**SCHEDULING STATUS**

**S4**

## 1. NAME OF THE MEDICINE

**ADCO TENOFOVIR 300 mg** Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar: Lactose monohydrate 163,998 mg.

For the full list of excipients, see section 6.1.

**WARNING:**

**LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE, SUCH AS ADCO TENOFOVIR 300 mg, OR IN COMBINATION WITH OTHER ANTIRETROVIRALS. FATAL CASES HAVE BEEN REPORTED (SEE SECTION 4.4).**

**THE SAFETY AND EFFICACY OF ADCO TENOFOVIR 300 mg HAS NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HEPATITIS B VIRUS (HBV), AND ADCO TENOFOVIR 300 mg IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HBV INFECTION. IN PATIENTS WHO ARE CO-INFECTED WITH HBV AND HAVE DISCONTINUED ADCO TENOFOVIR 300 mg, SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED. IN PATIENTS CO-INFECTED WITH HBV, HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS AFTER ADCO TENOFOVIR 300 mg IS DISCONTINUED. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE SECTION 4.4).**

## 3. PHARMACEUTICAL FORM

Film-coated tablets.

ADCO TENOFOVIR 300 mg is light blue, almond-shaped, film-coated tablets debossed with ‘H’ on one side and ‘123’ on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ADCO TENOFOVIR 300 mg is indicated for the treatment of HIV-1 infection in adults in combination with other antiretroviral medicines. This indication is applicable to treatment-naïve and treatment-experienced adults, based on analyses of plasma HIV-1 RNA levels and CD4 cell counts.

### 4.2 Posology and method of administration

**Posology**

***Adults:***

The usual dose of ADCO TENOFOVIR 300 mg is 300 mg once daily, with or without food.

**Special populations**

***Dose adjustment in renal impairment:***

Refer to sections 4.3 and 4.4.

***Geriatric use:***

It should be taken into consideration that geriatric patients are more likely to have age-related renal function impairment; therefore caution may be required in this group when receiving ADCO TENOFOVIR 300 mg treatment.

**Paediatric population**

***Paediatric and adolescent use:***

Safety and efficacy in paediatric patients and in patients < 18 years of age has not been established.

**Method of administration**

For oral administration.

**4.3 Contraindications**

- ADCO TENOFOVIR 300 mg is contraindicated in patients with hypersensitivity to tenofovir, or any of the excipients of the product listed in section 6.1.
- Renal impairment: ADCO TENOFOVIR 300 mg should not be administered to patients with a creatinine clearance < 60 ml/min (see section 4.4).
- Chronic hepatitis B virus infection: The safety and efficacy of ADCO TENOFOVIR 300 mg in patients co-infected with HBV and HIV has not been established (see "BOXED WARNING" above and section 4.4).
- Pregnancy and lactation (see section 4.6).
- ADCO TENOFOVIR 300 mg should not be used in combination with fixed-dose combination medicines containing emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg, or other fixed dose combination medicines that contain tenofovir disoproxil fumarate, since it is an ingredient of these medicines.

**4.4 Special warnings and precautions for use**

There have been no studies demonstrating the effect of ADCO TENOFOVIR 300 mg on the clinical progression of HIV-1.

**Renal impairment and monitoring:**

*Renal impairment:*

ADCO TENOFOVIR 300 mg should be used with caution in patients with renal impairment, or in patients at risk of, or with a history of renal dysfunction. In patients with moderate to severe renal impairment, the terminal half-life of ADCO TENOFOVIR 300 mg is increased due to

decreased clearance. **Significantly increased medicine exposure has been reported when tenofovir, as contained in ADCO TENOFOVIR 300 mg, was administered to patients with moderate to severe renal impairment (see section 4.3).**
The use of ADCO TENOFOVIR 300 mg has been associated with renal insufficiency, elevated creatinine and renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia).
*Renal monitoring:*
It is recommended that creatinine clearance be calculated in all patients prior to treatment initiation. Furthermore, it is recommended that renal function (creatinine clearance and serum phosphate) is also monitored after two to four weeks of treatment, after three months of treatment and every three to six months thereafter in patients without renal risk factors. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to treatment initiation, and periodically during treatment with ADCO TENOFOVIR 300 mg. In such at risk patients, more frequent monitoring of renal function is required.
Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be performed in patients with mild renal impairment.
In patients concomitantly using nephrotoxic medicines, careful monitoring for changes in serum creatinine and phosphorus is required (see warning for nephrotoxic medicines below and section 4.5).
Interrupting ADCO TENOFOVIR 300 mg treatment should be considered in cases of progressive renal function decline when no other cause has been identified.
*Nephrotoxic medicines*:
As ADCO TENOFOVIR 300 mg is primarily renally eliminated, concurrent administration of ADCO TENOFOVIR 300 mg with nephrotoxic medicines, other medicines eliminated via active tubular secretion or recent use of nephrotoxic medicines is not recommended (see section 4.5).

**Lactic Acidosis / Severe Hepatomegaly with Steatosis:**
Lactic acidosis and severe hepatomegaly with steatosis may occur in patients with hepatic disease or in patients with known risk factors for hepatic disease. Particular caution should be exercised in such patients. Cases have, however, been reported in patients with no known risk factors. Fatal cases have been reported. These cases have occurred with the use of ADCO TENOFOVIR 300 mg alone or in combination with other antiretrovirals. Risk factors may include obesity and prolonged nucleoside exposure, and a majority of these cases have been in women. Treatment with ADCO TENOFOVIR 300 mg should be stopped in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).
**Lactic acidosis / hyperlactataemia:**
Potentially fatal lactic acidosis can result as a consequence of mitochondrial dysfunction.
Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include mild raised transaminases,

raised lactate dehydrogenase (LDH) and/or creatine kinase.
In patients with suspicious symptoms or biochemistry, measure the venous lactate levels (normal < 2 mmol/L) and serum bicarbonate, and respond as follows:

- **Lactate 2 to 5 mmol/L**: monitor regularly, and be alert for clinical signs; with minimum symptoms, switch to medicines that are less likely to cause lactic acidosis.
- **Lactate 5 to 10 mmol/L without symptoms**: monitor closely.
- **Lactate 5 to 10 mmol/L with symptoms and/or with reduced standard bicarbonate**: STOP all therapy. Once hyperlactataemia has resolved, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma, hyperthyroidism).
- **Lactate ≥ 10 mmol/L**: STOP all therapy (80 % mortality in case studies).

Patients with predisposing factors, such as patients with decompensated liver disease, or patients receiving concurrent medication known to induce lactic acidosis, are at increased risk of severe lactic acidosis, including fatal outcomes. Caution should be exercised when ADCO TENOFOVIR 300 mg is given to patients with known risk factors for liver disease.

**Bone effects:**
ADCO TENOFOVIR 300 mg may cause a reduction in bone mineral density. The effects of tenofovir disoproxil fumarate-associated changes in bone mineral density on long-term bone health and future fracture risk are currently unknown.
Decreases in bone mineral density of spine and changes in bone biomarkers from baseline are significantly greater with tenofovir disoproxil fumarate, as contained in
ADCO TENOFOVIR 300 mg. Decreases in bone mineral density of the hip are significantly greater. Clinically relevant bone fractures have been reported. If bone abnormalities are suspected, then appropriate consultation should be obtained.
HIV-infected patients should be observed for evidence of bone abnormalities. Bone monitoring should be considered for HIV infected patients with a history of pathologic bone fractures or those at risk of osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients.
Due to bone abnormalities associated with tenofovir disoproxil and the limitations of long-term data on the impact of tenofovir disoproxil on bone health and fracture risk, alternative treatment regimens should be considered for patients with osteoporosis or with a history of bone fractures.
Bone abnormalities, including osteomalacia and infrequently contributing to fractures, may be associated with tenofovir disoproxil-induced proximal renal tubulopathy (see section 4.8). Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in patients at risk. 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 taking ADCO TENOFOVIR 300 mg.

**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 use of combination antiretroviral therapy (cART) (see section 4.8). Patients should be advised to seek medical advice if they experience joint stiffness or difficulty in movement.

**Co-infection with HIV and hepatitis B virus (HBV):**
ADCO TENOFOVIR 300 mg is not indicated for the treatment of chronic HBV infection; the safety and efficacy of ADCO TENOFOVIR 300 mg in patients co-infected with HIV and HBV has not been established. Before initiation of antiretroviral therapy, all patients with HIV should be tested for the presence of chronic HBV.
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. Severe, acute exacerbations of HBV have been reported when ADCO TENOFOVIR 300 mg is discontinued. In patients co-infected with HIV and HBV and who discontinue ADCO TENOFOVIR 300 mg, hepatic function should be closely monitored with both clinical and laboratory follow-up for at least several months.

**Lipodystrophy and metabolic abnormalities:**
Lipodystrophy (accumulation/ redistribution of fat) including central obesity, dorsocervical fat enlargement (buffalo hump), Cushingoid appearance, facial and peripheral wasting and breast enlargement as well as elevated serum lipid and glucose levels are associated with combination antiretroviral therapy, including ADCO TENOFOVIR 300 mg. The mechanism and long-term consequences of these effects are not known.
Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment and lipid disorders should be managed as clinically appropriate.

**Immune reconstitution syndrome (IRIS):**
Immune reconstitution syndrome (inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy (cART), including ADCO TENOFOVIR 300 mg, in HIV-infected patients with severe immune deficiency. IRIS is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation. 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 and other generalised and/or focal mycobacterial infections, cytomegalovirus retinitis, cryptococcal meningitis, and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated, 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 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.

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

**Pancreatitis:**
Pancreatitis has been observed in some patients taking tenofovir disoproxil fumarate, as contained in ADCO TENOFOVIR 300 mg. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue treatment with ADCO TENOFOVIR 300 mg until diagnosis of pancreatitis is excluded.

**Liver disease:**
Use of ADCO TENOFOVIR 300 mg can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of ADCO TENOFOVIR 300 mg has not been established in patients with significant underlying liver disorders/diseases. Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during cART and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

**Opportunistic infections:**
Patients taking ADCO TENOFOVIR 300 mg 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 health care professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

**Concurrent medicines:**
Didanosine: Concurrent administration of ADCO TENOFOVIR 300 mg with didanosine should be undertaken with caution. ADCO TENOFOVIR 300 mg increases the plasma concentrations of didanosine (see section 4.5).
Atazanavir and lopinavir-ritonavir combination: ADCO TENOFOVIR 300 mg concentrations

are increased when administered with atazanavir and lopinavir-ritonavir combination (see section 4.5). ADCO TENOFOVIR 300 mg should be discontinued in patients who develop ADCO TENOFOVIR 300 mg-associated adverse events.

**Use in the elderly:**
There is insufficient information available on the use of tenofovir disoproxil fumarate, as contained in ADCO TENOFOVIR 300 mg, in subjects aged 65 years and above. In general, dose selection for elderly patients should be done with caution, keeping in mind the greater frequency of decreased hepatic, renal or cardiac function, as well as concurrent disease or other medicine therapy.

**Excipients:**
ADCO TENOFOVIR 300 mg contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

ADCO TENOFOVIR 300 mg contains less than 1 mmol sodium (23 mg) tablet; that is to say it is essentially 'sodium-free'.

**4.5 Interaction with other medicines and other forms of interaction**
*Concomitant use not recommended:* ADCO TENOFOVIR 300 mg should not be used concurrently with other medicines containing tenofovir disoproxil fumarate (see section 4.3), or with medicines containing tenofovir alafenamide or adefovir dipivoxil.
Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP450 mediated interactions involving tenofovir, as contained in
ADCO TENOFOVIR 300 mg, is low.
Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Concurrent use of ADCO TENOFOVIR 300 mg with medicines that are eliminated by active tubular secretion may increase serum concentrations of either tenofovir or the co-administered medicine, due to competition for this elimination pathway. Medicines that decrease renal function may also increase serum concentrations of tenofovir (see "Nephrotoxic medicines" below).
Tenofovir disoproxil fumarate, as contained in ADCO TENOFOVIR 300 mg, has been evaluated in healthy volunteers in combination with abacavir, atazanavir, didanosine, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, ledipasvir/sofosbuvir, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir, sofosbuvir, sofosbuvir/velpatasvir, tacrolimus and tipranavir/ritonavir. No clinically significant interactions have been observed between tenofovir disoproxil fumarate and efavirenz, methadone, nelfinavir, oral contraceptives, ribavirin or sofosbuvir. 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 reportedly similar to those observed in previous studies, thereby indicating a lack of clinically significant medicine interactions between these medicines and tenofovir disoproxil fumarate, as contained in ADCO TENOFOVIR 300 mg.

Tables 1 and 2 summarise the pharmacokinetic effects of co-administered medicines on the pharmacokinetics of tenofovir disoproxil fumarate, as contained in ADCO TENOFOVIR 300 mg, and the effects of tenofovir disoproxil fumarate on the pharmacokinetics of co-administered medicines, respectively. Table 3 summarises the interaction between tenofovir disoproxil fumarate and didanosine.

*Table 1: Reported changes in the pharmacokinetic parameters of tenofovir disoproxil fumarate, as contained in ADCO TENOFOVIR 300 mg, in the presence of the co-administered medicine*

| **Co-administered medicine** | **Dose of Co-administered medicine** | **Pharmacokinetic Parameters** | | |
|---|---|---|---|---|
| | | **$C_{max}$** | **AUC** | **$C_{min}$** |
| Abacavir | 300 mg once daily | ⇔ | ⇔ | NC |
| Atazanavir | 400 mg once daily for 14 days | ⇑ | ⇑ | ⇑ |
| Didanosine (enteric-coated) | 400 mg once daily | ⇔ | ⇔ | ⇔ |
| Didanosine (buffered) | 250 mg or 400 mg once daily for 7 days | ⇔ | ⇔ | ⇔ |
| Efavirenz | 600 mg once daily for 14 days | ⇔ | ⇔ | ⇔ |
| Emtricitabine | 200 mg once daily for 7 days | ⇔ | ⇔ | ⇔ |
| Indinavir | 800 mg three times daily for 7 days | ⇑ | ⇔ | ⇔ |
| Lamivudine | 150 mg twice daily for 7 days | ⇔ | ⇔ | ⇔ |
| Ledipasvir/ Sofosbuvir | 90/400 mg once daily for 10 days | ⇑ | ⇑ | ⇑ |
| Ledipasvir/ Sofosbuvir | 90/400 mg once daily for 14 days | ⇑ | ⇑ | ⇑ |
| Lopinavir/ Ritonavir | 400/100 mg twice daily for 14 days | ⇔ | ⇑ | ⇑ |
| Nelfinavir | 1250 mg twice daily for 14 days | ⇔ | ⇔ | ⇔ |
| Saquinavir/ Ritonavir | 1000/100 mg twice daily for 14 | ⇔ | ⇔ | ⇑ |

| | | | | |
|---|---|---|---|---|
| | days | | | |
| Sofosbuvir | 400 mg single dose | ⇑ | ⇔ | ⇔ |
| Sofosbuvir/ Velpatasvir | 400/100 mg once daily | ⇑ | ⇑ | ⇑ |
| Tacrolimus | 0,05 mg/kg twice daily for 7 days | ⇑ | ⇔ | ⇔ |
| Tipranavir/ Ritonavir | 500/100 mg twice daily | ⇓ | ⇓ | ⇑ |
| | 750/200 twice daily (23 doses) | ⇓ | ⇑ | ⇑ |

Increase = ⇑
Decrease = ⇓
No Effect = ⇔
NC = Not Calculated

*Table 2: Reported changes in pharmacokinetic parameters for co-administered medicine in the presence of tenofovir disoproxil fumarate, as contained in ADCO TENOFOVIR 300 mg*

| **Co-administered medicine** | **Dose of Co-administered medicine** | **Pharmacokinetic Parameters** | | |
|---|---|---|---|---|
| | | **$C_{max}$** | **AUC** | **$C_{min}$** |
| Abacavir | 300 mg once daily | ⇑ | ⇔ | NA |
| Atazanavir | 400 mg once daily for 14 days | ⇓ | ⇓ | ⇓ |
| Atazanavir | Atazanavir/ Ritonavir 300/100 mg once daily for 42 days | ⇓ | ⇓ | ⇓ |
| Efavirenz | 600 mg once daily for 14 days | ⇔ | ⇔ | ⇔ |
| Emtricitabine | 200 mg once daily for 7 days | ⇔ | ⇔ | ⇑ |
| Entecavir | 1 mg once daily x 10 days | ⇔ | ⇑ | ⇔ |
| Indinavir | 800 mg three times daily for 7 days | ⇓ | ⇔ | ⇔ |
| Lamivudine | 150 mg twice daily for 7 days | ⇓ | ⇔ | ⇔ |
| Lopinavir/ Ritonavir | 400/100 mg twice daily for 14 days | ⇔ | ⇔ | ⇔ |

| | | | | |
|---|---|---|---|---|
| Methadone | 40 to 110 mg once daily x 14 days | ⇔ | ⇔ | ⇔ |
| Nelfinavir M8 metabolite | 1250 mg twice daily for 14 days | ⇔ | ⇔ | ⇔ |
| Oral Contraceptives | Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen) once daily for 7 days | ⇔ | ⇔ | ⇔ |
| Ribavirin | 600 mg once daily | ⇔ | ⇔ | NA |
| Saquinavir/ Ritonavir | 1000/100 mg twice daily for 14 days | ⇑ | ⇑ | ⇑ |
| Tacrolimus | 0,05 mg/kg twice daily for 7 days | ⇔ | ⇔ | ⇔ |
| Tipranavir/ Ritonavir | 500/100 mg twice daily | ⇓ | ⇓ | ⇓ |
| | 750/200 mg twice daily (23 doses) | ⇓ | ⇓ | ⇓ |

Increase = ⇑
Decrease = ⇓
No Effect = ⇔
NA = Not Applicable

*Table 3: Pharmacokinetic parameters for didanosine in the presence of tenofovir disoproxil fumarate, as contained in ADCO TENOFOVIR 300 mg*

| **Didanosine Dose / Method of Administration** | **TDF Method of Administration** | **Pharmacokinetic Parameters** | |
|---|---|---|---|
| | | **$C_{max}$** | **AUC** |
| Buffered tablets | | | |
| 400 mg once daily x 7 days | Fasted 1 hour after didanosine | ⇑ | ⇑ |
| Enteric-coated capsules | | | |
| 400 mg once daily, fasted | With food, 2 hr after didanosine | ⇑ | ⇑ |
| 400 mg once daily, with food | Simultaneously with didanosine | ⇑ | ⇑ |
| 250 mg once daily, fasted | With food, 2 hr after didanosine | ⇓ | ⇔ |

| | | | |
|---|---|---|---|
| 250 mg once daily, fasted | Simultaneously with didanosine | ⇔ | ⇧ |
| 250 mg once daily, with food | Simultaneously with didanosine | ⇩ | ⇩ |

Increase = ⇧
Decrease = ⇩
No Effect = ⇔

**Nephrotoxic medicines**:
Concomitant administration of ADCO TENOFOVIR 300 mg with nephrotoxic medicines, recent use of a nephrotoxic medicine or other medicines eliminated via active tubular secretion is not recommended. Examples of such medicines include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides, amphotericin B, foscarnet, pentamidine, vancomycin, interleukin-2 and high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs). Plasma concentrations of either tenofovir or the nephrotoxic medicines may be increased due to competition for elimination. Higher tenofovir concentrations could potentiate the associated adverse events, including renal disorders. Renal function should be monitored weekly should the use of nephrotoxic medicines be unavoidable (refer to section 4.4).

Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir disoproxil fumarate, as contained in ADCO TENOFOVIR 300 mg. Some patients required hospitalisation and renal replacement therapy. If ADCO TENOFOVIR 300 mg is used concurrently with a NSAID, renal function should be monitored adequately. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.
A higher risk of renal impairment has been reported in patients receiving tenofovir disoproxil fumarate, as contained in ADCO TENOFOVIR 300 mg, in combination with a ritonavir or cobicistat boosted protease inhibitor. A close monitoring of renal function is required in these patients. In patients with renal risk factors, the co-administration of tenofovir disoproxil with a boosted protease inhibitor should be carefully evaluated.
As tacrolimus can affect renal function, close monitoring is recommended when it is used concurrently with ADCO TENOFOVIR 300 mg.

**Didanosine:**
Caution should be exercised when using ADCO TENOFOVIR 300 mg with didanosine, since ADCO TENOFOVIR 300 mg increases the plasma concentrations of didanosine: the $C_{max}$ and AUC of didanosine, administered as either the buffered or enteric-coated formulation, is reported to increase significantly (see Table 3 above) when administrated with tenofovir, as contained in ADCO TENOFOVIR 300 mg. Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis, lactic acidosis and neuropathy (refer to section 4.4).
**Co-administration of ADCO TENOFOVIR 300 mg and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for**

**didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events.**
The didanosine dose should be reduced to 250 mg in adults weighing > 60 kg when it is used together with ADCO TENOFOVIR 300 mg. For patients weighing < 60 kg, there is no available data to recommend a dose adjustment of didanosine. Didanosine should be discontinued in patients who develop didanosine-associated adverse events. When ADCO TENOFOVIR 300 mg and a didanosine enteric-coated formulation are used concomitantly, they can be taken under fasting conditions or with a light meal. When ADCO TENOFOVIR 300 mg and a didanosine buffered tablet formulation are used concomitantly, they should be taken under fasting conditions.

**Atazanavir and lopinavir-ritonavir combination:**
Concurrent administration of ADCO TENOFOVIR 300 mg and atazanavir may result in decreased plasma concentrations of atazanavir and increased plasma concentrations of ADCO TENOFOVIR 300 mg. However, this effect is significantly reduced when ritonavir is used as a booster (refer to section 4.4). Atazanavir without ritonavir should not be co-administered with ADCO TENOFOVIR 300 mg. It is recommended that atazanavir 300 mg is given with ritonavir 100 mg when co-administered with ADCO TENOFOVIR 300 mg.
The plasma concentration of ADCO TENOFOVIR 300 mg is increased when used with a lopinavir-ritonavir combination (refer to section 4.4). The mechanism of this interaction is unknown.
The increased exposure of tenofovir due to concurrent use with atazanavir or a lopinavir-ritonavir combination can potentiate tenofovir-associated adverse events, including renal disorders (see section 4.4).
**Patients receiving atazanavir or a lopinavir-ritonavir combination with ADCO TENOFOVIR 300 mg should be monitored for tenofovir-associated adverse events and renal function should be closely monitored. ADCO TENOFOVIR 300 mg should be discontinued in patients who develop ADCO TENOFOVIR 300 mg-associated adverse events.**

**Lamivudine:**
Plasma concentrations of lamivudine are decreased when used concomitantly with
ADCO TENOFOVIR 300 mg. There is a high level of treatment failure and emergence of resistance when a once-daily triple nucleoside regimen of ADCO TENOFOVIR 300 mg, lamivudine and either abacavir or didanosine is used. This combination should be avoided.

**Indinavir:**
Concomitant administration of ADCO TENOFOVIR 300 mg and indinavir results in increased plasma concentrations of ADCO TENOFOVIR 300 mg and decreased plasma concentrations of indinavir.
**Ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/ velpatasvir/voxilaprevir:**
Co-administration of tenofovir disoproxil fumarate, as contained in
ADCO TENOFOVIR 300 mg, and ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir combination has been reported to increase tenofovir

exposure (see Table 1 above). Patients on a treatment regimen of ADCO TENOFOVIR 300 mg concurrently with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir should be monitored for adverse reactions associated with tenofovir disoproxil fumarate.

**4.6 Fertility, pregnancy and lactation**

ADCO TENOFOVIR 300 mg is contraindicated in pregnancy and lactation (see section 4.3). Safety in pregnancy and lactation has not been established.

**Pregnancy**

Adequate and well-controlled studies have not been done in pregnant women.
ADCO TENOFOVIR 300 mg should not be used during pregnancy (see section 4.3).

**Breastfeeding**

Breastfeeding is not recommended during ADCO TENOFOVIR 300 mg therapy (see section 4.3).
**Nursing Mothers: HIV-infected mothers should not breastfeed their infants, to avoid risking postnatal transmission of HIV.**
It is reported that tenofovir, as contained in ADCO TENOFOVIR 300 mg, was secreted in human milk at low levels in samples of breast milk obtained from HIV-1 infected mothers in the first post-partum week. Tenofovir-associated risks, including the risk of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with
ADCO TENOFOVIR 300 mg are unknown. 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 if they are receiving ADCO TENOFOVIR 300 mg (see section 4.3).**

**4.7 Effects on ability to drive and use machines**

ADCO TENOFOVIR 300 mg has minor influence on the ability to drive and operate machinery. Since adverse reactions such as dizziness have been reported in patients taking tenofovir, as contained in ADCO TENOFOVIR 300 mg, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that ADCO TENOFOVIR 300 mg does not adversely affect their ability to do so (see section 4.8).

**4.8 Undesirable effects**

**List of adverse reactions**

**Blood and lymphatic system disorders:**
*Frequency unknown*: Anaemia, neutropenia.

**Immune system disorders:**
*Frequency unknown:* Allergic reaction (including angioedema), immune reconstitution syndrome (see section 4.4).

**Metabolism and nutrition disorders:**
*Frequent:* Hypophosphataemia.

*Less frequent:* Anorexia, hypokalemia, lactic acidosis.
*Frequency unknown:* Lipodystrophy (accumulation/redistribution of fat) including central obesity, dorsocervical fat enlargement (buffalo hump), Cushingoid appearance, facial and peripheral wasting and breast enlargement, hypertriglyceridemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, hyperlactataemia and hyperlipasaemia.

**Psychiatric disorders:**
*Frequent:* insomnia.
*Frequency unknown:* Abnormal behaviour, depression, anxiety.

**Nervous system disorders:**
*Frequent:* Dizziness, headache.
*Frequency unknown:* Convulsions, hypertonia, peripheral neuropathy.

**Respiratory, thoracic and mediastinal disorders:**
*Frequency unknown:* Dyspnoea, pneumonia.
**Gastrointestinal disorders:**
*Frequent:* Diarrhoea, nausea, vomiting, abdominal pain, abdominal distension, flatulence.
*Less frequent:* Pancreatitis.
*Frequency unknown:* Dyspepsia.

**Hepato-biliary disorders:**
*Less frequent:* Hepatic steatosis, hepatitis.
*Frequency unknown:* Hepatotoxicity, including severe hepatomegaly with steatosis.

**Skin and subcutaneous tissue disorders:**
*Frequent:* rash.
*Frequency unknown:* Sweating, pruritus.

**Musculoskeletal and connective tissue disorders:**
*Frequent:* bone mineral density decreased.
*Less frequent:* Rhabdomyolysis, muscular weakness, myopathy, osteomalacia.
*Frequency unknown:* Myalgia, arthralgia, myositis, osteonecrosis (see section 4.4).

**Renal and urinary disorders:**
*Less frequent:* Proximal renal tubulopathy (including Fanconi syndrome), acute renal failure, renal failure, acute tubular necrosis, nephritis (including acute interstitial nephritis, including acute cases), nephrogenic diabetes insipidus.
*Frequency unknown:* Renal insufficiency, proteinuria, polyuria.

**General disorders and administration site conditions:**
*Frequent:* Asthaenia, fatigue, fever, weight loss, pain, back pain, chest pain.

**Investigations:**

*Frequent:* Increased transaminases.
*Less frequent:* Increased creatinine.
*Frequency unknown:* Increased serum amylase concentrations, elevated creatine phosphokinase.

**Description of selected adverse reactions**
Myalgia, arthralgia, myositis and rhabdomyolysis have been reported, particularly when nucleoside analogues are given with protease inhibitors.
Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term use of combination antiretroviral therapy.
Myopathy and osteomalacia are both associated with proximal renal tubulopathy. Hypophosphataemia, hypokalaemia, rhabdomyolysis and muscular weakness may also occur as a consequence of proximal renal tubulopathy. These adverse reactions are not considered to be causally associated with tenofovir disoproxil in the absence of this condition.
Osteomalacia can manifested as bone pain and infrequently contribute to fractures.
Elevated creatine phosphokinase has been reported particularly when nucleoside analogues are given with protease inhibitors.

**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 drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHRA) and eReporting platform (who-umc.org) found on SAHPRA website.

**4.9 Overdose**
There is limited clinical experience at higher than therapeutic doses (300 mg) of
ADCO TENOFOVIR 300 mg. The effect of a higher dose is not known.
Treatment of an overdose should be symptomatic and supportive. Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric counselling. Patients should be monitored for evidence of toxicity.
ADCO TENOFOVIR 300 mg is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %. A four-hour haemodialysis session removed approximately 10 % of the administered 300 mg ADCO TENOFOVIR 300 mg dose.

**5. PHARMACOLOGICAL PROPERTIES**
**5.1 Pharmacodynamic properties**
Category and Class: A: 20.2.8 Antimicrobial (chemotherapeutic) medicines. Antiviral medicines.
Pharmacotherapeutic group: Nucleoside and nucleotide reverse transcriptase inhibitors.
ATC code: J05AF07.

**Pharmacodynamic effects**
Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analogue of

adenosine 5'-monophosphate. As the parent compound has very poor oral bioavailability, tenofovir is available as the prodrug tenofovir disoproxil fumarate, which substantially improves oral absorption and cellular penetration. Tenofovir disoproxil fumarate is rapidly hydrolyzed to tenofovir, and then undergoes phosphorylation by cellular kinases to form tenofovir diphosphate, the active metabolite. Tenofovir diphosphate competitively inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and is incorporated into DNA, thus causing chain termination. Tenofovir diphosphate has a low affinity for human DNA polymerases alpha, beta and gamma.

*Resistance and cross-resistance:*
Viral replication in the presence of suboptimal concentrations of tenofovir can select for mutations that confer resistance. A single substitution at codon 65 of reverse transcriptase K65R results in specific resistance to tenofovir, reducing *in vitro* sensitivity 3 to 4 fold. In patients harbouring HIV isolates with high-level resistance (M41L, L120W) to zidovudine or stavudine, sensitivity to tenofovir and virologic efficacy are also reduced. Only partial resistance to tenofovir is apparent in HIV variants that are resistant to zidovudine. The M184V mutations associated with lamivudine or emtricitabine resistance, partially restores susceptibility in tenofovir-resistant HIV harbouring the K65R mutation.
In initial clinical studies, the K65R mutation was reported in only 2 to 3 % of patients treated with tenofovir, and was not usually associated with treatment failure. Very high early rates of virologic failure or non-response are associated with once-daily combinations of 3 nucleosides, and specifically tenofovir + didanosine and tenofovir + abacavir + lamivudine.

**5.2 Pharmacokinetic properties**
The oral bioavailability of tenofovir disoproxil fumarate is 25 %. The oral bioavailability is increased to 39 % following intake with a high-fat meal, but it can be taken without regard to food. The plasma elimination half-life of tenofovir is 14 to 17 hours; the intracellular elimination half-life of tenofovir triphosphate is 10 to 50 hours. This is the reason once-daily dosing is possible. Plasma protein binding of tenofovir is not significant (< 8 %). Tenofovir is eliminated by both glomerular filtration and active tubular secretion; 70 to 80 % of tenofovir is eliminated unchanged in the urine. In patients with renal insufficiency, doses should be decreased.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**
Croscarmellose sodium.
FD&C blue #2 / Indigo carmine aluminium lake.
Hypromellose.
Lactose monohydrate.
Magnesium stearate.
Microcrystalline cellulose.
Pregelatinized starch.
Titanium dioxide.
Triacetin.

**6.2 Incompatibilities**
Not applicable.

**6.3 Shelf life**
2 years.

**6.4 Special precautions for storage**
Store at or below 30 °C in tightly closed containers.
Protect from light and moisture. Keep in the original container.

**6.5 Nature and contents of container**
28's, 30's, 56's or 100's tablets are packed in a white, opaque HDPE container with a white, child-resistant, ribbed plastic closure with a pulp liner. Purified rayon coil and a silica gel desiccant are placed in the container. The container is placed in a printed carton.
500's or 1 000's tablets are packed in a white, opaque HDPE container with a white, ribbed plastic closure with continued threading with a pulp liner. Purified rayon coil and a silica gel desiccant are placed in the container. The container is placed in a printed carton.
Not all pack sizes or types are necessarily marketed.

**6.6 Special precautions for disposal**
No special requirements.
Any unused medicine or waste material should be disposed of in accordance with local requirements.

**7. HOLDER OF CERTIFICATE OF REGISTRATION**
Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

**8. REGISTRATION NUMBER(S)**
44/20.2.8/0332

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
30 September 2011

**10. DATE OF REVISION OF THE TEXT**
08 November 2024