatosis and hepatitis.
Frequency unknown		Raised liver enzyme (including ALT, AST and gamma GT).
Skin and subcutaneous tissue disorders		
Frequent	Rash event (including rash, pruritus rash, maculopapular rash, urticaria, vesiculobullous rash and pruritus and skin discolouration, manifested by hyperpigmentation[2]	Rash (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash and pustular rash).
Musculoskeletal and connective tissue disorders		
Frequent	Creatine kinase elevation.	

Less frequent	Arthralgia, myalgia.	Rhabdomyolysis[1], osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1,3], muscular weakness[1] and myopathy.
Frequency unknown	Myopathy, osteomalacia (both associated with proximal renal tubulopathy), rhabdomyolysis, muscular weakness.	Bone density decreased (see **section 4.4**).
Renal and urinary disorders		
Less Frequent		Increased creatinine, proteinuria, proximal renal tubulopathy including Fanconi syndrome, renal failure (acute and chronic), acute tubular necrosis, nephritis (including acute interstitial nephritis)[3] and nephrogenic diabetes insipidus.
Frequency unknown	Renal insufficiency, renal failure, proteinuria.	
General disorders and administration site conditions		
Frequent	Pain, asthenia	Asthenia
Frequency unknown		Fever, sweating, and weight loss.

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

[2] Anaemia was common and skin discolouration (increased pigmentation).

[3] This adverse reaction was identified through reported post-marketing surveillance**.**

Renal impairment

As DIDIVIR may cause renal damage monitoring of renal function is recommended (see **section 4.4**).

Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some HIV-1 infected patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant AD nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see **section 4.4**).

Lactic acidosis

Cases of lactic acidosis have been reported with tenofovir disoproxil alone or in combination with other antiretrovirals. Patients with predisposing factors such as patients with decompensated liver disease, or patients receiving concomitant medications known to induce lactic acidosis are at increased risk of experiencing severe lactic acidosis during tenofovir disoproxil treatment, including fatal outcomes.

Metabolic parameters

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

Immune Reactivation Syndrome

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

Osteonecrosis

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

Paediatric population

Assessment of adverse reactions related to emtricitabine is based on experience in three paediatric studies where treatment-naïve and treatment-experienced paediatric HIV infected patients aged 4 months to 18 years were treated with emtricitabine in combination with other antiretroviral medicine. In addition to the adverse reactions reported in adults, anaemia and skin discolouration occurred more frequently in clinical trials in paediatric patients than in adults (see **section 4.8**).

Assessment of adverse reactions related to tenofovir disoproxil is based on studies in 1 HIV-1 infected paediatric patients (aged 2 to < 18 years) who received treatment with tenofovir disoproxil or placebo/active comparator in combination with other antiretroviral medicine (see **section 5.1**). The adverse reactions observed in paediatric patients who received treatment with tenofovir

disoproxil were consistent with those observed in clinical studies of tenofovir disoproxil in adults (see **section 4.8** and **5.1**).

Reductions in BMD have been reported in paediatric patients. In HIV-1 infected adolescents (aged 12 to < 18 years), the BMD Z-scores observed in subjects who received tenofovir disoproxil were lower than those observed in subjects who received placebo. In HIV-1 infected children (aged 2 to 15 years), the BMD Z-scores observed in subjects who switched to tenofovir disoproxil were lower than those observed in subjects who remained on their stavudine- or zidovudine containing regimen (see **sections 4.4** and **5.1**).

In a study of HIV-1 infected paediatric patients with a median age of 7 years (range 2 to 15 years) were exposed to tenofovir disoproxil. Patients discontinued the study drug due to renal adverse events. Five subjects had laboratory findings clinically consistent with proximal renal tubulopathy, 4 of whom discontinued tenofovir disoproxil therapy. Seven patients had estimated glomerular filtration rate (GFR) values between 70 and 90 mL/min/1,73 m^2. Among them, 3 patients experienced a clinically meaningful decline in estimated GFR during therapy which improved after discontinuation of tenofovir disoproxil.

Other special populations

Individuals with renal impairment

Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in any adults with renal impairment receiving DIDIVIR (see **sections 4.2**, **4.4** and **5.2**). The use of DIDIVIR is not recommended in individuals under the age of 18 years with renal impairment (see **sections 4.2** and **4.4**).

HIV/HBV or HCV co-infected patients

The adverse reaction profile of emtricitabine and tenofovir disoproxil in a reported HIV-infected patient study who were co-infected with HBV or HCV was similar to that observed in patients infected with HIV without co-infection. However, as would be expected in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population. Exacerbations of hepatitis after discontinuation of treatment in HBV infected patients, clinical and laboratory evidence of hepatitis have occurred after discontinuation of treatment (see **section 4.4**).

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 requested to report any suspected adverse reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see **section 4.8**), and standard supportive treatment applied as necessary.

Emtricitabine

Haemodialysis treatment removes approximately 30 % of the emtricitabine dose over a 3-hour dialysis period starting within 1,5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and

a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir disoproxil fumarate

Tenofovir is poorly removed by haemodialysis with an extraction coefficient of approximately 54 %. Following a single 300 mg dose of tenofovir, a four-hour haemodialysis session removed only approximately 10 % of the administered tenofovir dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 20.2.8.

Pharmacotherapeutic group: Antimicrobial (chemotherapeutic) agents. Antiviral agents.

ATC code: J05AR03

Pharmacodynamic effects

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 (RT) 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 polymerase α, β, ε and mitochondrial DNA polymerase γ.

Tenofovir disoproxil fumarate

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

Resistance

Emtricitabine and tenofovir disoproxil fumarate

HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected *in vitro*. Genotypic analysis of these isolates identified the M184I/V and/or K65R amino acid substitutions in the viral RT. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in reduced susceptibility to tenofovir**.**

In a clinical study of treatment-naïve patients (emtricitibine + tenofovir + efavirenz versus zidovudine + lamivudine + efavirenz), resistance analysis was performed on HIV isolates from all virologic failure patients with > 400 copies/ml of HIV-1 RNA at week 144 or early discontinuations. Development of efavirenz resistance-associated mutations occurred most frequently and was similar between the treatment arms.

The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/19 analysed subject isolates in the emtricitabine + tenofovir disoproxil fumarate group and in 10/29 analysed subject isolates in the zidovudine/lamivudine group. Through 144

weeks of this study, no subjects have developed a detectable K65R substitution in their HIV-1 as analysed through standard genotypic analysis.

The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/12 (17 %) analysed patient isolates in the emtricitabine + tenofovir disoproxil fumarate group and in 7/22 (32 %) analysed patient isolates in the zidovudine/lamivudine group.

Emtricitabine

Emtricitabine-resistant isolates of HIV have been selected *in vitro* and *in vivo***.** Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV RT gene at codon 184, which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral medicine. In a clinical study, viral isolates from 6/16 (37,5 %) treatment-naïve patients with virological failure showed > 20-fold reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV RT gene.

Tenofovir disoproxil fumarate

The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1-infected patients treated with abacavir or didanosine.

HIV-1 isolates with the K65R and K70E substitutions also showed reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these NRTIs may occur in patients whose virus harbours the K65R or K70E substitutions.
HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R mutation in RT and showed a 2 to 4-fold reduction in susceptibility to tenofovir.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir in combination with certain antiretroviral medicines.

HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in RT and showed a 2- to 4-fold reduction in susceptibility to tenofovir. Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir in combination with certain antiretroviral medicine. In treatment-naïve patients, 8/47 (17 %) isolates from patients on tenofovir + lamivudine + efavirenz through week 144 showed > 1,4 fold (median 3,7) reduced susceptibility in cell culture to tenofovir. In treatment-experienced patients, 14/304 (5 %, Studies 902 and 907) isolates from patients failing tenofovir through week 96 showed > 1,4 fold (median 2,7) reduced susceptibility to tenofovir.
Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

iPrEx Trial: In a clinical study of HIV-1 seronegative men who have sex with men, no amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 48 subjects in the emtricitabine and tenofovir disoproxil fumarate group

and 83 subjects in the placebo group who became infected with HIV-1 during the trial. Ten subjects were observed to be HIV-1 infected at time of enrolment. The M184V/I substitutions associated with resistance to emtricitabine were observed in 3 of the 10 subjects (2 of 2 in the emtricitabine/tenofovir disoproxil fumarate group and 1 of 8 in the placebo group) who were HIV-1 positive at time of enrolment. One of the two subjects in the emtricitabine/tenofovir disoproxil fumarate group harboured wild type virus at enrolment and developed the M184V substitution 4 weeks after enrolment. The other subject had indeterminate resistance at enrolment but was found to have the M184I substitution 4 weeks after enrolment.

Partners PrEP Trial: In a clinical study of HIV-1 seronegative partners of heterosexual couples of whom one of the partners was HIV-1 infected, no variants expressing amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 12 subjects in the emtricitabine/tenofovir disoproxil fumarate group, 15 subjects in the tenofovir disoproxil fumarate group, and 51 subjects in the placebo group. Fourteen subjects were observed to be HIV-1 infected at the time of enrolment (3 in the emtricitabine/tenofovir disoproxil fumarate group, 5 in the tenofovir disoproxil fumarate disoproxil fumarate group, and 6 in the placebo group). One of the three subjects in the emtricitabine/tenofovir disoproxil fumarate group who was infected with wild type virus at enrolment selected an M184V expressing virus by week 12. Two of the five subjects in the tenofovir disoproxil fumarate group had tenofovir-resistant viruses at the time of seroconversion; one subject infected with wild type virus at enrolment developed a K65R substitution by week 16, while the second subject had virus expressing the combination of D67N and K70R substitutions upon seroconversion at week 60, although baseline virus was not genotyped and it is unclear if the resistance emerged or was transmitted. Following enrolment, 4 subjects (2 in the tenofovir

disoproxil fumarate group, 1 in the emtricitabine/tenofovir disoproxil fumarate group, and 1 in the placebo group) had virus expressing K103N or V106A substitutions, which confer high-level resistance to non-nucleoside reverse transcriptase inhibitors but have not been associated with tenofovir or emtricitabine and may have been present in the infecting virus.

Cross-resistance

Emtricitabine and tenofovir disoproxil fumarate

Cross-resistance among certain nucleoside reverse transcriptase inhibitors (NRTIs) has been recognised. The M184V/I and/or K65R substitutions selected *in vitro* by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine.

Therefore, cross-resistance among these medicines may occur in patients whose virus harbours either or both of these amino acid substitutions.

Emtricitabine

Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine, but retained susceptibility *in vitro* to didanosine, stavudine, tenofovir, zidovudine and NNRTIs (delavirdine, efavirenz, and nevirapine). Isolates from heavily treatment-experienced patients containing the M184V/I amino acid substitution in the context of other NRTI resistance-associated substitutions may retain susceptibility to tenofovir. HIV-1 isolates containing the K65R substitution, selected *in vivo* by abacavir, didanosine, tenofovir and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F,

K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to emtricitabine.

Tenofovir disoproxil fumarate

HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3' zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N) showed a 3,1-fold decreased susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

Antiviral activity

Emtricitabine and tenofovir disoproxil fumarate

In combination studies evaluating the *in vitro* antiviral activity of emtricitabine and tenofovir together, synergistic antiviral effects were observed.

5.2 Pharmacokinetic properties

Emtricitabine

The pharmacokinetic properties of emtricitabine are summarised in Table 7. Following oral administration of emtricitabine (200 mg), emtricitabine is rapidly absorbed, with peak plasma concentrations occurring at 1 to 2 hours post-dose. *In vitro* binding of emtricitabine to human plasma proteins is < 4 % and is independent of concentration over the range of 0,02 to 200 µg/mL. Following administration of radiolabelled emtricitabine, approximately 86 % is recovered in the urine and 13 % is recovered as metabolites. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate.

Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of emtricitabine (200 mg), the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir disoproxil fumarate:

The pharmacokinetic properties of tenofovir disoproxil fumarate are summarised in Table 7. Following oral administration of tenofovir, maximum tenofovir serum concentrations are achieved in 1,0 ± 0,4 hour. *In vitro* binding of tenofovir to human plasma proteins is < 0,7 % and is independent of concentration over the range of 0,01 to 25 µg/mL. Approximately 70 tob80 % of an intravenous dose of tenofovir is recovered unchanged in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of tenofovir disoproxil fumarate, the terminal elimination half-life is approximately 17 hours.

Table 7: Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir in Adults[1]

	Emtricitabine	Tenofovir
Fasted Oral Bioavailability[2] (%)	92 (83,1 to 106,4)	25 (NC to 45,0)
Plasma Terminal Elimination Half-Life[2] (hr)	10 (7,4 to 18,0)	17 (12,0 to 25,7)
Cmax[3] (µg/mL)	1,8 ± 0,724	0,30 ± 0,09
AUC[3] (µg·hr/mL)	10,0 ± 3,124	2,29 ± 0,69
CL/F[3] (mL/min)	302 ± 94	1043 ± 115
CL_{renal}[3] (mL/min)	213 ± 89	243 ± 33

[1.] NC = Not calculated

[2.] Median (range)

[3.]Mean (± SD)

[4.] Data presented as steady state values

Effects of food on oral absorption

The combination tablet may be administered with or without food. Administration of the combination tablet following a high fat meal (49 g of fat) or a light meal (8 g of fat) delayed the time of tenofovir C_{max} by approximately 0,75 hour. The mean increases in tenofovir AUC and C_{max} were approximately 35 % and 15 %, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In previous safety and efficacy studies, tenofovir was taken under fed conditions. Emtricitabine systemic exposures (AUC and C_{max}) were unaffected when the combination tablet was administered with either a high fat or a light meal.

Special Populations

Race

Emtricitabine

No pharmacokinetic differences due to race have been identified following the administration of emtricitabine (200 mg).

Tenofovir disoproxil fumarate

There are insufficient data on racial and ethnic groups other than Caucasian, to adequately determine potential pharmacokinetic differences among these populations following administration of tenofovir disoproxil fumarate.

Paediatric population

Pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in paediatric patients less than 12 years of age, weighing less than 35 kg (see **section 4.4**).

Geriatric patients

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

Patients with impaired renal function

The pharmacokinetics of emtricitabine and tenofovir are altered in patients with renal impairment (see **section 4.3 and section 4.4.**

In patients with creatinine clearance < 50 mL/min, C_{max}, and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased.

DIDIVIR should not be used in patients with creatinine clearance < 50 mL/min or in patients with end-stage renal disease requiring dialysis (see **section 4.3** and **section 4.4).**

Do not use **DIDIVIR** for a Pre-Exposure Prophylaxis (PrEP) indication in HIV-1 uninfected individuals with creatinine clearance below 60 mL/min (see **section 4.3 and section 4.4).**

Patients with hepatic impairment

The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir disoproxil fumarate were 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.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- croscarmellose sodium
- lactose monohydrate
- magnesium stearate
- microcrystalline cellulose
- pregelatinised starch
- *coating*
- opadry blue
    - FD&C Blue #2 / Indigo carmine AL 3-5%
    - hypromellose
    - lactose monohydrate
    - titanium dioxide
    - triacetin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C.

The bottle must be kept tightly closed.

Do not use if seal over bottle opening is broken or missing.

6.5 Nature and contents of container

DIDIVIR is packed in a HDPE container with a non-child resistant cap and a silica gel bag desiccant.

Pack sizes: 30.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO MANUFACTURING (PTY) LTD.

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Mobeni

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4052

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8. REGISTRATION NUMBER(S)

44/20.2.8/0446.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 04 June 2010.

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

13 March 2025